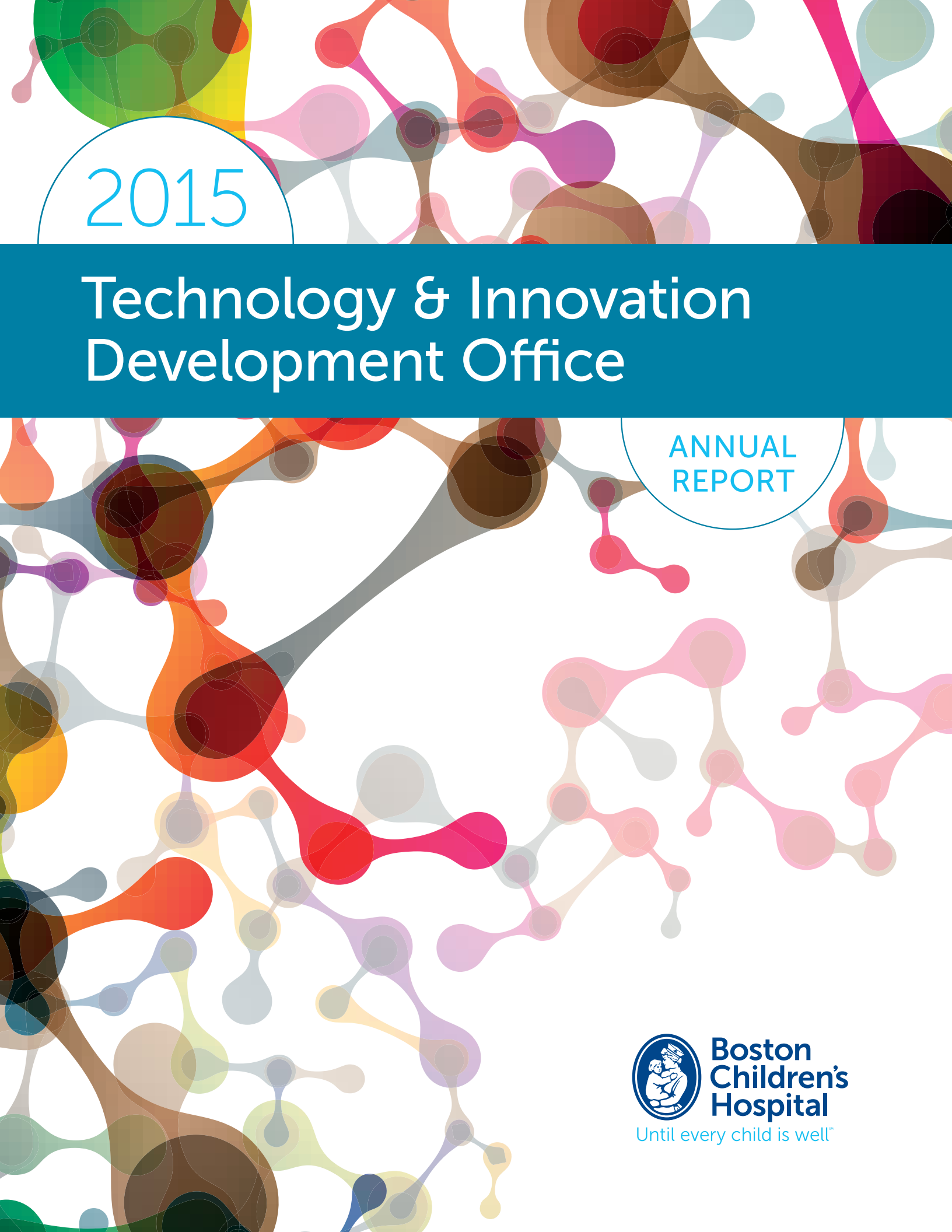




2015

Technology & Innovation Development Office

ANNUAL
REPORT



**Boston
Children's
Hospital**

Until every child is well™



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Children's
Hospital**

Until every child is well™

Boston Children's Hospital is a 404-bed comprehensive center for pediatric health care. *U.S. News & World Report* named Boston Children's the number one pediatric hospital in the United States for 2015–16, and seven individual clinical specialties were deemed to be the best in the nation.

Boston Children's is home to the world's largest research enterprise based at a pediatric hospital. More than 600 faculty researchers and 700 postdoctoral fellows are actively pursuing innovations to solve the most pressing challenges in pediatric medicine today. Our research community includes seven members of the National Academy of Sciences, 11 members of the Institute of Medicine, 10 members of the Howard Hughes Medical Institute 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.

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

\$290 M

Total Research Funding

\$9.2 M

Gross Licensing Revenue

\$7.7 M

Net Licensing Revenue

\$15.1 M

Industry Sponsored
Research Revenue
(up 32%)

48

License Agreements
(up 42%)

43

Research
Agreements

162

Invention Disclosures

4

Startups Created

Imagine building a system to maximize innovation: would it look like this?

Gather the most talented scientists under one roof. Give them the tools and freedom to explore the most interesting problems of their time. Motivate them by having them compete for resources by outperforming their peers. And see what they discover. This is the academic research model, and it has led to the greatest innovations in healthcare in our time.

At Boston Children's Hospital, we are not only the top pediatric hospital in the nation, we are also the fourth largest recipient of NIH funding among independent hospitals in the U.S. By combining the world's best clinicians and most renowned scientists with the mission of improving children's health, we are transforming the way diseases are treated.

The breadth of discovery at Boston Children's is tremendous and unlimited. Our research is leading to novel anesthetics that will transform surgery, new treatments to cure cancer and treat inflammation, low cost consumer diagnostics that will be widely available, revolutionary digital health technologies that mine social media and public information to identify disease outbreaks days before health authorities, and a standardized platform for apps that can interface with any electronic health record system, unlocking the tremendous potential of big data. These innovations are setting the stage to transform hospital care by reducing costs and improving outcomes.

The Technology and Innovation Development Office (TIDO) at Boston Children's helps our innovators and researchers advance their discoveries to market by identifying discoveries with commercial potential and building business strategies around them. These strategies include intellectual property protection, market intelligence and deal formation. TIDO's business development and marketing team interfaces with companies and investors to attain research funding and support for our entrepreneurial faculty. Our Technology Development Fund invests in and advances projects with commercial potential to late-stage opportunities sought by licensees and investors. Finally, we support the hospital's research endeavor by bringing in licensing royalties, attracting industry sponsored research, and negotiating material transfer agreements.

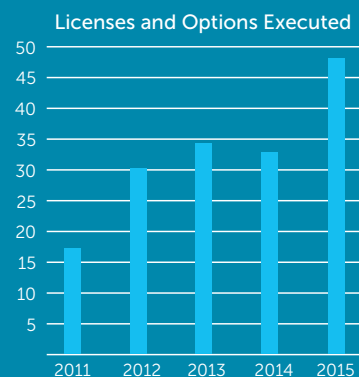
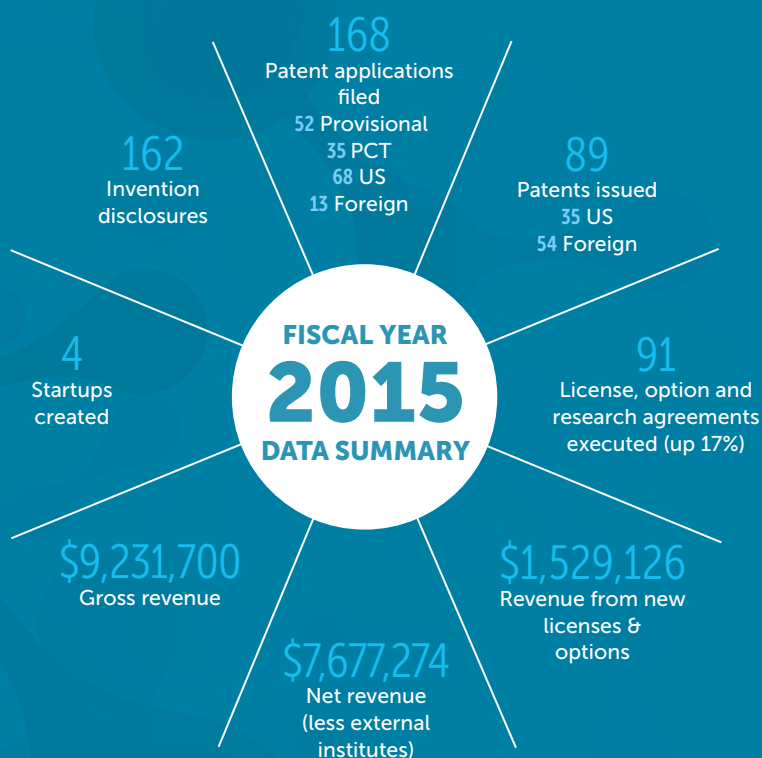
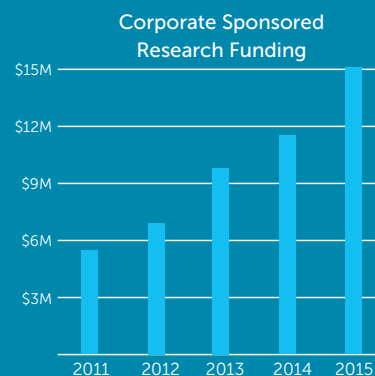
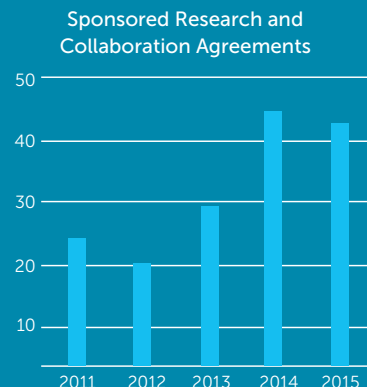
This year, TIDO helped a number of these innovations move forward by facilitating partnerships with industry. We partnered with Boston Scientific to develop methods to prevent cardiac damage by transplanting a patients' own mitochondria into the heart. Four startup companies were launched, focusing on novel cancer therapies and new methods to treat inflammation. We entered into new collaborative research projects with our pharmaceutical neighbors to explore the fields of rare disease, inflammation and neurodegeneration.

In this annual report, you will see the outcomes of this work facilitating the transfer of innovations from our researchers and clinicians into the hands of industry partners to be developed into products and therapies that improve human health.



Irene Abrams
Senior Director,
Technology & Innovation
Development Office

By the Numbers



Issued US Patents

Kohane, Daniel

8,975,281 Neosaxitoxin combination formulations for prolonged local anesthesia

Kohane, Daniel

8,975,268 Neosaxitoxin combination formulations for prolonged local anesthesia

del Nido, Pedro

8,951,275 Trocar for use during endoscopy

Ingber, Donald

8,931,490 System and methods for nanomagnetic actuation of molecular cell signaling

Rufo, Paul

9,072,728 Treatment of severe distal colitis

Packard, Alan

9,101,673 Fluorine-18 labeled rhodamine derivatives for imaging with positron emission tomography

Packard, Alan

9,066,985 Fluorine-18 labeled rhodamine derivatives for imaging with positron emission tomography

Zetter, Bruce

9,151,758 Methods to predict and prevent resistance to taxoid compounds

Clapham, David

9,068,018 Voltage-gated proton channel, Hv1, and uses thereof

Ingber, Donald

9,220,831 Device and methods for combined microfluidic-micromagnetic separation of material in continuous flow

Imam, Farhad

8,954,134 Light-guided transluminal catheter

Zon, Leonard

9,028,811 Methods for promoting HSC self-renewal

Teng, Yang Dong (Ted)

9,101,695 Methods and compositions for the treatment of open and closed wound spinal cord injuries

Levy, Hara

9,133,518 Method for determining predisposition to pulmonary infection

D'Amato, Robert

9,090,707 Pro-angiogenic fragments of prominin-1 and uses thereof

Malley, Richard

9,125,863 Synergistic immunogenic fusion protein-polysaccharide conjugate

Bischoff, Joyce

9,220,716 Methods and compositions for the treatment of proliferative vascular disorders

Ingber, Donald

9,156,037 Microfluidic device and uses thereof

Zon, Leonard

9,051,548 Methods for enhancing hematopoietic stem/progenitor cell engraftment

Zon, Leonard

9,056,085 Methods for enhancing hematopoietic stem/progenitor cell engraftment

Zon, Leonard

9,040,286 Diagnosis and treatment of cancer

Rao, Anjana

9,163,078 Regulators of NFAT

Lieberman, Judy

8,927,510 Compositions and methods for inhibition of retroviruses

Rao, Anjana

9,115,386 Selective oxidation of 5-methylcytosine by Tet-family proteins

Dvir, Tal

9,114,009 Nanowired three dimensional tissue scaffolds

Blagg, Julian

9,169,234 Sepiapterin reductase inhibitors for the treatment of pain

Ozcan, Umut

9,186,393 Methods and compositions for reducing blood glucose

Ingber, Donald

9,078,856 Improving efficacy of cancer therapy

Kohane, Daniel

9,168,389 Harmonic generation for activation of species and/or delivery of species to a target environment

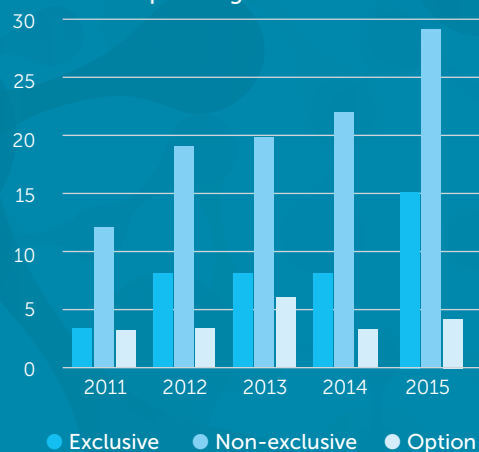
Beggs, Alan

8,957,044 Systemic gene replacement therapy for treatment of X-linked myotubular myopathy (XLMTM)

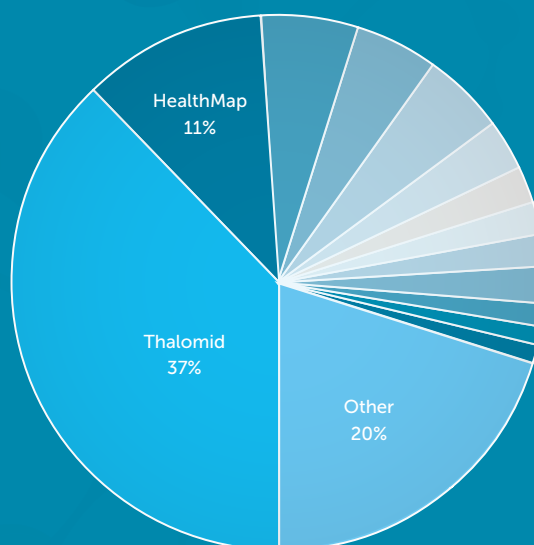
Madsen, Joseph

9,138,568 CSF shunt flow enhancer, method for generating CSF flow in shunts and assessment of partial and complete occlusion of CSF shunt systems

Breakdown of License & Option Agreements



Sources of Licensing Revenue



Alprolix and Elocate	5.5%
Cancer Immunotherapy	5%
Memantine	5%
Research Antibodies	3%
ProHema	2%
Beloranib	2%
Gene Therapy Constructs for Hemoglobinopathies	2%
BCL11A Targets	2%
LiRIS	1.5%
GEN-04	1%
Circular Mutagenesis Kit	1%

Issued Foreign Patents

Watnick, Randolph

Australia, 2008268461

Methods and uses thereof of prosaposin

Zon, Leonard

Mexico, 330957

Method to modulate hematopoietic stem cell growth

Malley, Richard

New Zealand, 614460

Vaccines and compositions against *Streptococcus pneumoniae*

Schachter, Asher

EPO*, 1599602

Predicting graft rejection

Zon, Leonard

China, 1740261

Method to modulate hematopoietic stem cell growth

Frank, Markus

EPO**, 2155248

Targeting ABCB5 for cancer therapy

Folkman, Judah

EPO***, 2170402

Metap-2 inhibitor polymersomes for therapeutic administration

Frank, Markus

EPO****, 2182005

A gene on human chromosome 7p15-21 encoding a multidrug resistance P-glycoprotein homologue, and uses

Atala, Anthony

Canada, 2,468,171

Methods of isolation, expansion and differentiation of fetal stem cells from chorionic villus, amniotic fluid, and placenta and therapeutic uses thereof

Springer, Timothy

Canada, 2554965

Antibodies specific for activated conformation of LFA-1

Corfas, Gabriel

Canada, 2,714,676

Treatment for neuropathy

Teng, Yang Dong (Ted)

Japan, 5746726

Methods and compositions for the treatment of open and closed wound spinal cord injuries

Ingber, Donald

Australia, 2009270821

Organ mimic device with microchannels and methods of use and manufacturing thereof

D'Amato, Robert

Australia, 2009276704

Prominin-1 peptide fragments and uses thereof

Kentsis, Alex

Australia, 2009335000

Method of predicting acute appendicitis

Kong, Sek Won

South Korea, 10-1482010

Ultrafast general search device and method for whole genome sequencing

Frank, Markus

Hong Kong, HK1129703

ABCB5 positive mesenchymal stem cells as immunomodulators

Ingber, Donald

Hong Kong, HK1159158

Organ mimic device with microchannels and methods of use and manufacturing thereof

Orkin, Stuart

Nigeria, NG/C/2011/257

Modulation of BCL11A for treatment of hemoglobinopathies

Cima, Michael

China, ZL200980140117.7

Implantable drug delivery device and methods of treating male genitourinary and surrounding tissues

*EPO: Belgium, Bulgaria, Cyprus, Czech Republic, France, Hungary, Ireland, Italy, Portugal, Romania, Slovak region, Spain, Switzerland, Turkey, UK

**EPO: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Monaco, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, UK

***EPO: France, Germany, UK

****EPO: Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Hong Kong, Ireland, Italy, Luxembourg, Monaco, Netherlands, Portugal, Spain, Sweden, Switzerland, Turkey, UK

Technology Development Fund

2015 grant awardees and projects

The TDF was created in 2009 to advance promising technologies of Boston Children's clinicians and researchers and support their translation into new devices, diagnostics and therapeutics for our patients and the broader public. In addition to financial support for selected projects, the TDF provides access to an external advisory board of industry experts in product development and business who serve as mentors. 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 2015 grant awardees — selected from 47 letters of intent submitted for consideration — include:

Targeting the Lin28 protein-RNA interface as a novel chemotherapeutic

George Daley, MD, PhD (Hematology/Oncology; Medicine) and Piotr Sliz, PhD (Harvard Medical School)

The team has shown that the Lin28 proteins promote cell transformation *in vitro* — and a variety of murine cancers *in vivo* — by interacting with and inhibiting the biogenesis of the let-7 family of miRNAs. The project's goal is to identify small-molecule inhibitors that disrupt the association of the Lin28 proteins with the let-7 tumor suppressors. Drs. Daley and Sliz will use TDF funds to retain a contract research organization to optimize their initial chemical hits with medicinal chemistry.

Unsaturated glycosphingolipid as a novel platform for drug delivery (and mucosal vaccines)

Wayne Lencer, MD and Dan Chinnappen, PhD (Gastroenterology; Medicine)

The team is developing a drug delivery platform to allow oral and nasal delivery of large proteins and peptides that otherwise cannot cross the membranes of mucosal epithelial and blood vessel endothelial cells. The team will use TDF funds to perform a proof-of-concept experiment and demonstrate the validity of the glycosphingolipid platform with a naturally occurring peptide.

Myocardial perfusion imaging (MPI) with F-18-labeled rhodamine 6G: First-in-human studies

Alan Packard, PhD (Radiology) and S. Ted Treves, MD (Brigham and Women's Hospital)

The team has developed a promising positron emission tomography (PET) MPI agent, F-18-labeled rhodamine 6G (¹⁸F-Rho6G), and has shown that it accumulates in the heart in a preclinical model of cardiovascular disease. The team will use TDF support to carry out first-in-human studies with ¹⁸F-Rho6G and translate the preclinical results into the clinic.

Novel natural products active against carbapenemase-producing *Klebsiella pneumoniae*

Paula Watnick, MD, PhD and Julie Liao, PhD (Infectious Diseases; Medicine)

The goal of the project is to develop new antibiotics active against infections caused by multi-drug-resistant bacteria of the *Enterobacteriaceae* family such as *Klebsiella pneumoniae* and *Escherichia coli*. The team will

use TDF support to screen a library of fungal extracts and subcontract with the Natural Products Discovery Institute to identify and characterize promising compounds.

DNA nanoswitches: A diagnostic platform

Wesley Wong, PhD and Mounir Koussa, PhD (Program in Cellular and Molecular Medicine; Medicine)

The team is developing a novel protein-detection platform technology for point-of-care and home diagnostic testing. Based on a proprietary DNA nanotechnology, the platform is 1,000,000 times more sensitive than standard ELISAs while being affordable and easy to use. TDF support, with supporting funds from Harvard University through the Blavatnik Biomedical Accelerator and the Wyss Institute, will be used to improve analyte detection and stability of the assay reagents.

Automated apparatus to detect and quantify rodent behavioral signs of injury, disease and drug effects

Clifford Woolf, MB, BCh, PhD and David Roberson, MBA, PhD (F.M. Kirby Neurobiology Center; Neurology)

To address the need for preclinical screening technologies that better predict clinical efficacy and adverse side effects of experimental drugs, the team has developed a device that permits unprecedented detection of central nervous system activity through prolonged observation of voluntary rodent behavior at pharmaceutically relevant drug doses. The team will use TDF funds to support software development and animal studies to compare the effects of previously developed therapeutic compounds.

Since 2009,
Technology
Development
Fund awards
have led to:

6 STARTUP COMPANIES, the most recent being Quartet Medicine. The new companies (medical device, therapeutics, vaccine and software) have collectively received **\$42M in seed funding** from various venture capitalists, the FDA and foundations.

\$24.4M 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.

8 LICENSES AND 1 OPTION. Most recently, Grunenthal GmbH licensed NeoSTX as a long-duration analgesic for up to \$85M in milestone payments.

SUPPORT FROM OTHER FUNDING PROGRAMS in the Boston area, such as Harvard University's Blavatnik Biomedical Accelerator, the Center for Integration of Medicine and Innovative Technology (CIMIT) and the Boston Biomedical Innovation Center (B-BIC). TDF has also established a network of 45 contract research organizations for drug, medical device and software development.



TDF awards ceremony



Agreements: Startups

Kindrdfood licenses web content to help families with dietary restrictions

In August 2015, Kindrdfood entered into a license agreement with Boston Children's Hospital to use pediatric nutrition content developed by Elizabeth Hait, MD, MPH, attending physician and co-medical director of the Eosinophilic Gastrointestinal Disease Program. Kindrdfood comprises of a web-based application and team of experts who guide families needing to change the way they eat due to a medical condition, a dietary restriction such as food allergy or a change in the family. Clients can access reliable information on the website and are matched with trained Kindrd nutritionists who guide them through live video or phone sessions.

Neuro'motion options emotional-control videogame technology

Neuro'motion entered an option agreement with Boston Children's to develop interactive computer games and toy technologies that use biofeedback to teach children emotional regulation. The evidence-based therapy will help children build important neural structures that support emotional regulation. The technology was developed by Jason Kahn, PhD, a researcher in the department of Psychiatry, along with his Psychiatry colleagues Joseph Gonzalez-Heydrich, MD, chief of the Psychopharmacology Program, and Peter Ducharme, LICSW, as well as Alex Rotenberg, MD, of Neurology. The technology aims to reduce stress and give clinicians an alternative to medications. These games can be played in the clinic, at home or on-the-go.

Piper Therapeutics licenses immunotherapy technology to stop tumor growth and retinopathy

Piper Therapeutics, a company focused on developing best-in-class cancer therapeutics, licensed intellectual property rights related to immunotherapy developed in the Boston Children's laboratory of Lois Smith, MD, PhD, professor of Ophthalmology. The intellectual property covers new approaches to modulate immune and inflammatory responses to abrogate tumor growth and retinopathy. There is a great need for therapeutics that inhibit pathological neovascularization in tumors and in retinopathy, without inhibiting normal angiogenesis, and that are superior to the prevalent anti-VEGF therapies.



Neuro'motion interactive computer games

Agreements: Licenses

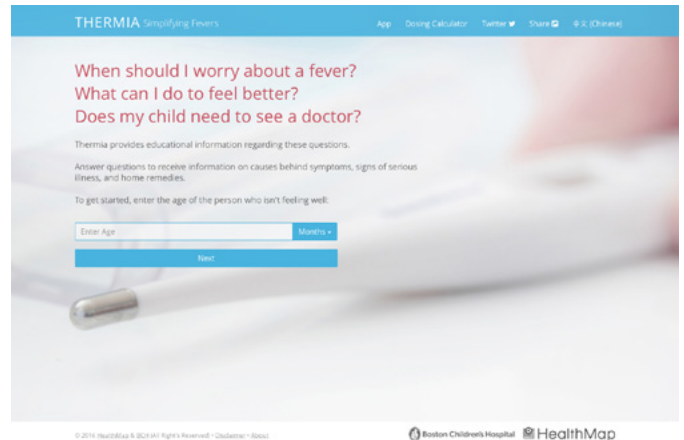
Janssen Pharmaceuticals exclusively licenses HIV vaccine technology

Janssen Pharmaceuticals, Inc. entered an exclusive license agreement for the HIV-1 trimeric envelope vaccine technology developed by Bing Chen, PhD, in the division of Molecular Medicine, and Stephen Harrison, PhD, HHMI investigator and chief of the division of Molecular Medicine at Boston Children's, and collaborators at Beth Israel Deaconess Medical Center. HIV/AIDS is a major global epidemic affecting 35 million people (0.8 percent of the worldwide population). The researchers have created biochemically stable trimers and developed methods to produce them. They have shown that these trimers elicit interesting antibody responses against a diverse array of HIV-1 isolates from clades A, B and C. These stabilized immunogens may contribute to ongoing research by Janssen to develop a preventive HIV vaccine.

Grünenthal partners with Boston Children's and Proteus S.A. to develop long-lasting local anesthetic

Grünenthal GmbH, a private, family-owned pharmaceutical company specializing in pain management, entered an exclusive partnership with Proteus S.A. and Boston Children's for the continued development of the novel anesthetic neosaxitoxin (NeoSTX). This product has the potential to revolutionize local anesthesia and post-operative pain management. Proteus S.A. and Boston Children's have worked together since 2010 on the development of NeoSTX, a site-1 specific sodium channel blocker derived from cyanobacteria. Boston Children's and Proteus will continue to actively participate in the product's development.

Proteus uses a proprietary technology to produce and purify NeoSTX in a clean, inexpensive and environmentally friendly manner. 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 have worked with this compound for more than 20 years. A Phase 1 clinical trial was conducted at Boston Children's in collaboration with Proteus, with support from the Anesthesia Foundation, Boston Children's Technology Development Fund, and the Technology and Innovation Development Office.



Raiing Medical Inc. licenses Thermia fever educational framework

Raiing Medical Inc. entered a commercial license agreement with Boston Children's for the Thermia™ education platform, designed to help parents learn more about fever, illness and fever management. The online educational framework has been integrated with Raiing's iThermometer device, a wearable thermometer with U.S. FDA 510(k) clearance.

Thermia was developed by John Brownstein, PhD, Chief Innovation Officer and director of the Computational Epidemiology Group at Boston Children's, and Jared Hawkins, PhD, a research fellow in the Computational Health Informatics Program. Under the license agreement, Raiing has incorporated the intellectual property from Boston Children's with the real-time body temperature information captured by iThermometer. Raiing will build an innovative solution to provide personalized fever education with the aim of increasing parents' knowledge about fever management, optimizing use of health care resources and reducing medical costs.

bluebird bio exclusively licenses gene therapy constructs for hemoglobinopathies

bluebird bio exclusively licensed intellectual property rights from Boston Children's for gene therapy constructs to treat hemoglobinopathies. Developed by David Williams, MD, chief of the division of Hematology/Oncology and director of Clinical and Translational Research, the intellectual property comprises novel miRNA-embedded shRNAs that enhance processing and efficiency in modulating a genetic target with a direct implication for hereditary hemoglobin disorders.

Agreements: Licenses

TICEBA exclusively licenses cancer stem cell technology

TICEBA GmbH entered into an exclusive license agreement with Boston Children's for a technology targeting ABCB5, a cell-surface marker found on cancer stem cells, developed by Markus Frank, MD, in the division of Nephrology Research, to treat cancers such as human malignant melanoma, a highly chemotherapy-refractory cancer. Currently, there are not many effective treatment options for such cancers. Dr. Frank's laboratory has shown that ABCB5 serves as a multi-drug resistance transporter in human malignant melanoma and other cancers, conferring resistance to chemotherapy *in vitro*. Targeting ABCB5 has the advantage of targeting tumorigenic cancer stem cells, whereas conventional therapeutics target only the bulk population of tumor cells. TICEBA, through its affiliated company RHEACELL GmbH & Co. KG, plans to develop fully human or humanized ABCB5 monoclonal antibodies for the treatment of ABCB5-expressing cancers.

ShuntCheck exclusively licenses intellectual property for shunt flow enhancer device

ShuntCheck Inc. and Boston Children's entered an exclusive license for intellectual property related to the cerebrospinal fluid (CSF) shunt flow device. Invented and validated in collaboration with Joseph Madsen, MD, director of Epilepsy Surgery, the device generates flow of CSF in an implanted shunt in patients with hydrocephalus, a disease caused by excess accumulation of CSF in the brain. The primary treatment for hydrocephalus is placement of a ventricular shunt, connected to a valve, into the fluid space of the brain to help regulate how CSF is drained. Research at Boston Children's with the ShuntCheck® thermal flow detector showed that even when shunts are patent, flow in these devices can be intermittent, making it difficult to distinguish a blocked shunt from a patent shunt by thermal flow detection. The Micro-Pumper device increases CSF flow in patent, but not blocked shunts, by generating a vibrating force. Results of a multicenter, operator-blinded test of this device will be announced this year.

Alcyone exclusively licenses shunt flusher device

Alcyone Lifesciences, Inc., has entered into an exclusive license with Boston Children's for a shunt-flushing device invented for patients with hydrocephalus by Joseph Madsen, MD, director of Epilepsy Surgery. A shunt can become obstructed at any time after insertion, and all points along the shunt course could be the cause of a malfunction. Patients with shunt obstruction usually present with clinical evidence of raised intracranial pressure. The shunt-flushing device, named the ReFlowVent, is being developed by Boston Children's in close collaboration with Alcyone to avert ventricular shunt system failures caused by ventricular catheter obstruction. The device was inspired by Dr. Madsen's pioneering work in understanding the novel field of bio-pulsatility. The ReFlowVent works seamlessly with existing shunt systems and includes an emergency outlet membrane that opens a specific pulsatile pressure point, thus producing an opening to re-induce flow in a non-flowing catheter. Through a sponsored research collaboration with Alcyone, Dr. Madsen is leading a study to test the safety and efficacy of the ReFlowVent Shunt System.

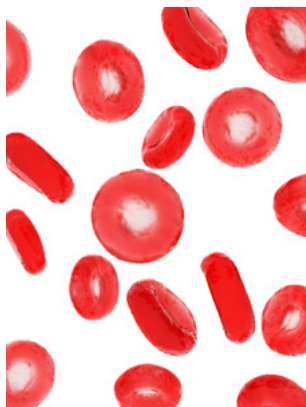
Cerner non-exclusively licenses the I-Pass handoff system

Christopher Landrigan, MD, MPH, research and fellowship director, Inpatient Pediatrics Service, and colleagues at Boston Children's and other institutions, have developed a clinical handoff methodology (I-PASS) and related electronic and written materials. Cerner entered into a non-exclusive license with Boston Children's to implement I-PASS into Cerner solutions such as PowerChart and PowerChart Touch. I-PASS was validated in a landmark multi-site research communication and patient safety study involving nine institutions in the U.S. and Canada. The research found that implementation of the IPASS handoff bundle — a bundle of interventions to improve resident-physician communication during patient handoffs — reduced preventable events by 30 percent.

Agreements: Sponsored Research

Biogen sponsors research to study β -globin disorders

Biogen Inc. and Boston Children's entered into a sponsored research agreement to study hematopoietic regulators and efficient genome engineering. The study, led by Stuart Orkin, MD, an HHMI investigator and associate chief of the division of Hematology/Oncology, aims to optimize genome modification of hematopoietic stem cells (HSCs) and perform screens for genes controlling HSC self-renewal and fetal hemoglobin (HbF) regulation. The lab seeks novel genes or pathways that can control the expansion or maintenance of HSCs, or regulate the level of HbF in adult cells. Knowledge of regulators of HSC self-renewal could be applied to *ex vivo* expansion of HSCs for genome modification and transplantation as an improved method of gene therapy. New pathways for HbF regulation could lead to novel therapeutics that reactivate HbF in patients with β -globin disorders, including sickle cell disease and thalassemia.



Colgate-Palmolive Company sponsors research to develop targeted delivery technologies

Colgate-Palmolive Company and Boston Children's entered into a sponsored research agreement to develop a novel active delivery technology. The research, led by Daniel Kohane, MD, PhD, director of the Laboratory for Biomaterials and Drug Delivery, will incorporate active agents into Dr. Kohane's proprietary particles platform to provide sustained release to oral surfaces.

Dompé Pharmaceuticals sponsors research on new targets to halt diabetic nephropathy

Dompé Pharmaceuticals entered into a sponsored research agreement with Boston Children's to define new targets for the treatment of diabetic nephropathy, one of the most serious complications faced by diabetic patients. Despite significant progress and overall improvement in the treatment of diabetic nephropathy, the development of chronic renal failure is nearly inevitable, and diabetes is rapidly becoming the leading cause of end-stage renal disease. Thirty percent of people with diabetes will develop diabetic nephropathy and will require dialysis. This study, led by investigator Paolo Fiorina, MD, PhD, in the division of Nephrology Research, aims to develop a novel and safe therapy for diabetic nephropathy. The study will investigate the potential role

of newly developed Dompé compounds in countering *in vitro* hyperglycemia-induced damage on podocytes and other renal cells. Promising compounds will be tested *in vivo* using different mouse models of diabetic nephropathy. The ultimate goal is to define new potential targets and develop a clinical trial to treat selected diabetic patients at the onset of diabetic nephropathy.

Fate Therapeutics sponsors research to develop immunoregulatory cell therapy for autoimmune diseases

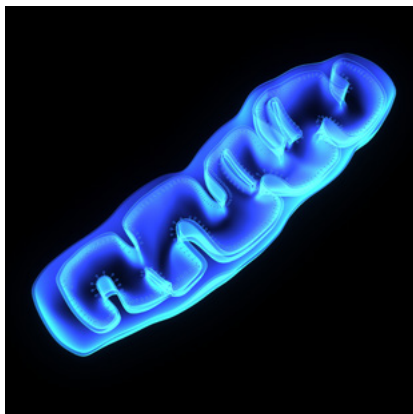
Fate Therapeutics, Inc. entered into a two-year sponsored research agreement with Boston Children's to accelerate the development of an immunoregulatory cell therapy to treat autoimmune diseases. The collaboration aims to assess the potential of a PD-L1 programmed CD34+ cellular therapeutic as a transformative treatment for type 1 diabetes. The study, led by Paolo Fiorina, MD, PhD, in the division of Nephrology Research, investigates the potential of this cellular therapy, developed in collaboration with Fate Therapeutics, to stop autoimmune activity responsible for the destruction of pancreatic beta cells and the development of type 1 diabetes. Dr. Fiorina and his team have extensively studied the cellular mechanisms and molecular pathways involved in the autoimmune-mediated destruction of pancreatic beta cells that result in insulin deficiency and type 1 diabetes. Preclinical data from Dr. Fiorina's laboratory show that genetically engineered PD-L1+ hematopoietic cells, adoptively transferred into hyperglycemic mice, traffic to the pancreas, reduce aberrant T-cell activity and reverse hyperglycemia in a well-established murine model of type 1 diabetes.



Agreements: Sponsored Research

Boston Scientific sponsors research to study mitochondrial transplantation to prevent heart cell death

Boston Scientific entered a sponsored research agreement with Boston Children's to study the clinical efficacy of mitochondrial transplantation to prevent heart cell death. James Donald McCully, PhD, associate professor of Cardiac Surgery, and collaborator Douglas Cowan, PhD, associate professor in the department of Anesthesiology, Perioperative and Pain Medicine Research, will study the effects of mitochondrial transplantation in an *in vivo*, clinically relevant, large-animal survival model of cardiac regional ischemia and reperfusion. In previous research, Drs. McCully and Cowan showed that transplantation of mitochondria, obtained from a patient's own skeletal muscle cells during a heart operation, can prevent heart cell death following blood vessel blockage or damage. The transplanted mitochondria stimulate the energy processes that enable the heart tissue to recover and regain function. These studies are being done in preparation for human clinical trials.



Merck and Boston Children's collaborate to identify primary immunodeficiency genes

Merck has entered a research collaboration with Boston Children's to identify and validate genes associated with primary immunodeficiencies (PIDs) through next-generation sequencing. PIDs are genetic disorders that impair the development and the function of host immunity, resulting in life-threatening infections, autoimmunity or malignancies. Led by Raif Geha, MD, chief of the division of Immunology, and Janet Chou, MD, specialist in Allergy Immunology at Boston Children's, and by Joshua McElwee, PhD, genetics lead for immunology at Merck, this study aims to unravel the genetic basis of PIDs of unknown etiology and validate the function of genetic targets in host immunity using Dr. Geha's platform of molecular, genetic and computational tools. Researchers will perform whole-exome sequencing in samples from clinically well-characterized patients who have PID of suspected novel causes. Measurable outcomes will include diagnostic yield, impact on patient care and identification of novel disease genes.

Takeda sponsors research on proteasome inhibitor's effects on triple-negative breast cancer

Takeda entered into a sponsored research agreement with Boston Children's to study the preclinical effects of its proteasome inhibitor ixazomib (NINLARO®) in triple-negative breast cancer. These especially aggressive tumors have the worst prognosis among all breast cancer subtypes. They comprise about 15 percent of all breast cancers and more than 75 percent of breast tumors arising in patients carrying BRCA1 germline mutations.

Previously, the lab of Judy Lieberman, MD, PhD, of the Program in Cellular and Molecular Medicine at Boston Children's, performed a genome-wide siRNA screen for breast cancer dependencies associated with a basal-like phenotype. The screen identified proteasome addiction as a common vulnerability of basal-like triple-negative breast cancer, including the subpopulation of tumor-initiating cells that are resistant to chemotherapy and deemed responsible for tumor recurrence and metastasis.

In vitro treatment with a low dose of bortezomib for 24 hours was selectively lethal to basal-like triple-negative breast cancer cell lines as compared with well-differentiated (luminal) breast cancer lines. However, the maximum tolerated dose of bortezomib was needed in mouse models to achieve robust proteasome inhibition. For the current study, Dr. Lieberman will examine ixazomib in preclinical models of triple-negative breast cancer.

Valerion sponsors research to study treatment for congenital myotubular myopathy

Valerion has entered into a sponsored research agreement with Boston Children's to study a treatment for congenital myotubular myopathy, a rare X-linked muscle disorder with an estimated incidence of 1 in 50,000 males. This is a continuation of a study started two years ago, led by Alan Beggs, PhD, director of the Manton Center for Orphan Disease Research, and financially supported by the Muscular Dystrophy Association. Researchers from Dr. Beggs's lab will conduct preclinical research of a novel enzyme replacement therapy aimed at restoring myotubularin gene function in skeletal muscles. The data from this project will be used in support of an IND submission to the FDA.

Technologies

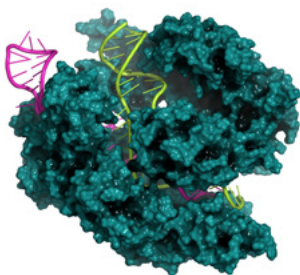
A new therapeutic target for retinopathy

Retinopathy is persistent or acute damage to the retina of the eye, and pathological neovascularization in retinopathy is a major cause of blindness. Currently there are no cures for retinopathy; treatments include eye surgery, or injections of hormones or steroids into the eye.

It is known that dietary omega-3 long-chain polyunsaturated fatty acids (LCPUFA) suppress pathological retinal neovascularization. In elucidating the mechanism of action of omega-3 LCPUFA on retinopathy, Lois Smith, MD, PhD, professor of Ophthalmology, has discovered a potential therapeutic target. Working in a mouse model of oxygen-induced retinopathy, Dr. Smith discovered that the enzyme cytochrome P450 epoxygenase 2C8 (CYP2C8) metabolizes omega-3 LCPUFA to produce angiogenic epoxides and increases in vascularization. CYP2C8 overexpression further potentiates retinal neovascularization. These findings suggest that inhibition of CYP2C8 might reduce retinal neovascularization by suppressing omega-3 LCPUFA and omega-6 LCPUFA diet-induced pro-retinopathy lipid metabolites.

New gene editing tool identifies off-target cuts

Gene editing technologies have exploded over the last decade, with CRISPR/Cas9, TALENs and Zn2+ Finger Nucleases leading the revolution. Though these double-stranded DNA break (DSB)-inducing methods are highly specific, even low levels of off-target cuts can ruin an experiment. Also, off-target events could be harmful to patients as gene editing-based therapies move into the clinic (imagine accidentally cutting a tumor suppressor gene, for example). There is a clear need for a sensitive method to detect and identify off-target DNA cutting events to increase gene therapy's likelihood of clinical success.



Researchers in the lab of Frederick Alt, PhD, director of the Program in Cellular and Molecular Medicine, have developed an improved method for high-throughput genome-wide translocation sequencing (HTGTS) to measure DSB activities due to outside agents or biological processes. Their method offers increased sensitivity in identifying off-target hotspots and the occurrence of non-specific

DSBs caused by outside agents. HTGTS will enable better characterization of collateral chromosomal damage due to engineered nucleases — a key factor in improving success in clinical and research applications of gene editing.



TriVox Health: Real-time symptom tracking

TriVox Health is a web-based platform that provides remote monitoring, real-time analysis and tracking of patients' disease symptoms and response to treatment over time. Currently monitoring thousands of children at Boston Children's and at several private practices, the system was developed by Eric Fleegler, MD, MPH, attending physician in Pediatric Emergency Medicine, and Eugenia Chan, MD, MPH, specialist in Developmental Medicine, to improve data gathering and medical decision-making. TriVox Health uses electronic surveys to gather data remotely from multiple responders, including patients, parents, teachers and ancillary providers, and provides the results to clinicians in a timely manner using graphical, tabular and natural language summary formats. The system monitors patients between visits to assess disease symptoms, response to medication and overall well-being, and currently is used for patients with ADHD, autism, anxiety, depression, epilepsy, asthma and other clinical conditions. With TriVox's accurate data in hand before the visit, clinicians can have more efficient patient encounters and focus more on treatment. The web-based questionnaires save time and resources by streamlining and automating data collection. To date, TriVox has gathered two million health data points through 25,000 online surveys, and research shows that families who use TriVox have the highest satisfaction rates with their appointments.

AudioHub app: Bringing hearing tests into the 21st century

36 million Americans have hearing loss. Nearly 15 percent of children ages 6 to 19 have some level of hearing problems. Yet the number of audiologists is predicted to decrease in the coming years, increasing the need to make audiology practices more efficient. With support from Boston Children's Technology Development Fund and a match from the Otology Foundation, the Hospital developed AudioHub, an iPad app designed to improve and enhance audiological assessment and documentation of test results. AudioHub is a fast, portable and highly accurate data capture platform that eliminates lengthy data entry and saves clinicians' valuable time. AudioHub improves patient record search, tympanometry documentation, and analysis and documentation for hearing technology testing, including capturing diagnostic test results and images of hearing instruments. Equipped with AudioHub, audiologists can now capture additional information that formerly was only available as a narrative in the patient record.

Technologies

Biofilms as the basis of vaccines and therapeutics for infectious diseases

A bacterial biofilm is a surface-associated structure comprised of cells embedded in a matrix of bacterial origin including polysaccharides, proteins and DNA. Biofilms allow for colonization and, to a degree, isolate microbes from some of the hazards of their environment. In fact, many pathogens employ biofilms to evade the immune system. Many hospital-acquired infections result from the inability to properly clean biofilm-encapsulated microbes from medical instruments. In contrast to biofilms' detrimental effects in health and medicine, biofilms have been employed to achieve positive results in areas such as wastewater treatment, bioremediation and controlled-release drug delivery.

Paula Watnick, MD, an infectious disease specialist at Boston Children's, seeks to further rehabilitate the reputation of the bacterial biofilm. She and her lab have discovered that *Vibrio cholerae* requires a specific set of proteins to build its biofilm, one of which is RbmA, and that RbmA undergoes proteolysis after its incorporation into the biofilm. Utilizing these new discoveries, the lab has determined that secreted proteins can be associated with the bacterial cell surface in abundance by fusing them to RbmA, and then removed by proteolysis. Dr. Watnick has devised several uses for these RbmA fusion proteins, including easy purification of secreted proteins, delivery of proteins or enzymes to an abiotic or host surface through biofilm formation and using killed or live-attenuated whole *V. cholerae* cells as a vaccine platform by attaching antigens to the cell surface.

Filtering out inflammation

Systemic inflammatory response syndrome (SIRS) is a physiologic reaction to a variety of harmful conditions and can result in tissue injury or death. SIRS-related conditions include pancreatitis, trauma, burns and septic shock (sepsis). Sepsis, which affects an estimated one million patients in the U.S., killing up to 50 percent, occurs as a result of infection in the bloodstream.

Brian McAlvin, MD, a specialist in the division of Critical Care Medicine, and Daniel Kohane, MD, PhD, director of the Laboratory for Biomaterials and Drug Delivery, have discovered a method to effectively treat SIRS by targeting specific cytokines relevant to the pathology of disease. Drs. McAlvin and Kohane recognized that some previous efforts to treat SIRS were hampered by non-specific targeting of numerous molecules released, some of which were beneficial. Other prior efforts did not take into account the two phases of SIRS: the initial pro-inflammatory response and the



anti-inflammatory response. Each phase is associated with a different set of cytokines; the removal of cytokines to treat the first phase might be harmful in the second.

With support from Boston Children's Technology Development Fund, Drs. McAlvin and Kohane have developed a filtration device capable of removing specific individual molecules from biological fluids, enabling removal of harmful cytokines without off-target effects. This treatment could significantly decrease deaths caused by sepsis and the \$20 billion financial burden the disease creates. This could not only be an effective treatment for any patient with a SIRS-related condition, but also, in theory, any condition in which a specific molecule needs to be removed from a body fluid (e.g. myoglobin in trauma). In 2015, this technology won an MIT \$100K Business Plan Competition as well as the Ignite competition at the Global Pediatric Innovation Summit.

Dialysis assistance through digital simulation

OPENPediatrics and Genuine Interactive, with support from Boston Children's Technology Development Fund, have teamed up

to produce an interactive Peritoneal Dialysis (PD) training simulator. OPENPediatrics was founded in 2008 by Jeffrey Burns, MD, MPH, and Traci Wolbrink, MD, MPH, both from the division of Critical Care Medicine, to improve patient care through access to peer-reviewed training materials at no cost to clinicians. To date, it has created and distributed innovative training materials to more than 2,000 hospitals in 137 countries. In addition to videos and tutorials, these include virtual simulators for practicing critical clinical skills. For example, the Virtual Ventilator is an interactive, immersive training software for learning how to use a mechanical ventilator.

The new PD simulator aims to improve the skills of clinicians caring for children with acute or chronic kidney failure undergoing peritoneal dialysis. It has been designed to mimic the clinic environment as much as possible, giving users a realistic training experience. The PD simulator will be especially impactful in developing countries, where usage of peritoneal dialysis increased 250 percent from 2000 to 2012, largely because of its significantly lower costs as compared to hemodialysis, and the ability of patients to be treated at home without having to travel to medical facilities.





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