2016

Technology & Innovation Development Office

ANNUAL REPORT

Boston Children's Hospital

Until every child is well™

Boston 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 2016–17, and 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 600 faculty researchers and 700 postdoctoral fellows are conducting research to solve the most pressing challenges in medicine today. Our research community includes nine 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.

The Technology & Innovation Development Office (TIDO) maximizes the impact of Boston Children's innovations on patient health, while enhancing research endeavors. The TIDO team comprises specialists in licensing, patenting, business development, marketing, startup formation and legal matters. We work closely with Boston Children's investigators and clinicians to advance innovations, protect and license intellectual property and enable collaborations with pharma/biotech, medical device, diagnostics, research tool and digital health companies.

2016 at a glance

140
INVENTION DISCLOSURES

$12.4 M
NEW INDUSTRY SPONSORED RESEARCH FUNDING

54
RESEARCH AGREEMENTS

32
LICENSING AGREEMENTS

$6 M
NET LICENSING REVENUE

5
STARTUPS CREATED

From the Director

Improving patients' lives drives the work we do at Boston Children's Hospital's Technology & Innovation Development Office (TIDO). Our focus is on developing paths to market for the incredible discoveries from Boston Children's innovative researchers and clinicians. TIDO's FY16 report highlights the impact of these efforts in terms of new product launches, patents filed, new company investments, industry research sponsorship, and information and materials exchanges between Boston Children's and our industry partners.

Some highlights you'll see include:

» Launching of Vonvendi®, a novel treatment developed by Shire for von Willebrand disease, a rare form of hemophilia. This product is the result of the discovery of the von Willebrand factor gene by Stuart Orkin, MD, associate chief, Division of Hematology/Oncology.

» Five Boston Children's startup companies which were launched this year collectively raised over $90 million in venture funding. One of these startups, Orchard Therapeutics, was named a 2016 Fierce 15 top biotech company. The company was formed around the scientific discoveries of David Williams, MD, senior vice president and chief scientific officer, chief of the Division of Hematology/Oncology, and president of the Dana/Farber Boston Children's Cancer and Blood Disorders Center, and Alessandra Biffi, MD, director of the Gene Therapy Program.

» Finally, our team negotiated over 30 license agreements and a record 54 industry sponsored research and collaboration agreements, each representing a new partnership that aims to advance Boston Children's discoveries to market.

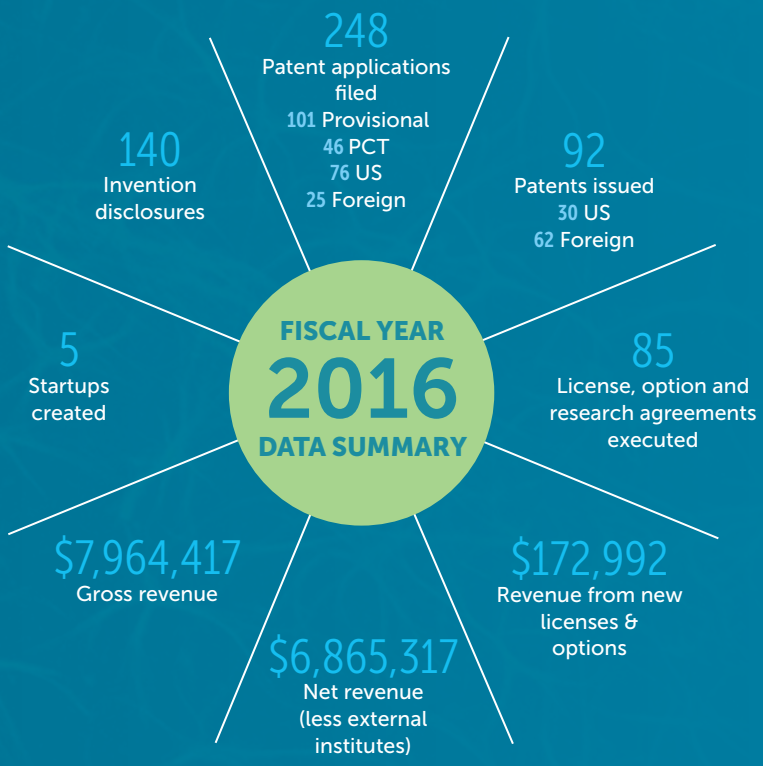
The numbers in this report tell only part of the TIDO story. We also work to create and sustain a vibrant culture of research translation and entrepreneurship among our researchers and clinicians through outreach and education efforts, service to our faculty, catalyst funding to develop projects with commercial potential, and building connections between our researchers and clinicians with their industry counterparts through networking and industry events.

As an example of TIDO's initiatives, our catalyst fund, the Technology Development Fund, has begun a formal effort to build a sense of community among our innovators to support each other in their entrepreneurial activities and to connect them to industry, which kicked off with a TDF awardee recognition event in March of 2016, which was attended by over 70 researchers. This was followed by an evening event focused on the path to market for therapeutics, which was attended by our researchers and industry experts.

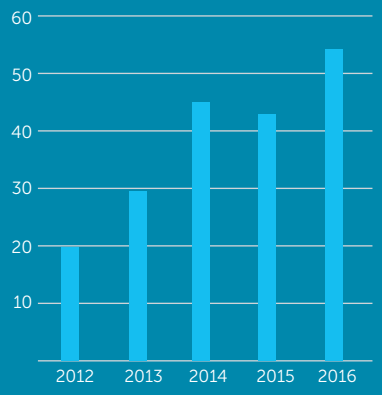
In FY17, we look forward to working with you to explore ways of working together to bring new therapies and technologies to patients that need them the most.

Irene Abrams
Senior Director,
Technology & Innovation
Development Office

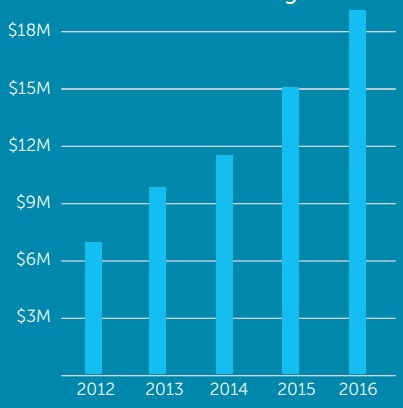
By the Numbers



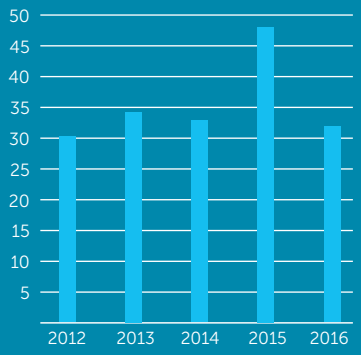
Sponsored Research and Collaboration Agreements



Corporate Sponsored Research Funding



Licenses and Options Executed



Issued US Patents

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

Rao, Anjana
9,163,078 Regulators of NFAT

Ingber, Donald
9,156,037 Microfluidic device and uses thereof

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

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

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

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

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

Orkin, Stuart H
9,228,185 Modulation of BCL11A for treatment of hemoglobinopathies

Tharin, Suzanne
9,261,496 Device for high throughput investigations of multi-cellular interactions

Frank, Markus
9,266,946 Targeting ABCB5 for cancer therapy

Beny-Ratsaby, Ofra
9,272,050 MetAP-2 inhibitor polymersomes for therapeutic administration

Rao, Anjana
9,271,997 Regulators of NFAT and/or store-operated calcium entry

Ozcan, Umut
9,283,277 Methods and compositions for the treatment of obesity

Rao, Anjana
9,284,297 Halofuginone analogs for inhibition of tRNA synthetases and uses thereof

Puder, Mark
9,295,662 Methods for enhancing, improving, or increasing fertility or reproductive function

Murray, Martha
9,308,242 Methods and products for tissue repair

del Nido, Pedro and Vasilyev, Nikolay
9,307,984 Tissue clip

Lieberman, Judy
9,347,089 Therapeutic and diagnostic strategies

Hensch, Takao
9,345,696 Methods for treating nicotinic acetylcholine receptor associated diseases

Williams, David
9,353,166 Chimeric peptides for the regulation of GTPases

Watnick, Paula
9,359,275 Natural product antibiotics and analogs thereof

Malley, Richard
9,393,294 Vaccines and compositions against Streptococcus pneumoniae

Zon, Leonard
9,402,852 Method to enhance tissue regeneration

Kohane, Daniel
9,408,846 Formulations and methods for delaying onset of chronic neuropathic pain

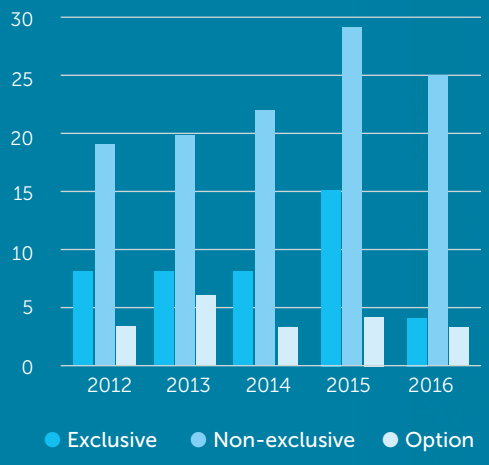
Beggs, Alan
9,415,120 Systemic gene replacement therapy for treatment of X-linked MyoTubular Myopathy (XLMTM)

Teng, Yang (Ted)
9,440,008 Methods and compositions for the treatment of open and closed wound spinal cord injuries

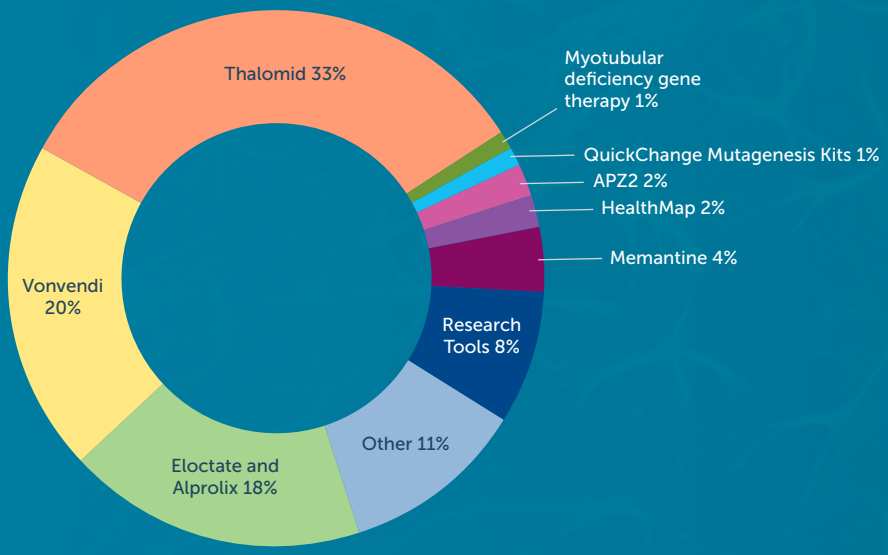
Beny-Ratsaby, Ofra
9,446,140 MetAP-2 inhibitor polymersomes for therapeutic administration

Rao, Anjana and Agarwal, Suneet
9,447,452 Selective oxidation of 5-methylcytosine by TET-family proteins

Breakdown of License & Option Agreements



Sources of Licensing Revenue



Issued Foreign Patents

von Andrian, Ulrich
Israel 205010
Polymer based nanoparticles comprising T-cell and B-cell antigens

Malley, Richard
New Zealand 614460
Vaccines and compositions against Streptococcus pneumoniae

Szallasi, Zoltan
New Zealand 628813
Methods for predicting anti-cancer response

Watnick, Randolph
EPO[1] 2190448
Methods and uses thereof of a fragment saposin a

Carroll, Michael
EPO[2] 2290077
Natural IGM antibodies and inhibitors thereof

D'Amato, Robert
EPO[1] 2318429
Prominin-1 peptide fragments and uses thereof

Kentsis, Alex
EPO[3] (Turkey) 2382466
Method of predicting acute appendicitis

Smith, Lois
Canada 2,429,615
Determination of risk and treatment of complications of prematurity

Atala, Anthony
Canada 2,468,171
Methods of isolation, expansion and differentiation of fetal stem cells from chrionic villus, amniotic fluid, and placenta and therapeutic uses thereof

He, Zhigang
EPO[4] 2502623
Promoting axon regeneration in the adult CNS through control of protein translation

Malley, Richard
Russian Fed. 2580299
Vaccines and compositions against *Streptococcus pneumoniae*

Szallasi, Zoltan
EPO[5] 2609216
Methods for predicting anti-cancer response

Zon, Leonard
Canada 2,647,201
Method to modulate hematopoietic stem cell growth

Teng, Yang (Ted)
Canada 2,650,804
Methods and compositions for the treatment of open and closed wound spinal cord injuries

Zon, Leonard
Canada 2,666,972
Method to enhance tissue regeneration

Benny-Ratsaby, Ofra
Canada 2,690,244
MetAP-2 inhibitor polymersomes for therapeutic administration

Levy, Ofer
EPO[6] 2694084
BPI and all its congeners as radiation mitigators and radiation protectors

Steen, Hanno
EPO[7] 2697653
Diagnostic markers and therapeutic targets of Kawasaki disease

He, Zhigang
Canada 2,724,199
Promoting axon regeneration in the adult CNS through control of protein translation

Ozcan, Umut
Canada 2,846,845
Methods and compositions for promoting glucose homeostasis

Rao, Anjana
Japan 5881270
Regulators of NFAT

Benny-Ratsaby, Ofra
Japan 5881779
MetAP-2 inhibitor polymersomes for therapeutic administration

Frank, Markus
Japan 5889527
Targeting ABCB5 for cancer therapy

Dimitrakoff, Jordan
Japan 5908279
"Implantable drug delivery device and methods of treating male genitourinary and surrounding tissues"

Malley, Richard
Japan 5931724
Vaccines and compositions against *Streptococcus pneumoniae*

Harrison, Stephen
Australia 2009303284
Biochemically stabilized HIV-1 env trimer vaccine

Malley, Richard
Australia 2010273708
Vaccines and compositions against *Streptococcus pneumoniae*

Szallasi, Zoltan
Australia 2011293635
Methods for predicting anti-cancer response

Malley, Richard
Australia 2012207089
Vaccines and compositions against *Streptococcus pneumoniae*

Teng, Yang (Ted)
Australia 2012227370
Methods and compositions for the treatment of open and closed wound spinal cord injuries

Ozcan, Umut
Australia 2012301876
Methods and compositions for promoting glucose homeostasis

Zon, Leonard
Australia 2013213727
Methods to enhance tissue regeneration

Puder, Mark
Australia 2013230896
Methods for enhancing, improving, or increasing fertility or reproductive function

Teng, Yang (Ted)
South Korea 10-1638471
Methods and compositions for the treatment of open and closed wound spinal cord injuries

Teng, Yang (Ted)
South Korea 10-1649457
Methods and compositions for the treatment of open and closed wound spinal cord injuries

Teng, Yang (Ted)
South Korea 10-1657106
Methods and compositions for the treatment of open and closed wound spinal cord injuries

Frank, Markus
Hong Kong HK1143823
A gene encoding a multidrug resistance P-glycoprotein homologue on chromosome 7P15-21 and uses thereof

Zon, Leonard
Hong Kong HK1173948
Method to modulate hematopoietic stem cell growth

Orkin, Stuart
Nigeria NG/C/2011/257
Modulation of BCL11A for treatment of hemoglobinopathies

Malley, Richard
Indonesia 41447
Vaccines and compositions against Streptococcus pneumoniae

Tharin, Suzanne
China ZL 201180057002.9
Device for highthroughput investigations of cellular interactions

Steen, Hanno
China ZL 201280024575.6
Diagnostic markers and therapeutic targets of Kawasaki disease

1. France, Germany, Switzerland, UK; **2.** France, Germany, UK; **3.** Turkey; **4.** Denmark, Finland, France, Germany, Ireland, Italy, Netherlands, Norway, Sweden, Switzerland, UK; **5.** Denmark, Liechtenstein; **6.** France, Germany, Ireland, Luxembourg, Monaco, Netherlands, Sweden, Switzerland, UK; **7.** Ireland, Italy

Technology Development Fund
2016 grant awardees and projects

Technologies funded by TDF range from therapeutics and devices, to diagnostics, vaccines and digital health in both pediatric and adult indications. In addition to providing financial support, TDF provides our clinicians and scientists with access to technical support and expertise through our network of service providers and collaborators, mentoring and coaching through an advisory board of industry leaders in product development, and active project management.

The 2016 grant awardees—selected from 37 applications submitted for consideration—include:

Treating otitis media with single-dose, local, and transtympanic delivery of antibiotics

Daniel Kohane, MD, PhD, and Rong Yang, PhD, Anesthesiology

Drs. Kohane and Yang are developing a novel drug delivery system for the treatment of otitis media. The proposed approach circumvents the need of oral antibiotics and the undesirable side effects, and uses ear drops instead. A single dose administered by a pediatrician at the time of diagnosis could treat pain and deliver antibiotics for 1–2 weeks. The TDF funds will be used to seek regulatory guidance. Based on the feedback they received, they will conduct studies necessary for a pre-clinical package.

Control of chronic viral infection by targeted activation of TMEM16F

Florian Winau, MD, Program in Cellular and Molecular Medicine

Dr. Winau's team is evaluating TMEM16F as a novel therapeutic target for chronic viral infections and tumors. The team demonstrated that mice lacking the lipid scramblase TMEM16F fail to clear viral infections due to compromised T cell responses and propose that activation of TMEM16F may prevent T cell exhaustion. TDF funds will be used to establish a novel mouse model to evaluate the effect of TMEM16F over activation on T cell response and infection control.

Wearable device for pelvic floor muscle therapy (PFMT)

Carlos Estrada, MD, and Jeanne Chow, MD, Radiology

Drs. Estrada and Chow are developing a novel device to support in-home treatment for stress urinary incontinence. This wearable device is comprised of an undergarment with electrodes and sensors that communicate with a smartphone app to guide PFMT, quantify incontinence and track treatment progress. TDF funds will be used to develop a device prototype for user testing.

Crisis Care: A smartphone app for suicidal adolescents

Elizabeth Wharff, PhD, and Kimberly O'Brien, PhD, Psychiatry

Drs. Wharff and O'Brien are creating a new tool to help vulnerable adolescents at risk for a suicide attempt. They have designed a smartphone app, Crisis Care, for adolescents and parents to use in between emergency care and outpatient visits. Crisis Care has dual modes for adolescents and parents and provides them with personalized coping skills and support networks. The TDF funds will turn the web-based prototype into fully functioning iPhone and Android apps to be tested in the clinic by depressed adolescents and their parents.

Optimization of *Pseudomonas aeruginosa* vaccines

Gregory Priebe, MD, Critical Care Medicine

Dr. Priebe is developing a new vaccine for prevention of *P. aeruginosa* infections. His research team discovered that the bacterial protein PopB stimulates Th17 cells to protect against pneumonia and wound infections in mouse models of infection. The team predicts that adding PopB to an existing OprF/I vaccine which elicits an antibody response will produce a broadly and potently protective vaccine. TDF funds will be used to test the immune response and protective efficacy of the PopB:PcrH and OprF/I combination in the relevant mouse models.

Novel dental device for infants with cleft lip and palate

James MacLaine, BDS, and Elizabeth Ross, DDS, Dentistry

Drs. MacLaine and Ross are developing a removable device to support cleft lip and palate repair. Cleft repair typically begins with physical manipulation of the upper jaw segments to bring them together prior to the initial lip repair surgery. The proposed device is removable, avoids anesthesia, and reduces the number of clinic visits. The TDF funds will be used to create an FDA compliant prototype device for use in first-in-human studies.

Since 2009, Technology Development Fund awards have led to:

$7.9 MILLION COMMITMENT
for the development of 70 hospital innovations. To date, approximately half of this amount has been spent and has led to $25M of follow-on funding for the investigators.

6 STARTUP COMPANIES,
which have collectively raised $56M from venture capitalists, government grants and foundations.

7 LICENSES AND 1 OPTION AGREEMENT
generating $1.5M revenue for the hospital.

Startup Highlights

Morphic Therapeutic exclusively licenses integrin targeting therapeutic

Morphic Therapeutic exclusively licensed intellectual property rights from Boston Children's for integrin targeting therapeutics developed by Timothy A. Springer, PhD, investigator in the Program in Cellular and Molecular Medicine. The company, co-founded by Springer, was formed to create the first oral integrin therapies for immunological, fibrotic, neoplastic and vascular diseases.

Springer's initial discovery of integrins in the 1980s fueled the first generation of integrin targeted research and development by industry. However, developing oral integrin therapies has been challenging. Morphic Therapeutic is leveraging recent discoveries from Springer's lab to overcome these challenges and enable the development of small molecule integrin inhibitors.

In June 2016, the company completed a $51.5 million Series A financing to advance multiple programs into the clinic. The round was co-led by SR One and Pfizer Venture Investments, joined by Omega Funds and AbbVie Ventures. They join founding investors Polaris Partners, T.A. Springer and Schrödinger, Inc., along with ShangPharma Investment Group.


Timothy Springer, PhD

Circulation licenses medical transportation know-how

Boston Children's licensed medical transportation know-how developed by John Brownstein, PhD, chief innovation officer, and Jared Hawkins, PhD, director of Informatics, both in the Innovation and Digital Health Accelerator, to startup company Circulation. The company launched in September 2016 with the first customizable, patient-centric digital transportation platform that seamlessly integrates with both healthcare systems and Uber's API. Health system coordinators can schedule and manage on-demand rides that are affordable and tailored around patients — all from one convenient interface. This unique integration is a significant step forward in providing reliable, non-emergency medical transportation for patients.

"The traditional healthcare transportation model is severely outdated," said Brownstein. "Every patient's experience begins and ends with their ride, which is why the integration of Uber and Circulation offers a smart, digital transportation platform for healthcare that customizes rides around patients' specific needs and ensures they get the care they deserve."

Orchard Therapeutics launched and announced collaboration with Boston Children's for development of gene therapies

Orchard Therapeutics launched in May 2016 with a £21 million Series A financing led by F-Prime Capital. The gene therapy startup company was created from the science developed by David Williams, MD, president of the Dana-Farber/Boston Children's Cancer and Blood Disorders Center, and chief scientific officer at Boston Children's, Alessandra Biffi, MD, director, Gene Therapy Program, and Luigi Notarangelo, MD, director, Research and Molecular Diagnosis Program on Primary Immunodeficiencies, along with University College London, Great Ormond Street Hospital for Children NHS Foundation Trust, the University of Manchester and the University of California Los Angeles. Orchard's development programs use *ex vivo* autologous hematopoietic stem cell gene therapy to restore normal gene function in primary immune deficiencies, rare and severe inherited metabolic diseases and CNS disorders.

Orchard employs a collaborative development model for its research programs, working closely with clinicians and researchers at leading academic centers. "Orchard builds on highly successful academic collaborations that have been in place for more than a decade," said Williams. "Each institution brings specific disease expertise and a significant experience in developing and carrying out gene therapy trials using autologous hematopoietic stem cells."

Orchard Therapeutics was named by FierceBiotech as one of 2016's Fierce 15 biotechnology companies, designating it as one of the most promising private biotechnology companies in the industry.

License Agreements

TICEBA exclusively licenses ABCB5+ technology for treatment of ocular and dermal diseases

TICEBA GmbH expanded an exclusive license agreement with Boston Children's to include the treatment of ocular and dermal diseases by targeting ABCB5, a cell-surface marker found on stem cells, developed by Markus Frank, MD, in the division of Nephrology Research. In collaborations with Schepens Eye Research Institute and the US Department of Veterans Affairs, Frank found that ABCB5 is expressed by limbal stem cells and in the retina of the mammalian eye and is required for normal corneal and retinal development. In another study with collaborators at the Brigham and Women's Hospital and US Department of Veterans Affairs, he found that using isolated human ABCB5+ dermal stem cells, co-grafted with a highly porous collagen-glycosaminoglycan scaffold, had superior regenerative wound healing capacity. The first technology has potential for corneal regeneration to treat blindness due to limbal stem cell deficiency, as well as retinal diseases such as macular degeneration or retinitis. The second could lead to novel treatments for burns or skin diseases, and is currently being investigated in a phase I/IIA human clinical trial for the indication of chronic venous ulcers (ClinicalTrials.gov Identifier: NCT02742844).

GRI Medial Products licenses a bed ventilator tubing holding product

GRI Medial Products entered a license with Boston Children's for a bed ventilator tubing (BVT) holder technology developed by Brian Walsh, RRT-NPS, clinical research coordinator in Anesthesiology Perioperative and Pain Medicine. Ventilator tubing is a life sustaining connection for those who cannot breathe on their own. It is big and bulky and can easily be knocked, tangled or kinked by the healthcare provider or patient if not properly secured. Mechanical arms and other securing devices have been developed to hold the tubing in place but they are cumbersome and hard to manage. Also, recent patient safety standards require the use of the bed railing in the up position. This increase in railing use and need for this tubing to be secured inspired Walsh to invent and develop the tubing holder. The device utilizes a unique design that is able to be secured to the railing on the majority of hospital beds, securing the tubing and keeping the weight of the circuit off of the patient interface, such as an endotracheal tube or mask.

Biorg options tissue engineering intellectual property

Biorg entered an option agreement with Boston Children's for tissue engineering intellectual property developed by Tony Atala, MD, director of the Wake Forest Institute for Regenerative Medicine and formerly in the Department of Urology at Boston Children's. While at Boston Children's, Atala's research led to new technologies to repair and treat tissue damage, and to manufacture replacement tissues or organs. Biorg will apply these technologies to pharmaceutical development — using miniaturized human organ-like structures to test and develop life-saving drugs.

PREMIER Biosoft licenses and sponsors research for glycan analysis database

PREMIER Biosoft has non-exclusively licensed a process and database to identify glycan compositions and structures from complex mixtures, developed by Boston Children's Richard S. Lee, MD, attending in Urology. Glycans are post translational modifications on proteins that affect the activity and function of the protein. For example, they play a critical role in the therapeutic efficacy and toxicity of monoclonal antibody proteins. In his research, Lee has developed a process to tag glycans, analyze them through mass spectrometry, and then identify the specific glycans by matching their mass spectrometry profile in a database. As part of the agreement, PREMIER Biosoft and Lee will collaborate to add a novel database functionality that rapidly identifies and quantifies dual modified glycans.

Claritas Genomics non-exclusively licenses a bone marrow failure NGS diagnostic test

Claritas Genomics, a pediatric clinical genomics spinout of Boston Children's, has non-exclusively licensed technology for the development of a genetic test for bone marrow failure, developed by Akiko Shimamura, MD, PhD, director, Bone Marrow Failure and Myelodysplastic Syndrome Programs and Mark Fleming, MD, DPhil, pathologist-in-chief (together with Inga Hofmann, MD, PhD). The panel includes pathogenic non-coding regions that are not covered by standard whole exome analysis. The panel is also complemented by adding array analysis for copy number variants. Drs. Shimamura and Fleming will provide expert consultation regarding the genes and variants.

Multiple non-exclusive licenses to The Comfort Ability

Boston Children's has non-exclusively licensed The Comfort Ability program curriculum and content to multiple institutions across the U.S. and Canada. The program, developed by Rachael Coakley, PhD, psychologist at Boston Children's, is an interactive one-day pain management workshop for youth with chronic pain and their parents. Designed to introduce psychological intervention as a component part of an effective pain management plan, this program provides targeted neuroscience education, introduces cognitive behavioral and bio-behavioral pain management strategies, and provides peer support. Due to high impact publications as well as national and international conference presentations demonstrating program success, many hospitals are seeking to run the program at their own institutions.

Industry Research Agreements

Megakaryon sponsors research to improve a therapeutic platelet generating platform

Megakaryon entered a sponsored research agreement with Boston Children's to evaluate and improve a therapeutic immortalized megakaryocyte progenitor cell line (imMK-CL)-platelet platform that is capable of generating a large number of particles, in an effort to create a safe, stable, and low cost supply of platelets that does not depend on blood donations. The studies, led by George Daley, MD, PhD, Samuel E. Lux, IV chair in Hematology/Oncology, and Alan Michelson, MD, director, Center for Platelet Research Studies, seek to identify the molecular mechanisms that underlie imMKCL and platelet heterogeneity, and attempt to isolate and expand the expand the functional imMKCLs and platelets. Lastly, they will screen for small molecules that promote imMKCL expansion, platelet production, and platelet functionality. These screens may identify novel pathways that are limiting imMKCLs and that can be leveraged to improve the platform.

Biogen sponsors research to characterize the role of GPR56 in postnatal brain development

G protein-coupled receptors (GPCRs) play a very important role in neurodevelopment, including neocortical development, myelination, synaptic pruning, and blood-brain barrier formation. GPCRs are a superfamily of cell surface receptors that are the targets for approximately 30 percent of all therapeutics on the market. Xianhua Piao, MD, PhD, investigator in the Division of Newborn Medicine, has found that GPR56, a member of the adhesion G protein-coupled receptor family, plays a crucial role in embryonic brain development due to loss of functional mutations that cause a devastating human brain malformation. Piao's lab will study the role of GPR56 in postnatal brain development and function. Because GPCRs are druggable, these research findings could likely be translated into a therapeutic.

Baxalta awards grant to support research to study the effects of rhADAMTS13 on post-thrombotic vessel fibrosis

Baxalta has entered into an investigator initiated research agreement with Boston Children's to study the therapeutic effects of rhADAMTS13 on post-thrombotic vessel fibrosis, led by Denisa Wagner, PhD, Edwin Cohn Professor of Pediatrics. In past studies, Wagner found that ADAMTS13 not only reduces platelet recruitment, but also dampens inflammatory responses including neutrophil recruitment. The Baxalta study will explore the therapeutic value of rhADAMTS13 in post-thrombotic syndrome, where the vessel wall becomes fibrotic after thrombosis. The lab will also study the effects of rhADAMTS13 on post-thrombotic vessel wall fibrosis following the stenosis of inferior vena cava.

Pfizer CTI sponsors research for phenotypic screen to rescue ALS iPSC-derived motor neuron hyper-excitability

Pfizer's Centers for Therapeutic Innovation has entered into a sponsored research agreement with Boston Children's to identify molecular targets that determine ALS patient iPSC-derived motor neuron hyper-excitability using Pfizer's drug development capabilities. Clifford Woolf, MB, BCh, PhD, director, F.M. Kirby Neurobiology Center, has been studying the use of human neurons generated by stem cell technology as models of neurological diseases, including ALS, Alzheimer's disease, epilepsy, pain and familial peripheral neuropathy as well as their utility for drug screens. Woolf and his collaborators recently found that motor neurons derived from iPSC lines (hMN) obtained from patients with familial ALS (fALS), are hyperexcitable relative to those from healthy human controls, which is the result of a decrease in a delayed rectifier potassium current. Decreasing such excitability increases survival.

This collaborative study by the Woolf lab and Pfizer will explore how the diverse mutations that lead to fALS act to produce the hyperexcitability disease phenotype. The goal of this research is to discover new targets that generate abnormal neuronal excitability in ALS.

Sage Therapeutics sponsors research to study proprietary compound in Shank3 mice

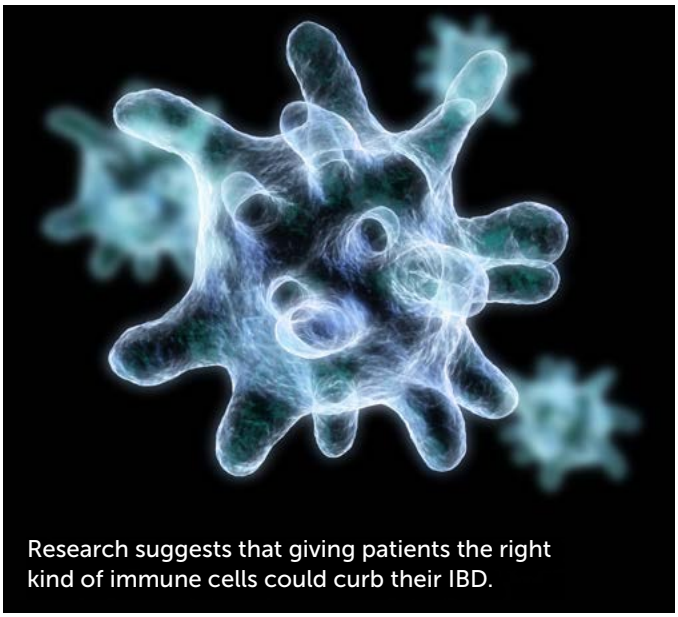
Autism symptoms are treated by specialized behavioral therapies, which are time-intensive, expensive, not widely available, and incompletely effective. There are no FDA approved therapeutics to directly treat the disease. Sage Therapeutics has developed a platform of glutamate and GABA receptor modulators that regulate the excitatory/inhibitory balance, including SGE-301, a novel oxysterol that enhances activity of the NMDA-type glutamate receptor, and may relieve symptoms of autism. This study, led by Alexander Rotenberg, MD, PhD, director of the Neuromodulation Program and the Experimental Neurophysiology Core, will evaluate the pharmacodynamic and pharmacokinetic profile of SGE-301 using in the Shank3 mutant mouse autism model. The researchers will use quantitative neurophysiological analysis of EEG data collected by wireless telemetry from Shank3 mice following treatment. The study will also collect plasma samples from the treated mice to support development of pharmacokinetic/ pharmacodynamics modeling.

EMD Serono sponsors research to resolve crystal structure of human IRAK1

EMD Serono entered a sponsored research agreement with Boston Children's to resolve the crystal structure of human IRAK1 or human IRAK1 in complex with small molecule inhibitors. Hao Wu, PhD, senior investigator, Program in Cellular and Molecular Medicine, will determine the structures with up to eight inhibitors.

Merck collaboration to study the use of novel inflammatory bowel disease mice for therapeutic evaluation

Merck has entered a collaboration agreement with Boston Children's to develop humanized mouse models of Inflammatory bowel disease (IBD), a debilitating disease affecting more than 1.6 million Americans. Various murine models exist to help study the pathology of disease and test compounds, however none allow for the analysis of human biologics. To bridge this gap, Merck will collaborate with Scott Snapper, MD, PhD, director of the Inflammatory Bowel Disease Center, and Dr. Jeremy Goettel, a junior faculty member working with Dr. Snapper, who have developed two humanized mouse models of IBD. These models take advantage of immunodeficient NSG mice, which lack murine MHCII and instead express human MHCII (HLA-DR1). Human CD4+ T cells are used to reconstitute the mouse immune system and mice are given an immune modulating agent that leads to either small or large bowel inflammation caused by human cells. This collaboration will use this animal model system to profile immune-modulating receptor expression on human cells, test the *in vivo* efficacy of human biologics, and evaluate if cells from patients with IBD respond differently than healthy controls.



Research suggests that giving patients the right kind of immune cells could curb their IBD.

Image: Shutterstock

LAM Therapeutics sponsors research to study efficacy of anti-seizure medications on human TSC neurons

LAM Therapeutics has sponsored research in the lab of Mustafa Sahin, MD, PhD, director of the Translational Neuroscience Center and the Translational Research Program to study the effects of anti-seizure medications on human Tuberous Sclerosis neurons. Patient-derived neurons are ideal for modeling disease and for preclinical screening of potential drug candidates, including existing, FDA-approved drugs. The neurons are created from induced pluripotent stem cells (iPSCs) taken from small skin or blood samples. These lab-created human neurons capture disease physiology at the cellular level in a way that neurons from rats or mice cannot. Dr. Sahin's lab is using neurons derived from patients with tuberous sclerosis complex (TSC), a rare condition often linked to autism and epilepsy, to test various compounds that might reverse the underlying disease pathology. This study will first look at the effects of eight drugs on the neurons at different doses. Next, Sahin's lab will study chronic treatment of the neurons using six drugs. Lastly, based on the successful results of these experiments, the researchers will study combination treatments. Dr. Sahin's research provides a new approach to select the best drug(s) for each person with TSC. Success with Dr. Sahin's research in TSC will form the basis for expanding the approach to find personalized medicines that treat any type of epilepsy.

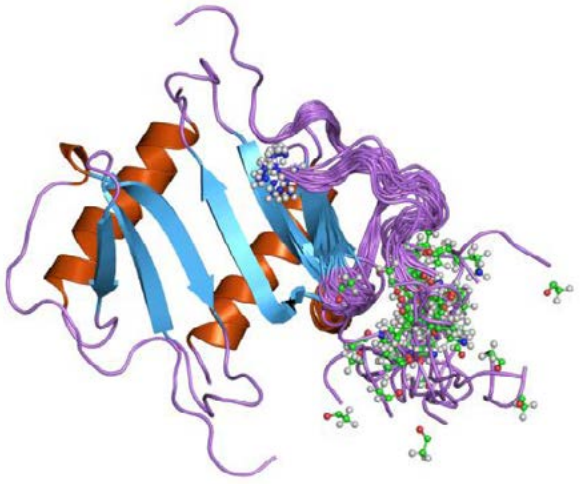
Regeneron enters collaboration to study genetic variants in very early onset inflammatory bowel disease

The Regeneron Genetics Center (RGC), a subsidiary of Regeneron Pharmaceuticals, Inc. is working with investigators at Boston Children's to identify and characterize mono-genetic variants and their role in very early onset inflammatory bowel disease (VEO-IBD). IBD is a complex disease with an unknown etiology and can present mildly or as a chronic and debilitating illness. IBD during childhood is very severe and medical response is often poor. The strongest risk factor for developing IBD is family history. Genetic studies into VEO-IBD could identify rare and causative genetic variants, which may lead to an improved understanding of the disease.

Led by Scott Snapper, MD, PhD, director of the Inflammatory Bowel Disease Center, this study will collect detailed clinical data and DNA from pediatric patients suspected of or diagnosed with inflammatory bowel disease. In collaboration with the RGC, the study will use whole exome sequencing and functional genomic techniques to identify novel causative protein-coding genetic variants in ~800 individuals with VEO-IBD and family members without the disease.

Dompé sponsors research to study lung transplantation

Dompé has entered a sponsored research agreement with Boston Children's to study the effects of blocking IL-8-CXCR1/2 in lung transplantation. There is a large need to stop chronic immunosuppression and chronic rejection in lung transplants — both are linked to the alloimmune response that leads to transplant failure. Cytokines play a role in the onset of alloimmune response. One cytokine, Interleukin-8 (IL-8), is a pro-inflammatory chemokine that has been shown to be produced by endothelial cells and by other stromal cells. An investigational drug blocking CXCR1/2 receptor is under clinical development (Reparixin) and has shown a good safety profile in humans. Paolo Fiorina, MD, PhD, investigator in the Division of Nephrology, will study whether graft fate during alloimmunity may be influenced in the long-term by IL-8-induced-CXCR1/2-dependent signaling. Disruption of the IL-8/CXCR1/2 pathway may generate a more favorable environment for transplantation, and therefore may provide the proof-of-principle for the use of anti-IL-8 targeting strategy in transplantation.



CXCR-1 N-terminal peptide bound to interleukin-8.

Image: ebi.ac.uk/pdbe/entry/pdb/1lip

Leap Therapeutics sponsors research to study the role DKK1 in non-small-cell lung carcinoma

Leap Therapeutics entered a sponsored research agreement with Boston Children's to study the mechanism of action of DKN01, a monoclonal antibody that targets DKK1 and the Wnt signaling pathway. DKN-1 has shown activity in non-small cell lung cancer, esophageal cancer, and cholangiocarcinoma in early clinical trials. The underlying molecular and cellular basis for this effect is unclear. The predominant mechanism of DKK1 action is to antagonize the Wnt/beta-catenin pathway through binding and inhibition of the co-receptor LRP6. Led by Xi He, PhD, research associate in the F.M. Kirby Neurobiology Center and a world-renowned expert in the Wnt pathway, this study will attempt to clarify the molecular basis of DKN-1 action with regard to WNT/beta-catenin signaling to enhance further development of DKN-1 as a potential cancer therapeutic.

Allele Diagnostics collaboration to study urinary stone disease genomics

Allele Diagnostics entered a research agreement with Boston Children's for a urinary stone disease genomics collaborative study with Friedhelm Hildebrandt, MD, chief, Division of Nephrology. The objective of this study is to determine whether Allele's proprietary microarray to identify gene copy number changes in early-onset urinary stone disease can be complemented by detecting gene variants identified by Dr. Hildebrandt, leading to better results in diagnosing the disease.

New Technologies

Ipsen sponsors research to develop improved botulinum neurotoxins

Botulinum neurotoxins (BoNTs) are FDA-approved treatments for a large number of medical conditions and also for aesthetic purposes. Enhancing the efficacy and specificity of BoNTs is poised to further improve their therapeutic usefulness and increase the list of medical conditions for which they are beneficial.

Before conducting research at Boston Children's, Min Dong, PhD, investigator in the Department of Urology, already worked with Ipsen, a global specialty driven pharmaceutical group, on the identification of such new modified recombinant botulinum toxins. Now at Boston Children's, Dong will continue this collaborative research to develop the engineered novel toxins for the treatment of serious neurologic diseases involving nervous system disturbance.

Restraining medical equipment during travel: a device to make it safe

Unsecured durable medical equipment (DME) in a car can become a dangerous projectile in an accident, posing a risk for significant bodily injury or death of passengers. Only eight percent of children with special health care needs (CSHCN), i.e. children that permanently need to be attached to their medical equipment, had their equipment properly restrained in their cars and none of the current recommendations for storing DME in vehicles ensures peoples safety.

Kathryn Gustafson RN, BSN, CCRN, staff nurse, Neonatal Intensive Care Unit, and Michele DeGrazia PhD, RN, NNP-BC, FAAN, director of nursing research, have developed a medical equipment adaptable travel restraint system (MEATR), thereby securing DME and ensuring the safe transportation of patients and their families. The system, similar to that of a backseat toy organizer, is a series of connected pockets of various sizes that are made of strong, heavy duty and durable materials. The safety system is solidly secured to a vehicle's seat. The system is able to restrain cardiorespiratory monitors, oxygen tanks and monitors, feeding pumps, suction apparatuses, and other DME. Adjustable straps and buckles make it easy to install and remove from any vehicle, allowing patients and their families to travel more freely and safely with their medical equipment.

Targeting telomerase in degenerative diseases

Telomeres are DNA-protein structures that protect chromosome ends, providing genome stability. Telomere shortening occurs as we age and limits tissue regeneration, but is counteracted by the enzyme telomerase, which preserves telomere length in our stem cells. Patients with genetic disorders of telomerase, including dyskeratosis congenita (DC) and idiopathic pulmonary fibrosis (IPF), have short telomeres in their cells and premature failure of their organs.

The lab of Suneet Agarwal, MD, PhD, a pediatric hematologist/oncologist in the Dana-Farber/Boston Children's Cancer and Blood Disorders Center, published a study in *Nature Genetics* that investigated why loss of the poly(A) ribonuclease gene (PARN) causes DC and IPF. They found that PARN mutations limit the biogenesis of the critical RNA component of telomerase (TERC), decreasing telomerase activity and compromising cellular self-renewal. Using patient cells, they found that telomerase deficiency due to PARN mutations can be rescued by inhibiting the non-canonical poly(A) polymerase PAPD5. These discoveries indicate that PAPD5 and PARN mediate opposing and non-redundant effects in the post-transcriptional maturation of TERC RNA, and that the balance of these enzymatic activities determines telomerase levels in human cells. Therefore, Agarwal's team proposes to develop therapeutic agents targeting PAPD5 and PARN to modulate telomerase activity and cellular self-renewal in DC, IPF, and a range of degenerative and malignant diseases.

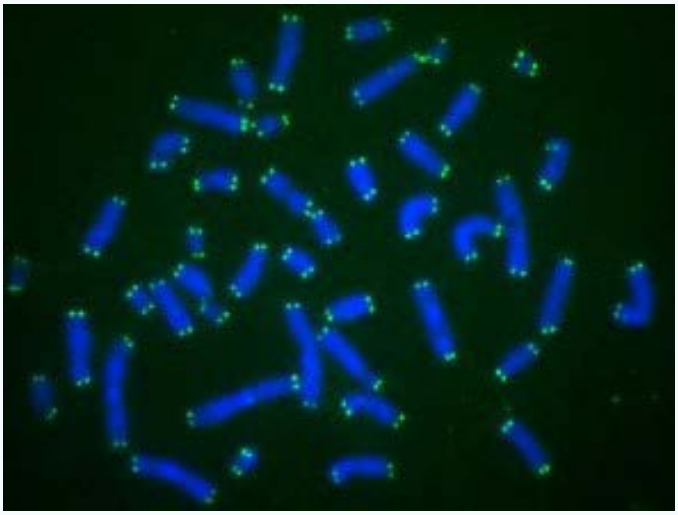


Image: Suneet Agarwal, MD, PhD

Telomeres (the green dots capping the blue chromosomes) shorten with age. In children with dyskeratosis congenita, genetic mutations make them get too short too quickly.

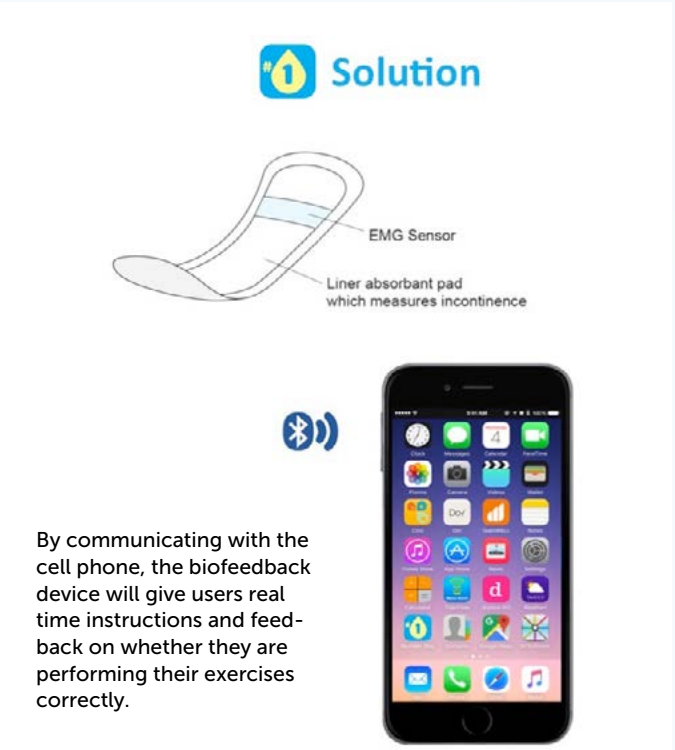
Novel x-ray technology to reduce repeat x-rays and radiation exposure

Radiation from x-rays may be associated with increased cancer risks. Size-specific x-ray exposure is challenging due to difficulty in obtaining relevant information about the patient thickness. Additionally, many causes of repeat imaging can be avoided if critical information is presented to the technologist in real-time.

Researchers at Boston Children's, led by Robert MacDougall, MSc, clinical medical physicist and Benoit Scherrer, PhD, research fellow, Radiology, along with Steven Don, MD, at St. Louis Children's Hospital, have developed a new technology that aims to improve x-ray imaging quality and safety. The device consists of a high-resolution video and depth camera using a Microsoft Kinect mounted to existing x-ray equipment and an advanced analytical algorithm. A graphical user interface (GUI) on a monitor in the control area provides a real-time video feed of the patient with overlaying information such as collimated x-ray field size and location, patient position relative to sensors, correct body part in the x-ray field, degree of patient motion and patient thickness. These features provide the technologist with information for dose optimization and tools to avoid repeats before an x-ray is acquired. This technology could drastically reduce the incidences of repeat x-ray caused by wrong body part, patient motion or mis-positioning, and reduce radiation dose to the pediatric population.

Targeting cancer with an optimized inhibitor of Rac1 GTPase pathway

Rac GTPases are proteins that regulate multiple kinase pathways to control cellular growth, survival, motility, and adhesion. Dysregulation of Rac has been observed in several cancers, including increased expression in breast and colon cancers and in specific types of leukemia. However, there are concerns over the druggability of Rac due its high sequence homology and flat protein surface (no deep pockets). David Williams, MD, chief scientific officer and chief of Hematology/Oncology, conducted *in silico* screening of small molecules that disrupt the Rac1-TIAM (T-cell lymphoma invasion and metastasis 1) interface and identified a series of initial candidate compounds. Additional PK/PD and SAR studies are underway to further optimize these candidates. Initial *in vivo* and *in vitro* studies showed that the candidate compounds are able to inhibit leukemia cell proliferation.



By communicating with the cell phone, the biofeedback device will give users real time instructions and feedback on whether they are performing their exercises correctly.

Biofeedback device and app to treat urinary incontinence

There are more than 65 million people with urinary incontinence in the U.S. Half of them are under 50, including women who have just had babies. Growing evidence shows that doing Kegel exercises during pregnancy can reduce the risk of incontinence after delivery. In addition, men who develop incontinence because of aging or after prostate surgery represent a growing and particularly under served population with few non-surgical options. Done properly, Kegels can have an 85 percent success rate; lacking feedback, most people give up on them prematurely. Apps for urinary incontinence already exist that provide "Kegel reminders," but none provide biofeedback.

Carlos Estrada, MD, director of the Spina Bifida Center and co-director of Urodynamics and Neurology, and Jeanne (Mei Mei) Chow, MD, director of Uroradiology, have developed a single-use, disposable pad that adheres to the perineal area that contains two kinds of sensors: electromyography sensors (to determine whether particular muscles are firing and quantify how strongly) and moisture sensors (to detect the degree of incontinence). As patients do their Kegel exercises, a Bluetooth connection would send real-time feedback to their Android or iPhone, like a Fitbit. The pad can be worn with any underwear.

Coached by industry mentors from MassChallenge and CIMIT, they created hardware and software prototypes, conducted market research to determine customer segmentation, devised a go-to-market strategy, and filed a provisional patent to protect their novel dual sensor pad. They founded a company and named it NumberOne LLC (based, of course, on "accidentally going #1") to further develop and commercialize the technology.

Targeting synapse loss in Alzheimer's to preserve cognition

Currently, FDA-approved drugs for Alzheimer's disease don't address the root causes of Alzheimer's cognitive decline. New drugs in development seek to eliminate amyloid plaque deposits or reduce inflammation in the brain, but by the time this pathology is detectable, it's unlikely medications can do much to slow the disease. Published in *Science*, Beth Stevens, PhD, research associate in Neurology, suggests ways in which Alzheimer's disease could be targeted much earlier to preserve cognitive function — before plaques or inflammation are evident.

Through more than a decade of research, Stevens has shown that normal developing brains have a built-in system to "prune" synapses that aren't utilized as they build their circuitry.

In multiple mouse models of Alzheimer's, Stevens and Soyon Hong, PhD, research fellow, showed that similar pruning mechanisms are wrongly activated later in life. By blocking these mechanisms, they were able to reduce synapse loss in the mice before amyloid plaque deposits could be observed.

The team found that synapse loss requires activation of the protein C1q, which "tags" synapses for elimination. C1q became visibly more abundant around vulnerable synapses in the mice. Cells known as microglia then came in and "ate" the tagged synapses, as they do during normal brain development.

When Stevens and colleagues blocked any of the following: C1q, a downstream protein called C3, or the C3 receptor on microglia in their mouse models, synapse loss did not occur.

Microglia and complement are known to be involved in Alzheimer's disease, but have been previously viewed as part of the plaque-related neuroinflammation that occurs in progressed stages of Alzheimer's.

The scientists note that this finding may have relevance for other conditions involving synapse loss, such as frontotemporal dementia, Huntington's disease, schizophrenia and glaucoma.

"Our study challenges this view and provides evidence that complement and microglia are involved much earlier in the disease process, when synapses are already vulnerable, and could potentially be targeted to preserve synaptic health," says Hong.

Treating otitis media with a one-dose antibiotic gel

Otitis media, or middle-ear infection, affects 75 percent of children and is the number one reason for antibiotic prescriptions in pediatrics. Typically, antibiotic treatment involves 7 to 10 days of oral medication, several times a day.

Daniel Kohane, MD, PhD, director, Laboratory for Biomaterials and Drug Delivery, and Rong Yang, PhD, a chemical engineer in Kohane's lab, in collaboration with investigators at Boston Medical Center and Massachusetts Eye and Ear, developed a single-application, bioengineered gel that could provide an entire course of therapy through a single squirt into the ear canal. Their results were published in Science Translational Medicine. The eardrum (a.k.a. the tympanic membrane) has until now been seen as an impenetrable barrier. To get antibiotics through it, Yang added chemical permeation enhancers (CPEs) to the gel. These compounds, already FDA-approved for other uses, are structurally similar to the lipids in the stratum corneum, the eardrum's outermost layer. The CPEs insert themselves into this membrane, and allow the antibiotics to seep through. The gel, loaded with ciprofloxacin, completely cured ear infections due to *Haemophilus influenzae* in 10 of 10 animals by day 7. (Ordinary ciprofloxacin ear drops cleared the infection in only 5 of 8 animals.) In addition to the convenience of a one-dose antibiotic treatment, the gel could potentially reduce systemic side effects and prevent development of antibiotic-resistant bacteria.

Kohane has received a large, five-year NIH grant to further the work and an award from Boston Children's Hospital's Technology Development Fund to move the patented technology toward clinical use.

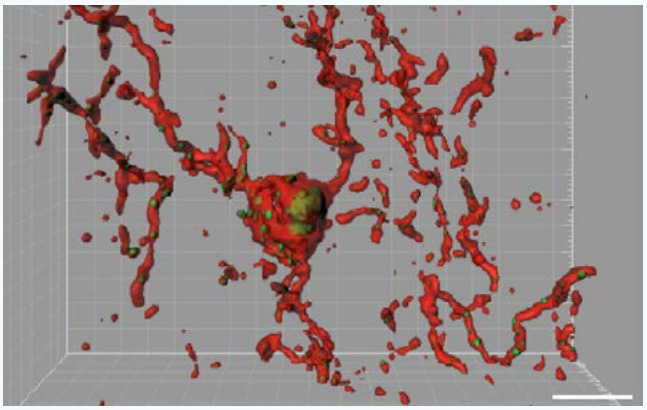


Image: Soyon Hong, Boston Children's Hospital

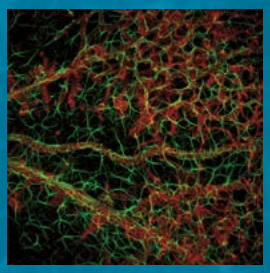
Microglia (in red) consume synapses (in green) after mice are injected with the oligomeric form of beta-amyloid, before plaques appear in the brain.

Boston Children's Hospital
Technology & Innovation
Development Office

300 Longwood Avenue, Mailstop 3183
Boston, MA 02115

617-919-3019
TIDO@childrens.harvard.edu

Search our list of promising health care and research technologies at
childrensinnovations.org



On the cover:
Retinal blood vessels surrounded by astrocytes in a retinal flat mount.

Image: Lois Smith, MD, PhD, Department of Ophthalmology, Boston Children's Hospital.