
Children's Hospital Boston
TECHNOLOGY &
INNOVATION
DEVELOPMENT
OFFICE
2002
annual report

THE TIDO TEAM

DIRECTOR

Erik Halvorsen, PhD
Director of Technology and Business Development
erik.halvorsen@childrens.harvard.edu

Abbey Coffin
Administrative Program Coordinator
abbey.coffin@childrens.harvard.edu

PATENTS AND LICENSING GROUP

(617) 919-3019

Licensing Managers

Kathleen Bass, PhD
Senior Licensing Manager
kathleen.bass@childrens.harvard.edu

Peter Hodges, PhD
Licensing Manager
peter.hodges@childrens.harvard.edu

Abbie Meyer, PhD
Licensing Manager
abbie.meyer@childrens.harvard.edu

Connie Caron, MBA
Licensing Manager
connie.caron@childrens.harvard.edu

Maude Tessier, PhD
Associate Licensing Manager
maude.tessier@childrens.harvard.edu

Alexander Augst, PhD
Associate Licensing Manager
alexander.augst@childrens.harvard.edu

Contracts and Intellectual Property

Christopher Geehan, JD
Contracts and Intellectual Property Specialist
christopher.geehan@childrens.harvard.edu

Stanley Tabi, JD
Patent Coordinator
stanley.tabi@childrens.harvard.edu

TECHNOLOGY DEVELOPMENT

(617) 919-3027

Monique Yoakim-Turk, PhD
Technology Development Manager
monique.yoakim@childrens.harvard.edu

BUSINESS DEVELOPMENT

(617) 919-3028

Nurjana Bachman, PhD
Business Development Manager
nurjana.bachman@childrens.harvard.edu

Marketing

David Altman
Marketing and Communications Specialist
david.altman@childrens.harvard.edu

Keeley Wray
Technology Marketing Specialist
keeley.wray@childrens.harvard.edu

CLINICAL TRIALS OFFICE

(617) 919-3019

Jay Kaplan, JD
Contracts Associate II
jay.kaplan@childrens.harvard.edu

Elizabeth (Lianne) Cleary, JD
Contracts Associate
elizabeth.cleary@childrens.harvard.edu

Ben Schiller, JD
Contracts Associate
benjamin.schiller@childrens.harvard.edu

Fernando Vallés, JD
Contracts Associate
fernando.valles@childrens.harvard.edu

Allison Hannibal
Business Analyst
allison.hannibal@childrens.harvard.edu

BUSINESS AND ADMINISTRATION GROUP

Sharon Jordan-Prioleau, MBA
Business Manager
sharon.jordan@childrens.harvard.edu

Lisa Pight
Financial Assistant
lisa.pight@childrens.harvard.edu

Karla Gunther
Administrative Associate
karla.gunther@childrens.harvard.edu

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LETTER FROM THE DIRECTOR

This past year was filled with many challenges—not just for Children's Hospital Boston (CHB) and our Technology & Innovation Development Office (TIDO) but for many of us in our personal lives. None of us were immune to the ongoing economic doldrums that the country continued to slog through—as unemployment rose, companies continued to tighten their belts and reduce spending in just about every sector, including those most relevant to our office: pharma, biotech, healthcare and early stage venture capital. In the face of this poor economic climate, it is remarkable that TIDO had one of its best years ever in terms of deal flow. Infrastructure changes within TIDO initiated in 2008, and further implemented in 2009, appear to have us poised to meet the challenges to our mission of bringing new diagnostics, devices and treatments to our patients and the public in 2010 and beyond.

With the launch of the Technology Development Fund in March, TIDO ushered in a new era at Children's where resources and product development expertise are brought to bear to advance the stage of development of hospital innovations—bringing them one step closer to the clinic. Guided by a top notch advisory board of industry experts (see page 4), TIDO awarded $1.2 million of funding to 11 projects including a platform technology for new vaccine development, a pediatric vision scanner, a point of care test for appendicitis, and potential new treatments for neuropathy, obesity and cancer. With the first round projects already underway, TIDO is gearing up for round two beginning in March 2010.

"...it is remarkable that TIDO had one of its best years ever..."

Along with integrating our newly created functions in Business Development, Technology Marketing and Communications into the office this past year, TIDO also welcomed two new key pieces to the team. In February 2009, the Immune Disease Institute became affiliated with CHB expanding our expertise in immunology and infectious disease research. In mid 2009, the Clinical Trials Office (CTO), which has worked closely with the patents and licensing group, officially joined TIDO further consolidating and strengthening the team, and allowing for better support of clinical research here at Children's. With many organization's oft stated but under realized goal to move research and clinical innovations from "bench to bedside"—the need for a strong CTO, well integrated with the other clinical research support groups at CHB is vital in order to solidify Children's as the world's greatest pediatric research hospital.

Looking ahead to 2010 it is clear that the challenges are not entirely behind us. There is hope that the economy will begin to make a slow recovery with biomedical research and healthcare technology leading the way. However, with industry continuing to trend towards "late stage" technology, we will continue to see even more responsibility shifted to academic research hospitals such as Children's to not only identify new tests and treatments for disease—but to validate, advance, de-risk, develop and clinically enable them. Some will ask if that is our role—and their question may be valid. However, my answer is that if others will not, then we must. Finding ways to translate our research and clinical innovation into new products is not only TIDO's mission but our obligation to our young patients and their families—and for the greater public good.

TIDO ACTIVITIES

With over $225 million in annual funding and 800,000 square feet of space, Children's Hospital Boston's research enterprise is the world's largest and most active at a pediatric center. Our investigators—basic scientists, clinical researchers and epidemiologists—are Harvard Medical School faculty who are accelerating the pace of medical discovery from brainstorm to bench to bedside. Children's garners more federal funding for research than any other pediatric hospital in the nation—and is fifth in the nation overall in NIH funding. The hospital is home to nine members of the National Academy of Sciences, 13 members of the Institute of Medicine, and 15 investigators supported by the Howard Hughes Medical Institute, the nation's largest private nonprofit source of funding for biomedical research and science education. Children's 1,100 scientists are experts in many fields, including stem cells, oncology, cardiovascular, neuroscience, genomics, vascular biology and informatics.

Invention Management Activity

In FY09, the Technology and Innovation Development Office (TIDO) had 523 inventions under active management. One-hundred and sixty-three of these were marketed within the fiscal year. Licensing managers supervised 209 ongoing license agreements, and facilitated the activities of outside patent attorneys to manage 962 pending patent applications on 363 inventions and maintain 984 issued U.S. and foreign patents.

INVENTION MANAGEMENT ACTIVITY

Inventions under active management	523
Inventions under initial evaluation	69
Inventions in marketing campaigns	163
Inventions in development	15
Inventions with license pending	10
Inventions with other institute leading	76
Current licenses	209
Issued U.S. patents	512
Issued foreign patents	572

Patent Filings

TIDO filed a total of 169 patent applications in FY09. Sixty-three were provisional patent applications and 33 were filed for U.S. and foreign rights under the Patent Cooperation Treaty mechanism. Forty-four applications were filed in the U.S. and 29 were filed in individual foreign countries.

Patent Issuances

Children's was granted 21 patents by the U.S. Patent and Trademark Office and 47 by foreign patent offices (Children's patents are filed with the Assignee designation of Children's Medical Center Corporation). These new patents are listed in Appendices 3 and 4.

Invention Disclosures

TIDO received 128 new invention disclosures from Children's clinicians and researchers, which is an increase of 10.3 percent over FY08.

FISCAL YEAR 2009 DATA SUMMARY

Invention disclosures	128
Patent applications filed	169
Provisional applications filed	63
PCT applications filed	33
U.S. applications filed	44
Foreign applications filed	29
Patents issued	68
U.S. patents issued	21
Foreign patents issued	47
Licenses & options granted	28
Gross revenues	$14,343,203
Net revenue (less external institutes)	$10,888,334
Revenue from new licenses & options	$338,106

Licensing Activity

TIDO negotiated and executed 28 license and option agreements for Children's technologies: 10 exclusive licenses, 16 non-exclusive licenses and two options. This is an increase of 27 percent in FY09. The revenue recognized from these new license and option agreements was $338,106. TIDO's overall performance and licensing and patenting activities over the past six years are illustrated in Appendices 1 and 2.

Clinical Trials Office

In collaboration with TIDO's licensing managers, the Clinical Trials Office (CTO) negotiated and executed 683 agreements in FY09: 58 clinical trial agreements, 617 academic and industry material transfer agreements and eight corporate sponsored and collaborative research agreements. The funding realized from these agreements was $5.1 million.

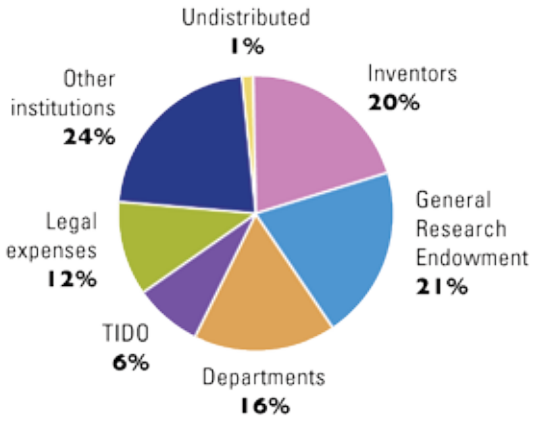
Distribution of Licensing Revenue

Gross revenue received in FY09 from all licenses was $14.3 million, a slight decrease from the previous year. Of the 209 active license agreements, 65 generated revenue. Thirty-one of these 65 licenses brought in less than $10,000 each, but four produced over $500,000 each. The net revenue received by Children's was $10.9 million, which is $14.3 million in gross revenue less $3.5 million distributed to other institutional co-owners. Of the $10.9 million in net revenue, $2.9 million was distributed to the inventors and $2.4 million was distributed to the inventors' departments and laboratories. The remaining $5.6 million to the hospital was apportioned to the general research endowment, unrecovered legal expenses and TIDO's operations.

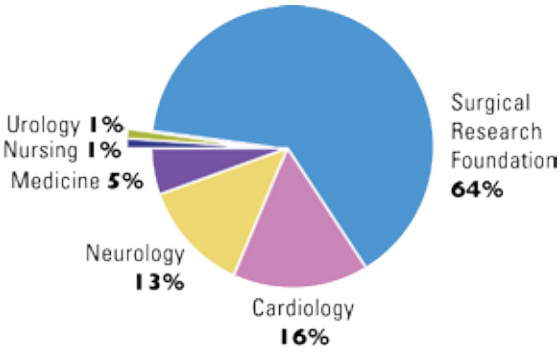
RECIPIENTS OF DISTRIBUTED LICENSING REVENUE

Inventors	$2,937,669
Research endowment	$2,982,262
Departments	$2,346,409
TIDO	$925,357
Legal expenses	$1,691,449
Other institutions	$3,454,869
Undistributed funds	$5,187
TOTAL	$14,343,203

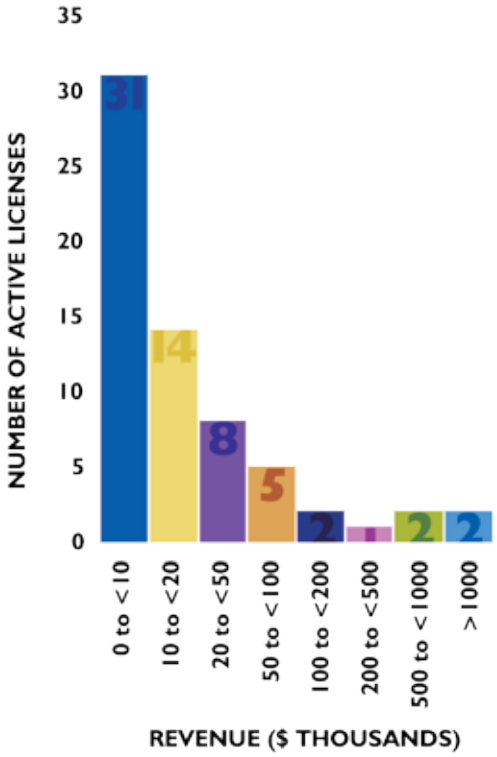
NET LICENSING REVENUE DISTRIBUTION FY09: $10.9 MILLION



DISTRIBUTIONS TO DEPARTMENTS FY09: $2.4 MILLION



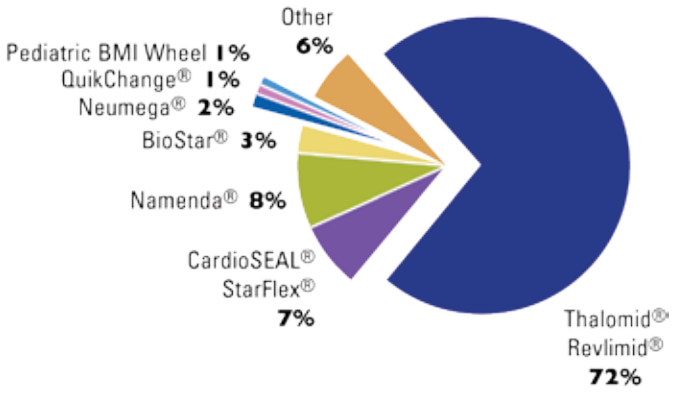
REVENUE GENERATING LICENSES FY09



Significant Revenue-Generating Inventions

Seventy-two percent of the total revenue was generated by sales of THALOMID® brand drug and REVLIMID® brand drug for the treatment of cancer. Other significant sources of revenue are royalties from the sales of CardioSEAL® and StarFlex® for minimally invasive repair of heart defects; Namenda® for the treatment of Alzheimer's disease; BioStar® to treat cardiac sources of migraine headaches, strokes and other potential brain attacks; Neumega®, which stimulates platelet production and is used in combination with chemotherapy by cancer patients; and the Sonnewheel body mass index (BMI) tool that allows clinicians to calculate BMI and provides sex- and age-specific percentiles for children ages 2 to 20.

SOURCES OF LICENSE REVENUE



TECHNOLOGY DEVELOPMENT FUND

Technology Development Fund Awards $1.2M

The Technology Development Fund, launched in March 2009, was created in response to the growing challenges faced by Children's—and its counterparts throughout the nation—in bringing new pediatric ideas and discoveries to market. These challenges, exacerbated by the current economic climate, result from the reluctance of industry to invest in and develop early-stage basic and clinical research. Instead, pharmaceutical, biotech and medical device companies have increasingly relied on academic institutions to validate technologies before considering them for licensing. While this trend is understandable given the cost of developing new drugs and medical devices, it has put tremendous pressure on academic institutions that typically lack adequate facilities and capabilities to move from basic research to product development.

The annual Technology Development Fund, managed by Monique Yoakim-Turk, PhD, at TIDO, was therefore created to advance our clinicians' and researchers' promising technologies that might otherwise be overlooked by investors and companies for being too early or too risky. The fund utilizes a three-pronged approach that combines an investment of capital into selected technologies; an external advisory board comprised of industry leaders in therapeutic, diagnostic and device product development; and a network of preferred contract research organizations equipped with the facilities and capabilities necessary to execute the desired project plan. "We are excited to be pushing this process forward and have found the right combination of efforts by engaging industry experts on our advisory board to work along side us in identifying, evaluating and mentoring the projects chosen for these awards," said Erik Halvorsen, PhD, director of TIDO.

TIDO issued a request for proposals for the first round of Technology Development Funds in March 2009, and approximately 30 letters of intent were submitted. After a preliminary internal review by TIDO, 17 applicants were invited to submit full grant proposals and present their projects to an external advisory board of industry experts with extensive product development experience.

The advisors recommended funding for 11 projects based on a number of criteria, including their potential for addressing important unmet medical needs and potential for the allocated funds to have a significant impact on the development of the technology. In August 2009, the Children's Hospital Boston Technology Development Fund announced that it would invest $1.2 million in these 11 innovations, which span pharmaceuticals, diagnostics, medical devices, vaccines and tissue engineering.

The funded projects are:

• **Slow-release antiangiogenic drug for treating eye diseases**—*Ofra Benny, PhD, and Robert D'Amato, MD, PhD, both from Vascular Biology Program*—This project's aim is to develop Lodamin as a "ready-to-use" antiangiogenic drug delivery product for ophthalmology uses. The award will be used to compare Lodamin to other anti-vascular endothelial growth factor therapies, characterize its physical properties and biodistribution in hydrogel solutions and perform pharmacokinetic studies in rats.

CHILDREN'S HOSPITAL BOSTON TECHNOLOGY DEVELOPMENT FUND ADVISORY BOARD

Dean Banks, MBA
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Venture Partner, Polaris Venture Partners

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Founder, Managing Partner, PureTech Ventures

• **Topical treatment of peripheral neuropathies**—*Gabriel Corfas, PhD, from Neurobiology*—Dr. Corfas's team has found that topical application of a small molecule that acts on neurotrophic receptors is an effective therapeutic strategy for peripheral neuropathies. This award will support studies to define key physical properties and biodistribution of the lead compound. Dr. Corfas believes that these studies will significantly clarify, and likely substantiate the commercial viability of this type of compound.

• **Fetal tissue engineering to repair congenital diaphragmatic hernia**—*Dario Fauza, MD, from Surgery*—This project is aimed at achieving the approval of the first human trial of neonatal diaphragmatic repair with an autologous engineered graft. It will also be the first clinical trial of a fetal cell-based engineered construct and of a mesenchymal amniocyte-based therapy. This award will fulfill pending requirements by the FDA and eventually bring this concept to clinical fruition. This development should also pave the way for other clinical trials involving a variety of mesenchymal amniocyte-based engineered grafts, already proven viable in preclinical models in Dr. Fauza's lab.

• **Semaphorin 3F as a treatment for prostate cancer**—*Elena Geretti, PhD, and Michael Klagsbrun, PhD, both from the Vascular Biology Program*—Class-3 semaphorins were originally described in the neuronal system as axon guidance molecules. However, their contribution to vascular/tumor biology is becoming evident. The goals of this project are to produce recombinant SEMA3F, study its pharmacokinetic and pharmacodynamic properties and assess its activity *in vivo*, in a transgenic tumor model.

• **Pediatric Vision Scanner—***David Hunter, MD, PhD, from Ophthalmology*—Dr. Hunter has developed the Pediatric Vision Scanner (PVS), a device that in a two-and-a-half second scan of the eyes can automatically detect strabismus, amblyopia, and other serious eye conditions in children as young as 2 years old. The award will allow the construction of several lighter, easier-to-use prototypes for pursuit of independent clinical validation of the device.

• **Urine diagnostic markers of acute appendicitis**—*Alex Kentsis, MD, PhD, from Hematology/Oncology, Richard Bachur, MD, from Emergency Medicine, and Hanno Steen, PhD, from Proteomics*—Our investigators have identified the leucine-rich alpha-2-glycoprotein (LRG) as a strong urine biomarker of acute pediatric appendicitis by using high accuracy mass spectrometry. This technology development award will fund the translation of the LRG test to an antibody based platform and will further validate this biomarker for appendicitis.

• **Packaging oxygen for intravenous injection**—*John Kheir, MD, from Anesthesia, Perioperative and Pain Medicine*—The goal of this project is to package oxygen in such a way that it can be administered intravenously. In this project, Dr. Kheir's team will expand the body of evidence in support of I.V. oxygen as a therapy. Specifically, they will test the efficacy of I.V. oxygen to improve outcomes during airway obstruction and cardiac arrest.

• **Novel pneumococcal vaccine**—*Ying-Jie Lu, PhD, and Richard Malley, MD, both from Infectious Diseases*—Drs. Lu and Malley have developed a new technology platform, which enhances both antibody and T-cell mediated immune response to create new vaccines that elicit potent immunity to pneumococcus and other targets. The main goal of this project is to evaluate the novel vaccine against pneumococcal colonization and disease in primates.

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• **Development of chemical chaperones to treat obesity and type 2 diabetes**—*Umut Ozcan, MD, from Endocrinology*—Dr. Ozcan and his collaborators have discovered several new chemical chaperones that have the ability to decrease endoplasmic reticulum stress at very low doses and resensitize the brains of obese mice to leptin. This project builds on this data and aims to perform pharmacokinetics and toxicology studies for the three most powerful compounds.

• **Development of an anti-metastatic peptide as a cancer therapeutic**—*Randolph Watnick, PhD, from Vascular Biology Program*—Dr. Watnick identified an endogenous protein, saposin A, which is secreted by weakly aggressive human breast and prostate cancer cells, and has demonstrated that it inhibits metastasis in a prostate cancer model *in vivo*. For this grant, Dr. Watnick will characterize several peptides of saposin A and test their efficacy in murine xenograft models.

• **Handheld solution to improve communication and coordinate Emergency Department care**—*Debra Weiner, MD, PhD, from Emergency Medicine*—The goal of this project is to develop a workflow-integrated communication network that coordinates Emergency Department (ED) patient care between the many providers, services and systems within the ED and throughout the hospital to impact patient care and the health of the ED system.

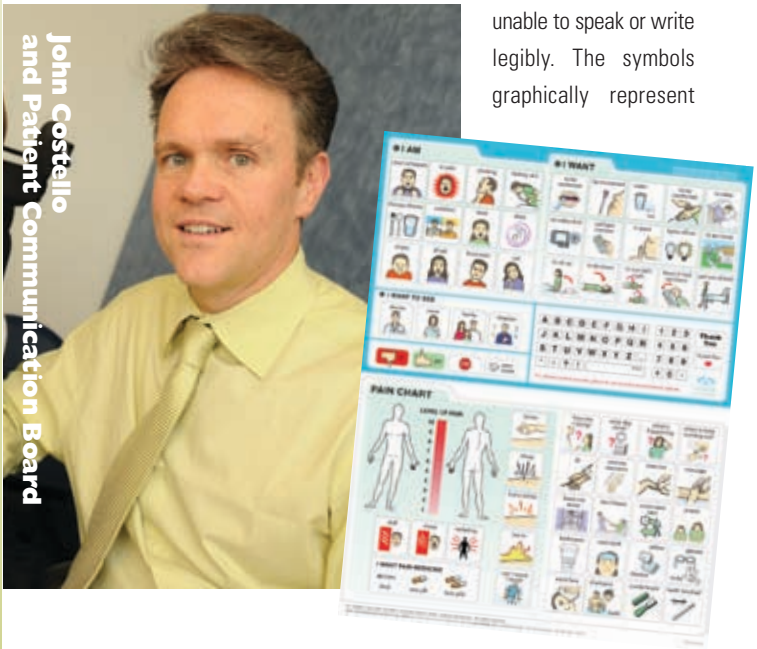
LICENSING AND COLLABORATION HIGHLIGHTS

Children's Exclusively Licenses Casper Zebrafish to Carolina Biological Supply Company

In March 2009, Children's signed an exclusive license with Carolina Biological Supply Company—a leading distributor of live animals and biological teaching materials to schools, colleges and research organizations—to distribute the Casper strain of zebrafish in the educational and research market. The Casper zebrafish were developed and characterized in the laboratory of Leonard Zon, MD, by Richard White, MD, PhD, a clinical fellow in the Stem Cell Program at Children's, and Anna Sessa, in Children's Aquatics Resources Program. The Casper fish lack two pigments due to mutations in genes required for their production—the black pigmentation produced in melanocytes, characterisic of the zebrafish stripes, and the shiny silver pigment produced by iridophores. As a result, the adult fish are nearly transparent, allowing the observation of internal organs in the live adult fish. Carolina Biological is preparing fish stocks and accompanying educational materials to launch the product offering in 2010.

Patient Communication Board Licensed to Vidatak

Children's has entered into an exclusive license agreement with Vidatak, LLC for use of the Children's Medical Symbol Set. John Costello, director of the Augmentative Communication Program, created the medical symbol set to address the needs of patients who are unable to speak or write legibly. The symbols graphically represent



words and phrases related to hospitalization. Since 2002, Children's has been using the symbols to create customized boards to aid patients in communicating with their health care providers. Last year, Children's and Vidatak collaborated to create a picture communication board using the hospital's medical symbol set. The communication board is currently available to purchase through Vidatak and was named a winner in the 2009 New Product and Technology Awards Program organized by the Mature Market Resource Center. Also, countries worldwide have requested translated picture boards and Vidatak has increased its distribution to both Iceland and Italy.

NeuroPace, Inc. Sponsors Research to Study Transcranial Stimulation Therapy for Neuropsychiatric Diseases

In February 2009, Children's signed a sponsored research agreement with NeuroPace Inc. to study the effect of skull fenestration on transcranial stimulation of neuronal tissue. In recent years, transcranial direct current stimulation (tDCS) has emerged as a promising therapeutic tool for several prevalent neuropsychiatric diseases, epilepsy, chronic pain and post-stroke deficits. The research performed by Alexander Rotenberg, MD, PhD, principal investigator in the Department of Neurology, in collaboration with Alvaro Pascual-Leone, MD, PhD, from Beth Israel Deaconess Medical Center, and collaborators at NeuroPace will test new methods and procedures aimed at improving the conventional tDCS technique.

Children's Normative Reference Dataset Package Licensed to Philips and Lumedx


Steve Colan, MD

In FY09, the Children's Normative Reference Dataset package, created by Steve Colan, MD, chief of Noninvasive Cardiology, was non-exclusively licensed to the Lumedx Corporation and Philips Healthcare (a division of Philips Electronics North America). Dr. Colan has gathered cardiac measurements on pediatric patients with normal heart structure and function. This is useful when incorporated into a standard echocardiography reporting system used by cardiologists, as it allows comparison of a patient of any age to the normal standard and shows whether the patient's measurement falls into the normal range. Currently, measurements from over 1,100 subjects with ages ranging from 0 to 20 years are included in the dataset.

Gene Therapy Patent Exclusively Licensed to Oxford Biomedica

Children's exclusively licensed a technology developed by Richard Mulligan, PhD, investigator from the Department of Genetics, and colleagues describing cell lines and methods for improving the safety of lentiviral vectors for gene therapy applications to Oxford Biomedica. The Children's patent, U.S. 6,958,226, "Packaging cells comprising codon-optimized gagpol sequences and lacking lentiviral accessory proteins," was found by the U.S. Patent and Trademark Office to be closely related to a patent filed by Oxford Biomedica at nearly the same time. As Oxford has several products in development that utilize the methods described in Children's patent, the hospital exclusively licensed the rights to Oxford.

Children's Increases the Distribution of the Sonnewheel BMI Tool

The Sonnewheel, developed by Kendrin Sonneville, RD, a registered dietitian at Children's, is an innovative tool that allows clinicians to calculate body mass index (BMI) and provides sex- and age-specific BMI percentiles for children ages 2 to 20. The wheel tool, which is based on up-to-date BMI data from the Centers for Disease Control and Prevention, has been well received in the health care community for the last two years. BMI is plotted on a standard chart, one for boys and one for girls, based on age, to monitor a child's development and track weight patterns. The Sonnewheel has been distributed widely by Children's Public Affairs and Marketing Department since its development in 2007.

Children's has licensed the design concept for the Sonnewheel to Harlow U.K., who specializes in the design, manufacture and distribution of U.K. National Standard Growth Charts. Harlow U.K. will utilize the U.K.-specific BMI scale data to include in their set of products. Through another agreement executed with a second company, over 600,000 specially labeled Sonnewheels will be delivered to families around the country as a part of an overall healthy lifestyle education campaign.

Children's Exclusively Licenses Potential Treatment for Pouchitis to AesRx


Wayne Lencer, MD

Children's Hospital Boston has exclusively licensed the development rights to the use of clotrimazole, an inhibitor of mucosal inflammation, for the treatment of patients with pouchitis, which is the inflammation of the bowel caused by the management of patients with ulcerative colitis. This treatment was developed by Paul Rufo, MD, MMSc, assistant in medicine in the Division of Gastroenterology, and Wayne Lencer, MD, chief of the Division of Gastroenterology. AesRx also believes this technology, called Aes-210, could be useful for the treatment of other inflammatory diseases of the lower intestine, such as distal ulcerative colitis and radiation induced proctitis. The technology is currently being evaluated for the treatment of pouchitis in a Phase II trial and has been designated an Orphan Drug.

STARTUP ACTIVITIES

Licensed Stem Cell Treatment Moves into the Clinic

In May 2009, Children's granted an exclusive license to Fate Therapeutics, Inc. for patent rights related to the use of compounds to stimulate stem cells. Fate was founded in 2007 with Leonard Zon, MD, director of Children's Stem Cell Program and a Howard Hughes Medical Institute investigator, as one of six founding scientists. Fate is using the fundamental biological mechanisms that guide cell fate to develop therapeutic stem cell modulators. The lead compound under the licensed rights is a stabilized prostaglandin E2 (16,16-dimethyl prostaglandin E2, also known as dmPGE2). Dr. Zon's group demonstrated that dmPGE2 improves hematopoietic stem cell engraftment in transplant models. Based on this work and prior published human safety data for dmPGE2, Dr. Zon was able to obtain approval for an Investigational New Drug (IND) application from the FDA for human clinical trials and the IND was transferred to Fate concurrently with the license.

"The agreement we signed with Children's Hospital and the technologies associated with it continue to expand our engine and accelerate the company's core mission..." said Paul Grayson, president and CEO of Fate Therapeutics.

Fate is currently conducting a Phase Ib trial at the Dana-Farber Cancer Institute and Massachusetts General Hospital to determine the safety and tolerability of introducing dmPGE2 during the standard course of a dual umbilical cord blood transplant in adult patients with hematologic malignancies, such as leukemia and lymphoma. Cord blood has less stringent matching criteria, so it can be available faster with lower incidence of graft-versus-host disease. While cord blood is commonly

Leonard Zon, MD

used for pediatric patients, it is used less frequently for adults because two cord blood units are often necessary to supply sufficient stem cells for successful engraftment. Stimulation of the cord blood stem cells may improve the transplant success, speed recovery of the immune system, provide more timely treatments and reduce the risk to patients.

"Taking the steps towards clinical use—for anything from a drug or device or a completely new platform technology—requires interfacing with industry," said Dr. Murray.

Connective Orthopaedics Formed Around Ligament Repair Technology

In November of 2008, Children's licensed a group of patents based on the work of Martha Murray, MD, an orthopedic surgeon and researcher in the Department of Sports Medicine, which formed the basis for a new company called Connective Orthopaedics. Dr. Murray's technology primarily addresses problematic tears of the anterior cruciate ligament in the knee, but also has other potential applications. See the full length story about the technology's development and transfer to Connective on pages 10-11.


Martha Murray, MD

Plagio Prevention LLC Licenses Corrective Plagiocephaly Device

In November 2008, Children's signed an exclusive license with Plagio Prevention LLC, for the development of infant care products to prevent and correct deformational posterior plagiocephaly. Posterior plagiocephaly or "flat head syndrome," occurs when an infant's skull is deformed by the pressure of lying on a flat surface, such as a crib or car seat. The incidence of positional head deformity has increased dramatically in the U.S. since the 1992 Back to Sleep campaign started by the American Academy of Pediatrics to reduce the number of infant deaths from sudden infant death syndrome. The company will further develop and test plagiocephaly devices originally designed by Gary Rogers, MD, JD, MBA, MPH, plastic surgeon at Children's, and James Miller of Boston Brace International Inc.


Gary Rogers, MD, JD, MBA, MPH

RECONNECTING THE ACL

As an orthopedic surgeon and researcher at Children's Hospital Boston, Martha Murray, MD, principal investigator in Orthopedic Surgery, treats many young athletes who have torn their anterior cruciate ligament (ACL). Her passion is developing ways to stimulate the healing of a patient's own ACL, rather than removing and replacing it. Her interest was piqued in graduate school when a friend tore his ACL and she wondered why it couldn't be stitched back together. Dr. Murray, who has a background in engineering, began by studying the underlying science of ACL regeneration. Over the years, she discovered a material that could facilitate ACL healing, tested it in animals and developed surgical devices for the repair procedure. However, she knew that bringing her innovations to the clinic would require a company partner.

Today her technologies are in the hands of a startup company, Connective Orthopaedics, which is developing these products for clinical use. "Without translation, all the basic science in the world can't fix the ACL," said Dr. Murray. "Taking the steps toward clinical use—for anything from a drug or device or a completely new platform technology—requires interfacing with industry."

Martha Murray, MD

In the 1970s, surgeons tried sewing the ACL's ends back together, but the surgery failed 90 percent of the time within five years. The current technique for treating ACL tears is surgical reconstruction, which involves removing the torn ligament and replacing it with a graft of a tendon from elsewhere in the body or from a cadaver. While this allows patients to return to sports in the short term, many will develop early arthritis of the knee.

In her laboratory studies, Dr. Murray and colleagues found that the ligament tries to heal itself—cells migrate to the wound, growth factors are secreted and blood vessels appear to nourish the new tissue—but the ligament ends never join. What was missing was something to bridge the gap. Dr. Murray found a solution—a gel made of collagen and platelet-rich blood plasma—that she and her team implanted into the torn ACLs of lab animals. Cells soon migrated into it, regenerated ligament tissue and made a permanent bridge, mending the tear. Dr. Murray's published findings (*J Orthop Res.* 2006 Apr;24(4):820-30) show good healing, appropriate biomechanical function and a 40 percent return in strength six weeks after ACL injury in a canine model.

Because she is a surgeon, Dr. Murray was always thinking about the end product that she would hold in her hands during a procedure. With initial funding from CIMIT (Center for Integration of Medicine and Innovative Technology), she developed the device prototype in collaboration with students at MIT. With the benefit of an innovative prototype, ongoing facilitation by CIMIT and additional funding from the Massachusetts Technology Transfer Center, she successfully engaged a local medical manufacturing company, Symmetry Medical Inc. (formerly TNCO) to refine the device. Dr. Murray further advanced the technology by conducting a number of large animal studies in both pigs and dogs with funding support from the NIH, the Orthopaedic Research and Education Foundation and the National Football League. In a recently published paper (*Am J Sports Med.* 2009 Dec;37(12):2401-10), the team has extended its results, with data in a pig model of ACL injury showing that the fix is effective for at least three months after surgery.

At that point in the technology's development, a company partner was needed to provide additional resources to translate the technology into clinical use. After exploring various partnering options, the Technology and Innovation Office (TIDO) at Children's and Dr. Murray determined that a small startup company would be the best development partner. "We wanted the flexibility and nimbleness of a small company and also wanted to have some say in directing the path of research within the company," said Dr.

Murray. TIDO of Children's agreed. "We knew that a startup would focus all of its efforts on development of the technology with the goal of bringing it to market as quickly as possible," said Nurjana Bachman, PhD, manager of Business Development at TIDO.

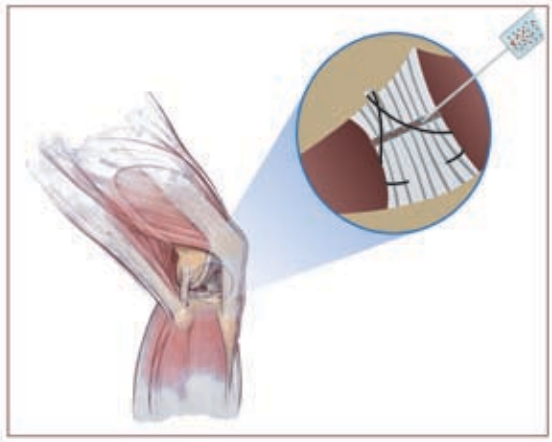
Before deciding on a startup company, TIDO marketed the technology to a number of potential partners of various types—including large medical device companies, large companies with a focus on tissue engineering and regeneration and medium sized companies with their own ground-breaking technologies. Each company was intrigued by the work, but since ACL repair had been declared a failure since the 1970s, the hurdle was particularly high. Further, the technology is disruptive in nature, with the potential to change the standard of care for ACL injuries. It represented an opportunity, but also a threat to large companies that currently have product lines that serve the current standard of care, ACL reconstruction.

"Martha has all of the components of a health care innovator. With her training as an engineer, scientist and surgeon, she not only sees problems with the standard of care, but has the training and experience to fix them," said Dean Banks.

Aaron Sandoski, managing director at Norwich Ventures, a venture capital firm, reviewed Dr. Murray's technology in 2008, and felt it had all of the components of a successful product. It had a "game changing" technology, a large market and unmet medical need, and a passionate and cutting-edge research leader in the field.

After ongoing talks with TIDO and Dr. Murray, the worldwide exclusive license agreement with a startup called Connective Orthopaedics, which received its initial funding from Norwich Ventures, was signed in 2008. At the time of the deal, 28 patent applications had been filed by TIDO. Once the intellectual property was transferred, the company hit the ground running. A research lab was up and in operation in two months. A month later, they reproduced the first generation material.

While negotiating with TIDO, Norwich also brought in Dean Banks as the CEO, a venture capitalist who had previous experience in company operations, to run the newly formed company. The CEO was impressed with the development Dr. Murray had done in five to 10 years with public funding. "Martha has all of the components of a health care innovator," said Banks. "With her training as an engineer, scientist and surgeon, she not only sees problems with the standard of care, but has the training and experience to fix them. On top of this, her determination and compassion drive her to move the technology forward and someday improve the lives of her patients."



Collagen gel inserted via a small knee incision [Image: P. Bibbins]

Connective Orthopaedics is located in the Boston area and has positioned itself as a medical device company specializing in soft tissue repair in sports medicine applications, with the ultimate goal of healing the torn, native ACL. The company's scientific advisors include co-founder Kurt Spindler, MD from Vanderbilt University, and a Scientific Advisory Board (SAB) comprised of world renowned clinicians and researchers in orthopedics, biomaterials and regenerative medicine.

At Connective, Dr. Murray acts as a scientific advisor and sits on the SAB and Board of Directors. Sandoski believes the company will succeed behind the team it has built. "The combination of Dr. Murray's scientific and clinical expertise, the broad knowledge of the SAB and the product development experience of Connective's phenomenal biomaterials team is a winning formula to change the way surgeons treat patients with ACL injuries."

The future looks bright for Connective Orthopaedics. "Connective has already achieved more than I ever could have hoped in getting this technology closer to being available for patients. Whatever else it accomplishes will be icing on the cake," said Dr. Murray.

CLINICAL TRIAL AGREEMENTS

Children's Hospital Boston investigators and clinicians design cutting-edge clinical research covering a variety of pediatric indications, making us a partner of choice for industry sponsors. The Clinical Trials Office (CTO) is the principal point of contact for establishing industry sponsored clinical and basic research. Children's has performed hundreds of clinical trials over the years, including 66 industry sponsored agreements in 2009 alone. In early 2009, the CTO joined TIDO, aligning complementary missions to translate laboratory and clinical research excellence into products for the public benefit. By way of example, the CTO is proud to highlight two of the many projects it helped facilitate during FY09:

Progeria Study

In the spring of 2009, the CTO oversaw negotiations of a follow-on "triple drug" Progeria study, led by Mark Kieran, MD, PhD, director of Pediatric Medical Neuro-Oncology. In 2002, the protein progerin and the attached farnesyl group were identified as being responsible for Hutchinson-Gilford Progeria Syndrome (Progeria), a rare and ultimately fatal disease causing premature age-related disorders. In early 2007, the CTO oversaw the negotiation of the original collaboration with the Progeria Research Foundation, Schering Plough Corporation (Schering), Dana-Farber Cancer Institute and Brigham and Women's Hospital in an effort to find a cure for Progeria. As part of the collaboration, Schering had donated a cancer drug thought to inhibit the attachment of the farnesyl group to progerin. Recent research has shown that the additional drugs studied in the current "triple drug" study have improved the disease in Progeria cells and extended lifespan in mouse models. The new study hopes to prove the same in humans. The original studies were funded by the Progeria Research Foundation and the study team has now received an NIH grant to continue its work on this rare disease.


Mark Kieran, MD, PhD

SCID-X1 Gene Therapy Study

Severe combined immunodeficiency (SCID) is a group of inherited immune disorders, the most common of which, the X-linked SCID-X1, accounts for 40 to 50 percent of all cases. Classic SCID-X1 has an extremely poor prognosis without treatment. If untreated, death usually occurs within the first year of life. Approximately 30 percent of diagnosed patients are eligible for family donated hematopoietic stem cell transplantation. However, the remaining subjects are treated with cells from matched unrelated donors, which can be problematic due to excessive transplant-related toxicity such as graft-versus-host disease and incomplete immune reconstruction. David Williams, MD, chief of Hematology/Oncology and director of the Translational Research Program at Children's, holds an Investigational New Drug exemption for a phase I/II gene therapy trial using a patient's own bone marrow to develop a new immune system to cure subjects suffering from classic SCID-X1. This is a multicenter, international trial with Children's serving as the lead center in the U.S. The trial utilizes a new, safer virus vector developed collaboratively with investigators in England, France and Germany as part of the Transatlantic Gene Therapy Consortium, which was developed and is run by Dr. Williams. The CTO negotiated a collaborative effort between a Japanese industrial partner supplying the drug and Cincinnati Children's Hospital Medical Center, which is supplying a GMP produced vector to conduct the study. Subjects are patients without matched family donors who are either under three-and-a-half years old or patients of any age with an active therapy-resistant infection.


David Williams, MD

SIGNIFICANT MILESTONES ON LICENSED TECHNOLOGIES

Genentech's Antitumor Therapeutic Enters Clinical Trials

In FY09, Genentech's novel antitumor therapy related to technologies licensed from Children's entered into a Phase Ib clinical trial. In November 2005, Children's granted Genentech (now a wholly owned member of the Roche Group) an exclusive license to anti-cancer technologies, such as use of neuropilin antagonists including

anti-neuropilin antibodies, as angiogenesis inhibitors. Michael Klagsbrun, PhD, senior associate in Medicine, and colleagues discovered in 1998 that neuropilins, previously known to be involved in nervous system development, also play a role in blood vessel formation. Therefore, blocking these neuropilins can inhibit angiogenesis and prevent tumor growth. Genentech scientists have since reported several studies on the antitumor effects of the anti-neuropilin 1 (NRP1) monoclonal antibodies, in preclinical animal studies and *in vitro* experiments. In the third quarter of 2008, Genentech initiated a Phase Ia dose escalation study in patients with locally advanced or metastatic solid tumors to evaluate the safety of the antibody therapy in humans. In the third quarter of 2009, they initiated a second Phase Ib trial evaluating the anti-NRP1 antibody in combination with Avastin® or Avastin® plus Paclitaxel.


Michael Klagsbrun, PhD

Baxter's Von Willebrand Factor Enters Phase I Clinical Trials

On December 4, 2008, Children's licensee Baxter Healthcare Corporation announced the dosing of the first patient in a Phase I clinical trial of its recombinant von Willebrand Factor (rVWF), an investigational drug for the treatment of von Willebrand Disease (VWD), based around patents from the work of Stuart Orkin, MD, a Howard Hughes Medical Institute investigator. The multicenter, controlled, randomized, single-blind prospective trial being performed in North America and Europe is evaluating the pharmacokinetics, safety and tolerability of rVWF in Type 3 VWD, the most common type of inherited bleeding disorder. Recombinant VWF is currently in development for the treatment of patients diagnosed with severe VWD and for other patients with VWD who are unresponsive or otherwise unable to receive Desmopressin, a synthetic hormone that promotes the release of natural VWF.


Stuart Orkin, MD

The Lodamin technology won a Technology Development Fund Award to develop a "ready-to-use" antiangiogenic drug delivery product for ophthalmology uses.

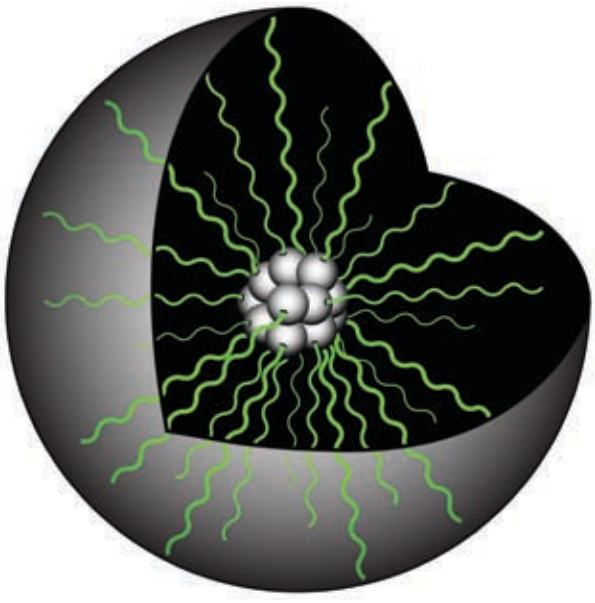
RESEARCH HIGHLIGHTS

VASCULAR BIOLOGY PROGRAM

The Vascular Biology Program (VBP) at Children's is dedicated to the study of conditions that are characterized by abnormal blood vessel growth. Angiogenesis, or the production of new blood vessels, contributes to more than 60 diseases, including a variety of cancers, degenerative eye diseases, chronic inflammatory diseases and obesity. After an exhaustive international search, Marsha Moses, PhD, interim director of the program, a member of the prestigious Institute of Medicine and a successful entrepreneur, was appointed the permanent director in 2009.

Lodamin for Treating Eye Diseases

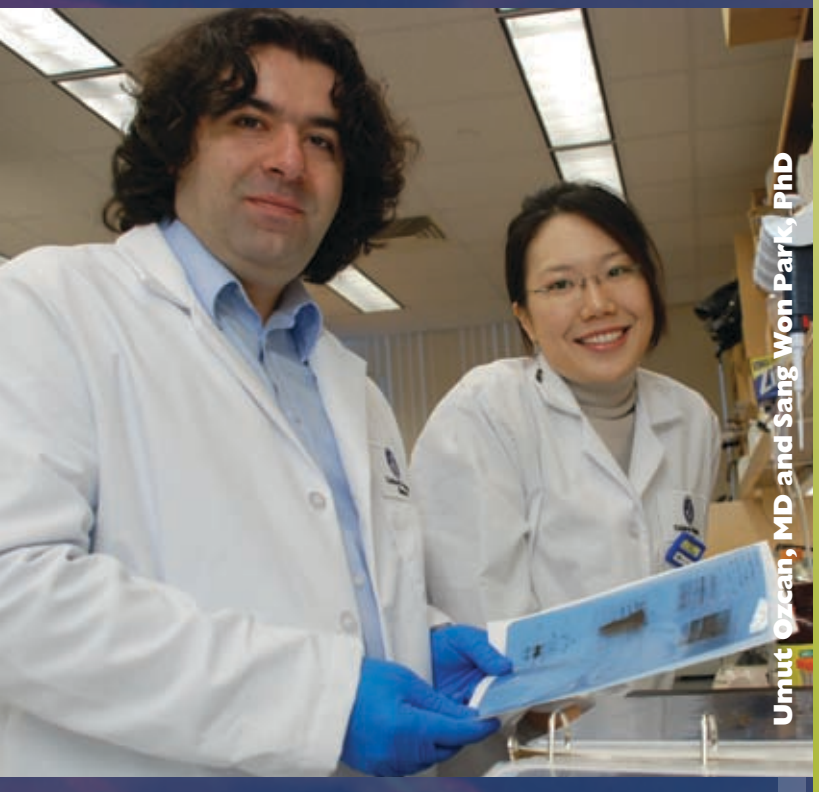
Lodamin is a novel antiangiogenic small molecule carrier drug that is a non-toxic conjugation of TNP-470. The antiangiogenic activity of Lodamin was successfully demonstrated in different tumor models in mice. Ofra Benny, PhD, research fellow in the VBP, the original inventor of Lodamin, and Robert D'Amato, MD, PhD, director of the Center for Macular Degeneration Research, found that it may be a novel therapy for age-related macular degeneration and potentially for diabetic retinopathy, two common angiogenesis-dependent eye diseases affecting millions of individuals in the U.S. alone. Unlike other available antiangiogenic treatments, Lodamin is able to inhibit both vessel growth and the leakage of fluid, and targets multiple growth factors other than vascular endothelial growth factor. This technology was recently granted a Technology Development Fund Award for Drs. Benny and D'Amato to develop a "ready-to-use" antiangiogenic drug delivery product for ophthalmology uses. TIDO has filed composition of matter and method of use patents on Lodamin and is speaking to several companies about exclusively licensing this promising compound.


A Lodamin nanoparticle (polymeric micelle)

NOVEL OBESITY TREATMENT

Umut Ozcan, MD, research associate in Endocrinology, studies metabolic pathways that are linked to obesity and obesity-related diseases with the goal of finding new treatments for these conditions. He has been studying the leptin receptor signaling pathway to understand why the hormone leptin loses its appetite-suppressing effect in the brains of obese people. In his studies thus far, Dr. Ozcan has discovered two potential treatments that facilitate leptin's effect. When obese mice are given either 4-phenyl butyrate (4-PBA) or taurine-conjugated ursodeoxycholic acid (TUDCA), followed by treatment with leptin, the mice have significant weight loss. These studies demonstrate that 4-PBA and TUDCA can resensitize the brain of obese mice to the appetite-suppressing effect of leptin (*Cell Metab.* 2009; 9:35-51). Both 4-PBA and TUDCA are known to be safe in humans and are already FDA approved for clinical use. Dr. Ozcan won a 2009 Technology Development Fund Award and is continuing his studies to find more potent treatments that will work without exogenous supplementation of leptin.

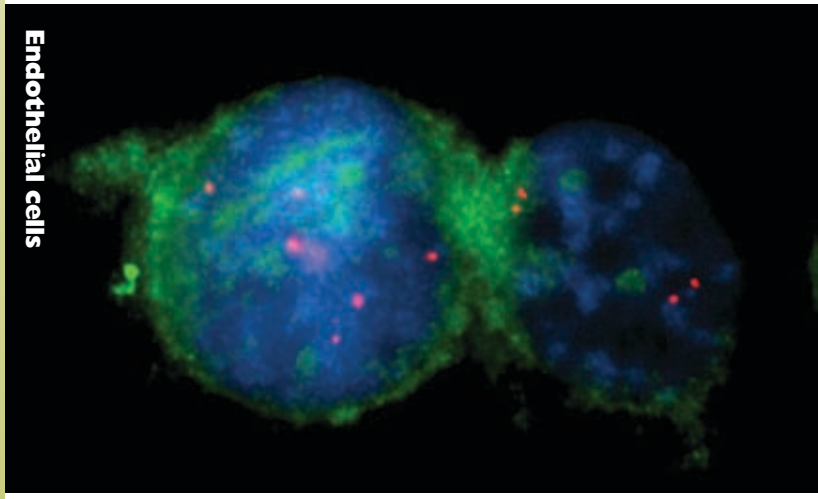
"I think our study will bring new hope for the treatment for obesity," says Dr. Ozcan.



Umut Ozcan, MD and Sang Won Park, PhD

Semaphorin Proteins as Antiangiogenic Therapeutics

Class-3 semaphorins (SEMA3A through SEMA3G) were originally described in the neuronal system as axon guidance molecules. Michael Klagsbrun, PhD, senior associate in Medicine in the VBP, and colleagues recently showed that SEMA3F is lost in highly metastatic prostate, bladder and melanoma cells. Their results also indicate that it is a potent inhibitor of angiogenesis, tumor growth, tumor cell migration and metastasis. Therefore, the protein may be a novel antiangiogenic and antimetastatic therapeutic for cancers like melanoma and prostate cancer. Since SEMA3F is a naturally occurring protein, it may show decreased toxicity and have advantages in receiving FDA approval. This technology was the recipient of a 2009 Technology Development Fund Award. Dr. Klagsbrun will use the award to produce recombinant SEMA3F, determine its pharmacokinetics and assess its activity in tumor models in mice. TIDO has filed composition of matter and method of use patents and an exclusive license to the technology is available.



Endothelial cells

Beta-35, a Novel Peptide Inhibitor of Angiogenesis

The late M. Judah Folkman, MD, and Yuen Shing, PhD, research associate in General Surgery, discovered a novel endogenous peptide with antiangiogenic properties, named Beta-35. The peptide was found to inhibit the growth of human pancreatic and melanoma tumor xenografts *in vivo*. There are about 38,000 new cases of pancreatic cancer and 62,480 new cases of melanoma each year in the U.S., with more than 40,000 deaths annually from these two cancers. This therapy could offer enhanced performance in pancreatic cancer and melanoma when used in combination with existing agents because of its complementary mechanism of action. Since this agent is derived from a naturally occurring protein, it may show decreased toxicity and have advantages in receiving FDA approval. TIDO has filed patents on the composition of matter and method of use and is looking for a development partner.

Dissection of Vascular Signaling Pathways in Zebrafish

The research of Joanne Chan, PhD, research associate in the VBP, focuses on defining the molecular mechanisms governing blood vessel formation under normal and pathological conditions, and uses molecular, chemical and genetic approaches to study zebrafish. The transparency, fecundity, rapid development and remarkable conservation of its genes make zebrafish an ideal, cost-effective vertebrate model for the live visualization of vasculature, investigation of angiogenesis and testing of potential treatments. Dr. Chan's group has developed a number of tools and assays, chemical inhibitor screening, vascular permeability assays and advanced imaging techniques, in embryonic, larval and adult zebrafish. This expertise can be applied to a variety of conditions, such as cancer, endometriosis, arthritis, diabetes, vascular anomalies and infectious and neurodegenerative diseases. Dr. Chan has successfully completed specific sponsored research projects with large pharmaceutical companies and TIDO has filed patents on her discoveries.

Joanne Chan, PhD

STEM CELL PROGRAM

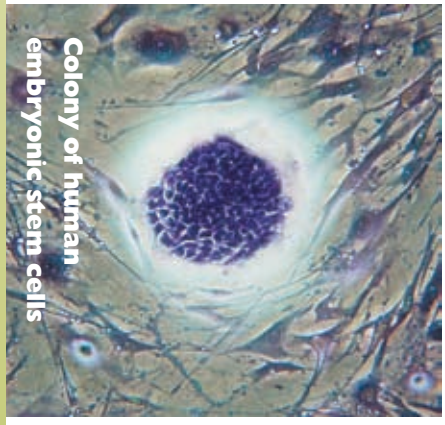
Stem cell research hit its stride in FY09, which has been reflected in the research activity of Children's Hospital Boston's Stem Cell Program. Under Director Leonard Zon, MD, and Associate Director George Daley, MD, PhD, the program has expanded with a new faculty hiring, and expansion of the affiliate membership to more than 40 researchers, and the participation in the Harvard Stem Cell Institute, which coordinates collaborative projects across Harvard-affiliated institutions.

Leonard Zon, MD and George Daley, MD, PhD

Renewed Attention on Embryonic Stem Cells

The stem cell community has been actively translating President Obama's executive order of March 2009, "Removing Barriers to Responsible Scientific Research Involving Human Stem Cells," into revised NIH guidelines for conducting human embryonic stem cell (hES cell) research. Several Children's experts provided public comments on the draft proposals, and the final NIH guidelines, released in July, were met with general approval and the anticipation that hES cell research would see renewed scientific attention.

Children's Stem Cell Program is committed to making hES cells available to the research community. Children's scientists have created 15 new hES cell lines. Under the new federal policy launched in December by President Obama, the NIH approved the first 13 hES cell lines to be eligible for federal funding, and 11 of the lines came from Children's. Since the announcement, Children's has received requests from 15 labs for over 100 cell lines. The Human Embryonic Stem Cell Core Facility at Children's, supported by the Harvard Stem Cell Initiative and directed by Thorsten Schlaeger, PhD, has provided the repository for maintaining and distributing these hES cell lines, as well as providing expertise and training to the stem cell community on stem cell culture.



Colony of human embryonic stem cells

As emphasized since the initial description of human induced pluripotent stem cells (iPS cells) reprogrammed from somatic cells, iPS cells are not identical to embryo-derived hES cells. The two cell types may show differences in their ability to differentiate into specific cells types or in their potential and suitability for therapeutic uses. This point was highlighted in a recent publication from the collaboration between Dr. Daley's group, Dr. Schlaeger, and researchers at the Johns Hopkins University, demonstrating the difference between iPS and hES cells at the epigenetic level, i.e. the methylation status of their genomes (*Nat Genet.* 2009 Dec;41(12):1350-3).

Worldwide Distribution of iPS Cell Lines

Excitement continues to grow around human iPS cells, their creation, research use and therapeutic potential. Dr. Daley and In-Hyun Park, PhD, have created a library of normal and disease-specific iPS cell lines (*Nature* 451, 2008 January 10;141-146; *Cell* 2008 134(5):877-86; *Blood.* 2009 May 28;113(22):5476-9). In an effort to support the research community, Dr. Daley has made more than 20 iPS lines available by request to the academic research community. In the first full year since, cell lines have been distributed to over 65 laboratories worldwide.

Recently, several iPS lines have been deposited in the new Massachusetts Stem Cell Bank, which was created under the "Massachusetts Life Science Strategy" as a centralized repository of new stem cell lines available to all public and private sectors of research.

Hematopoietic Stems Cells/Embryo's Heartbeat Drives Stem Cell Formation

Biologists recognized the enigma that the embryonic heart begins beating long before the tissues actually need to be infused with blood. Two groups of researchers from Children's, along with collaborators, presenting multiple lines of evidence from zebrafish, mice and embryonic stem cells, have shown that a beating heart and blood flow provide signals that are necessary for development of the blood cells.

"In learning how the heartbeat stimulates blood formation in embryos, we've taken a leap forward in understanding how to direct blood formation from embryonic stem cells in the petri dish," says Dr. Daley.

One team, led by Dr. Zon, discovered that lethal mutations in zebrafish that prevent the development of a beating heart also disrupt the development of hematopoietic stem cells (HSCs). The signals that are known to regulate blood flow (such as nitric oxide, adrenergic agents and calcium channel blockers) also regulate HSC formation, independent of blood flow.

The second team, led by Dr. Daley, and Guillermo García-Cardeña, PhD, Brigham and Women's Hospital, along with scientists from Indiana University, investigated the effects of mechanical stimulation on blood formation in cultured mouse embryonic stem cells. They showed that shear stress—the frictional force of fluid flow on the surface of cells lining the embryonic aorta—increases the expression of master regulators of blood cell formation, including Runx1, and increased formation of hematopoietic progenitor cells that give rise to specific lineages of blood cells (red cells, lymphocytes, etc.).

The authors of the two papers speculate that drugs that mimic the effects of embryonic blood flow on blood precursor cells, or molecules involved in nitric oxide signaling, might be therapeutically beneficial for patients with blood diseases.

Translating Stem Cells into Therapies

Stem cell technologies continue to be translated into medical treatments, with a number of clinical trials initiated worldwide using stem cells to regenerate failing or diseased tissues, and drugs that act to stimulate the patient's own stem cells to treat diseases. See the progress of Children's prostaglandin E2 therapeutic licensed to Fate Therapeutics, highlighted on page 8.

The Secret Lives of Stem Cells

Fernando Camargo, PhD, joined the Stem Cell Program this year. His research focuses on the role of stem cells in the maintenance of adult body tissues. His work on the Hippo cell signaling pathway has identified a gene that is critical for determination of organ size by expanding the populations of undifferentiated progenitor cells. The manipulation of the YAP1 gene in the liver, for example, can reversibly increase liver size by four-fold in mice. In the hematopoietic system, he has identified a gene that is key to the generation of lymphoid cells (B cells, T cells and NK cells) from multipotent progenitors. In 2009, Dr. Camargo received a NIH Director's New Innovator Award, which is a "high risk" research award given to early stage investigators whose projects have the potential for unusually high impact.

Fernando Camargo, PhD

CLINICAL RESEARCH

Motivation and inspiration to excel in patient care and research often comes from patient encounters while treating children with problematic and traumatic conditions. Even though Children's Hospital Boston applies the latest cutting-edge medical procedures and technologies available, there are still many formidable challenges to be solved and questions to be answered in order to further patient care. Clinical researchers at Children's at the intersection of research and patient care are solving these challenges with highly innovative concepts that have the potential to translate into breakthrough technologies and become the standard of care in the clinics.

I.V. Oxygen Using Injectable Microbubbles

Keeping blood oxygenated for a short period of time during cardiac arrest or under other circumstances in which a patient can't breathe can prevent tissue and brain damage. Low oxygen levels also cause death or severe disability in a variety of diseases affecting both adults and children. Current methods of emergency oxygenation are dependent upon removing blood from the body and circulating it through a machine, which is tedious, expensive and limiting. Hoping to find another solution to this problem, John Kheir, MD, fellow in Critical Care Medicine and Cardiology, has developed a novel liquid suspension containing very high concentrations of oxygen gas packaged into microbubbles designed for intravenous injection.

PEDIATRIC CARDIOVASCULAR DEVICE CONSORTIUM

Pedro del Nido, MD, chief of Cardiac Surgery, and his group were recipients of a $500,000 grant from the Pediatric Device Consortia Grant Program, part of the FDA's Orphan Grants Program. The Pediatric Cardiovascular Device Consortium at Children's, led by Dr. del Nido, will address one of the key impediments to pediatric device development: the need for extensive resources required not only to design, prototype and perform preclinical testing, but also to conduct the Phase I and Phase II clinical trials required for market approval. The consortium will encompass three cores to address the key steps in successful device development:

1. **The Clinical Trials Core** will be run by the NIH Pediatric Heart Network (PHN). It will provide the infrastructure for scientific decision-making, clinical centers highly skilled in the conduct of multicenter pediatric research, and activities and execution of clinical studies with methods in data management, central laboratories and biostatistics.

2. **The Engineering Core** will be at the Georgia Institute of Technology (GIT). The team at GIT has carried out a number of projects to develop novel therapeutic devices for children with congenital heart defects. It will provide engineering expertise and support the projects with its prototyping capabilities and development and testing facilities.

3. **The Business, Commercialization and Regulatory Core** will be a joint effort by several entities: the PHN, which has long-standing relationships and collaboration with the FDA and other organizations; the New England Research Institutes, which has a wealth of regulatory experience conducting clinical trials in the U.S., Canada, European Union, Latin America and Australasia; and Children's Hospital Boston which will provide patenting, licensing and business development support through TIDO and aid in the approval processes through Children's Regulatory Affairs Office.

The hope is that this collaborative effort will accelerate the pace of innovation and fulfill the Pediatric Cardiovascular Device Consortium's primary goal of developing and evaluating novel therapies for children with heart defects.

Pedro del Nido, MD and Nikolay Vasilyev, MD

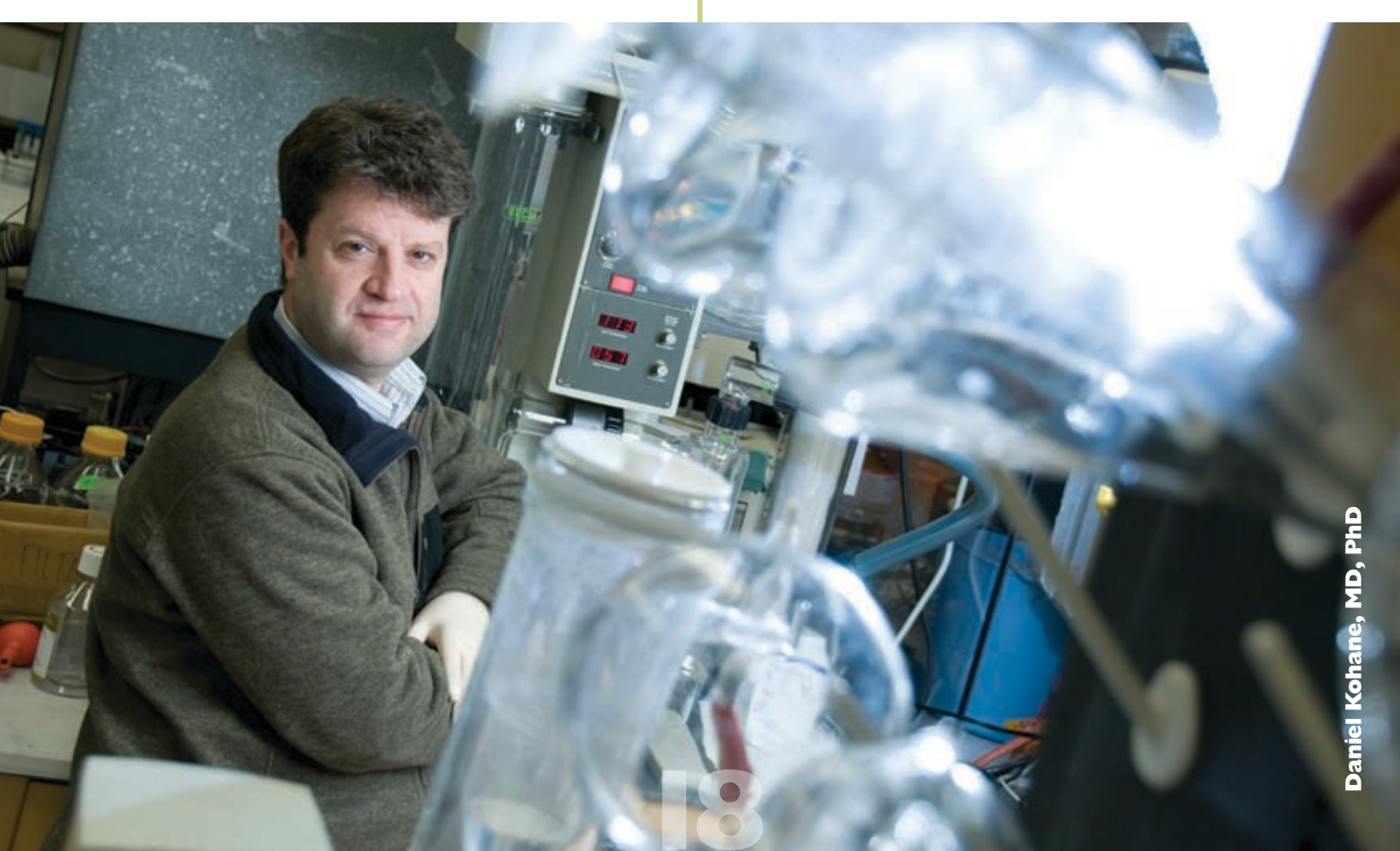
This technology has the potential to deliver oxygen to the deoxygenated tissues quickly and directly, providing it with essential metabolic energy. The technology has the potential to be deployed in every ambulance, operating room and emergency room, which represents a large market opportunity. Dr. Kheir recently won a Children's' Technology Development Fund Award and will utilize these funds to refine and test his microbubble formulations.

Controlled Local Anesthesia

Daniel Kohane, MD, PhD, principal investigator in Anesthesiology, is developing new methods for maintaining long-lasting local anesthesia. To do this, his lab has developed innovative approaches to encapsulate anesthetics in liposomes, which are tiny lipid spheres that release the drug gradually. Dr. Kohane has also discovered that the coadministration of certain chemicals and anesthetics can lead to a selective nerve blockade. In standard local anesthetics, numbness usually coincides with the loss of motor function. This new method would allow successful sensory suppression while enabling the patient to move the affected muscle. This technology may be used for epidurals for painless baby deliveries and could lead to faster recovery from surgery.

Novel Algorithm for High Speed Medical Image Processing

Medical imaging is an integral part of modern diagnostics and continues to make rapid advances. A number of modalities exist today, such as ultrasound, magnetic resonance imaging (MRI), computed tomography (CT) and positron emission tomography. The amount and quality of data has increased significantly with these technologies, which makes a number of standard image analysis techniques computationally intensive, time consuming and difficult to perform. Simon Warfield, PhD, director of the Computational Radiology Laboratory, and his group at Children's have developed a new high speed image processing algorithm that allows for the exact matching of two or more related images, which is a key requirement in many image analysis methods such as in 3D reconstruction of MRI, CT and ultrasound data, and the processing of movie sequences. The capabilities of this software were demonstrated using large transmission electron microscopy images, where the time it took to align two images was reduced from several days to a few minutes. This new algorithm will open new possibilities in neuroscience, disease modeling, surgical planning, intervention simulation and diagnosis, and it may be a key piece in the development of real-time technologies.



Daniel Kohane, MD, PhD

VACCINES

Children's Hospital Boston has been on the forefront of vaccine development since the 1940s and 1950s when Nobel Prize winner John Enders enabled the invention of the Salk and Sabin polio vaccines by creating a way to grow large amounts of virus outside the human body. Carrying on his tradition, Children's researchers, most in the building named after Dr. Enders, are working on modern vaccine research aimed at finding safe, highly effective and affordable vaccines. Ofer Levy, MD, PhD, associate physician in Medicine, and his group, led by Victoria Philbin, PhD, research fellow in Pediatrics, recently won research funding from the Bill and Melinda Gates Foundation for their work with Toll-like receptor agonists, which can be used as vaccine adjuvants to stimulate a more robust response to vaccinations in infants. In a neighboring lab, Richard Malley, MD, senior associate physician in Medicine, and Ying-Jie Lu, PhD, research fellow in Pediatrics, are creating multiple approaches to protect children worldwide with broadly protective and inexpensive *Streptococcus pneumoniae* vaccines. Drs. Lu and Malley also received a grant from the Bill and Melinda Gates Foundation to further their research on a novel fusion conjugate technology to enhance the systemic and mucosal immune responses to vaccine antigens. Stephen Harrison, PhD, chief of the Division of Molecular Medicine and a Howard Hughes Medical Institute investigator, is a pioneer in the field of structural biology and is using the increasingly sophisticated technologies for protein structure determination to design vaccines based on the shape of viral proteins. His work may lead to new platforms and methods for vaccine development to enhance their efficacy and safety. TIDO is exploring opportunities to further the development of these vaccine innovations to reach those in need worldwide.

"The advantage of a whole-cell vaccine is that it can broadly protect against all pneumococcal strains and would be very inexpensive to produce and administer," says Dr. Malley.

PATH-funded Whole Cell Vaccine for *Streptococcus Pneumoniae*

Through a partnership funded by PATH (an international nonprofit organization that is accelerating the development of safe, effective and affordable vaccines to protect children worldwide), Dr. Malley is making strides toward a safe, effective and inexpensive pneumococcal vaccine. *Streptococcus pneumoniae* kills about one million children each year, mostly from pneumonia but also from sepsis and meningitis. There are pneumococcal vaccines that protect children in the developed world, but less expensive vaccines are urgently needed to protect children in low income countries, where most pneumococcal deaths occur.

Dr. Malley, his group at Children's Hospital Boston and a team of vaccine development experts from around the world have created a unique whole cell pneumococcal vaccine, manufactured under GMP conditions at Instituto Butantan in Brazil, and are planning human trials in the U.S. within the next year. In contrast to Prevnar, which is effective in the developed world but covers only a minority of pneumococcal strains and is prohibitively expensive for the developing world, this vaccine will cost less than a dollar a dose and should cover all strains that cause disease in both the developed and the developing world.


Richard Malley, MD

HIV Vaccine

Dr. Harrison has dedicated his research to understanding the dynamic role of protein conformation in viral infections. He is a world renowned expert in protein structure


Ofer Levy, MD, PhD and Pablo Chao

DRUG DELIVERY PLATFORM SYSTEM

Wayne Lencer, MD, chief of the Division of Gastroenterology and Dan Chinnapen, PhD, fellow in Gastroenterology, have developed a platform system designed to aid drug delivery into cells. The permeability and half-life are often limiting factors in the development of new drugs, particularly large molecules. This technology exploits a pathway that a pathogen normally uses to direct intracellular trafficking of its toxin, harnessing it to enable safe macromolecular transport of drugs across mucosal epithelial barriers while increasing that drug's serum half-life. This invention could avoid the need for parenteral administration of large protein drugs and potentially overcome unintended side effects. Coupling therapeutic molecules to this delivery platform could enhance the therapeutic potential of new molecules.

determination, by X-ray crystallography and more recently through cryo-electron microscopy. Key proteins on virus particles alter their shape on contact with their target cell, a conformation shift that facilitates the entry of the virus into the cell. Antibodies that bind to the proteins as they exist in the virus particle are often ineffective in neutralizing the virus, i.e. stopping it from infecting cells. Conversely, antibodies that recognize the shifted protein conformation are often much better at preventing viral infection. This is particularly true of human HIV, where vaccines developed from the viral proteins have been notoriously bad at eliciting an antibody response that protects the vaccinated person against infection. Dr. Harrison and his colleague in the Division of Molecular Medicine, Bing Chen, PhD, assistant professor in Pediatrics, have developed strategies to lock HIV proteins into a form that induces strong neutralizing antibodies in hosts. The first approach involves forcing the HIV proteins into a conformation similar to the shifted form adopted during entry into the cell, which can be induced by the removal of a specific loop of the protein. The second approach comes from recognizing that the viral proteins naturally form trimers, three intertwined copies of the protein. Drs. Harrison and Chen have identified biochemically stable HIV-1 envelope trimers, which could act as more effective vaccines to induce protective antibodies.

BIOMARKERS

Pathologic and genetic biomarkers are increasingly important for both diagnosing disease and guiding treatment decisions. Personalized medicine, the tailoring of therapies to each individual's unique genetic background, depends on the understanding of the molecular markers that correlate with disease progression and predicted therapeutic efficacy. As an increasing number of molecular markers are found to be associated with positive outcomes from specific treatments, drugs that are developed in parallel with companion tests of these markers will have increased safety and efficacy.

The ability to discover a strong biomarker depends on access to both a robust array of patient samples and a detailed clinical understanding of each individual patient—Children's Hospital Boston has both. Interdisciplinary teams at Children's have used this rich data to discover several biomarkers for a number of different diseases; a few of these discoveries are highlighted below.

Diagnostic Markers for Urologic Chronic Pelvic Pain Syndrome

Urologic chronic pelvic pain syndrome (UCPPS) is a debilitating condition characterized by recurring pain in the bladder and the surrounding pelvic region, often accompanied by voiding and sexual dysfunction. Currently there are 12 million men and women in the U.S. with UCPPS, yet there are no reliable, definitive diagnostic tests available. Since other conditions can produce similar symptoms, UCPPS is currently diagnosed by using an exclusion method. Jordan Dimitrakov, MD, PhD, staff scientist in Urology, and colleagues have identified 16 proteins that are differentially expressed in the urine and serum samples of patients with UCPPS. These proteins have the potential to become diagnostic and therapeutic biomarkers for this condition. This technology could be translated into a noninvasive lab test to diagnose and then adequately treat patients with UCPPS. TIDO has built a patent portfolio around these markers and an exclusive license is available.

Prosaposin as a Biomarker of Metastasis

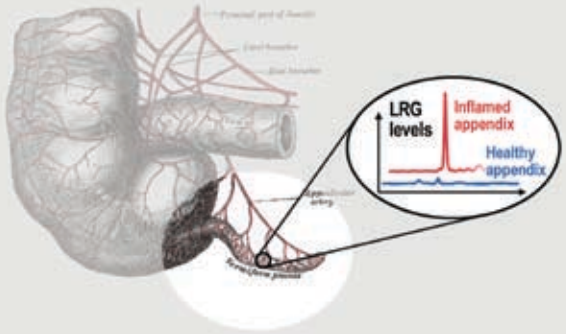
Metastasis, the migration of cancer cells to other parts of the body, accounts for 90 percent of deaths in cancer patients and there is no approved therapy for inhibiting the process or effectively treating patients with advanced metastatic disease. Randolph Watnick, PhD, research associate in the Vascular Biology Program, has isolated a protein called prosaposin that makes distant organs refractory to metastases by causing the production of factors that block the growth of blood vessels. He found that cells from localized prostate and breast tumors, which didn't metastasize, secreted high levels of prosaposin, while metastatic tumors secreted very little. These findings could translate into a diagnostic test that would correlate the level of prosaposin to survival in cancer patients. Also, prosaposin itself could be added to standard cancer therapies to repress metastasis. TIDO has filed


Randolph Watnick, PhD

patents on both of these applications and is actively marketing this discovery. This project is a recipient of a Technology Development Fund Award that will focus on demonstrating the efficacy of prosaposin and its derivatives against tumor growth.

Highly Sensitive Diagnostic Test for Acute Appendicitis

Appendicitis is the most common childhood surgical emergency, but the diagnosis can be challenging, often leading to either unnecessary surgery when appendicitis isn't present, or a ruptured appendix and serious complications when the condition is missed. The consequences of misdiagnosis are severe, and increasingly expensive diagnostic tests have become the standard of care.



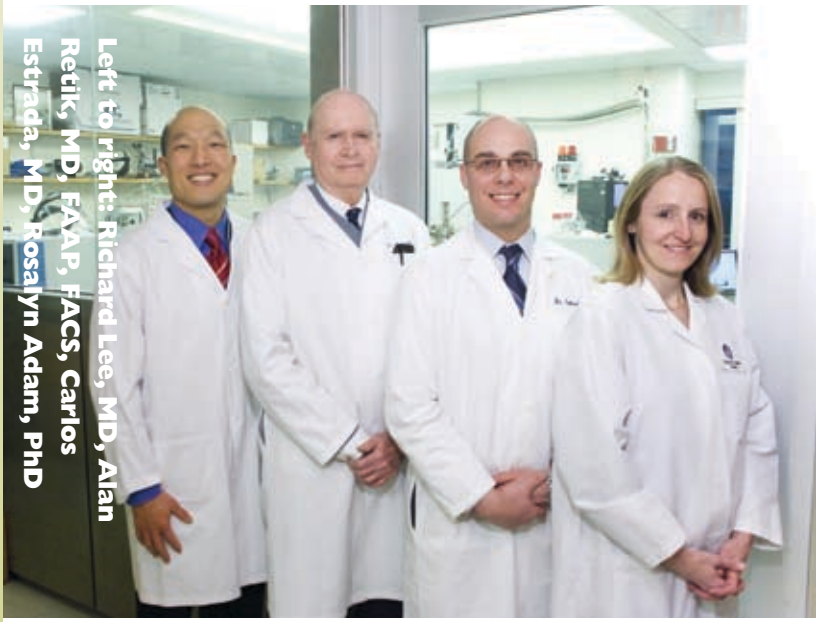
A protein biomarker in urine, called LRG, was elevated in patients with appendicitis.

In a collaborative project between Emergency Medicine and the Proteomics Center at Children's, Alex Kentsis, MD, PhD, fellow in Hematology/Oncology, Richard Bachur, MD, chief of Emergency Medicine, and Hanno Steen, PhD, director of the Proteomics Center, have identified protein biomarkers in patient urine that distinguish acute appendicitis from other conditions. The marker discovery was based on deep proteomic analysis of patient urine, assessing over 2,000 proteins by mass spectroscopy. The strongest single biomarker, leucine-rich alpha-2-glycoprotein (LRG), showed a tremendous increase in abundance during the progression of appendix inflammation. With an award from Children's Technology Development Fund, the team will translate the LRG test to an antibody based platform, and will further validate this biomarker for appendicitis. The clinical laboratory and point-of-care immunoassay tests would be valuable in reducing expensive diagnostic scans, unnecessary surgeries and the number of cases that progress to rupture before surgery, all leading to improved patient outcome.

DEPARTMENT HIGHLIGHTS

UROLOGY

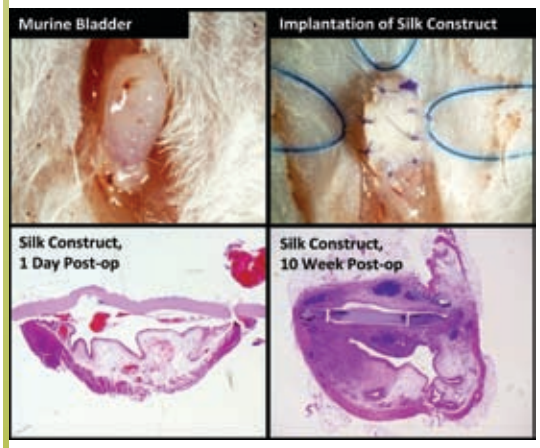
Under the direction of Alan Retik, MD, FAAP, FACS, urologist-in-chief, clinicians and researchers in the Department of Urology at Children's Hospital Boston are working to provide a new basic understanding of the genitourinary tract, which has been poorly studied in comparison to other organ systems. As the largest pediatric urology service in the world, the department performs 3,100 surgical procedures and cares for 18,000 children each year. The team's fundamental knowledge of urological tissues and its access to a large patient population is paving the way for innovative therapies for a variety of common and rare illnesses affecting patients.



Left to right: Richard Lee, MD, Alan Retik, MD, FAAP, FACS, Carlos Estrada, MD, Rosalyn Adam, PhD

Silk-based Tissue Engineering Method for Bladder Repair

In addition to his clinical responsibilities, Carlos Estrada, MD, assistant in Urology, is conducting cutting-edge tissue engineering research with a focus on bladder repair. Recent regenerative medicine approaches using conventional biomaterials, the patients' own smooth muscle cells and the cells lining the bladder have had some success. Dr. Estrada and Joshua Mauney, PhD, research fellow in Urology, have shown that silk scaffolds support bladder augmentation and the maintenance of organ functionality in a defect mouse model. Silk is thought to provide an exceptional combination of physical characteristics that are well suited to support bladder function and are readily amenable to modifications that encourage appropriate degradation and integration into host tissue. Drs. Estrada and Mauney are currently working on moving their technology into large animal models and focusing on optimizing the ideal source of cells for the bladder augmentation. TIDO is looking for an industry partner to help move this technology forward.



Novel Urinary Markers of Urinary Tract Obstruction and Vesicoureteral Reflux

The research interests of Richard Lee, MD, assistant in Urology, are in the field of urinary proteomics and biomarker discovery. In particular, Dr. Lee is focusing on identifying clinically significant urinary markers of urinary tract obstruction (UTO) and vesicoureteral reflux (VUR). Currently, five to seven percent of all prenatal ultrasounds identify findings consistent with possible UTO or VUR. Unfortunately, there are no appropriate guidelines or indicators to determine which children are at risk for renal damage or who should be tested, and postnatal tests are invasive and involve radiation. These biomarkers will be helpful in determining which children with these conditions require either surgical or medical intervention or observation. Through his research, Dr. Lee has developed a translational platform for discovery based quantitative urinary proteomics. Additionally, through his clinical interactions, he has assembled a unique pediatric urinary specimen repository. TIDO is looking for a development partner to translate this discovery into a product for the benefit of patients.

Growth Factor Function in Prostate and Bladder Conditions

Rosalyn Adam, PhD, associate director of Urology Research, studies growth factor function and mechanical signaling in urologic diseases. She and her colleagues have identified novel functions for heparin-binding epidermal growth factor-like growth factor in prostate and bladder cancers. Dr. Adam is also interested in understanding the regulation of gene expression in bladder smooth muscle cells exposed to mechanical stretch and growth factor stimulation. These studies relate to the mechanisms underlying pathologic remodeling of the bladder wall that leads to voiding dysfunction. Dr. Adam and Aruna Ramachandran, PhD, post doctoral fellow in Urology, have recently shown distension-induced expression of thrombomodulin in a rat model of bladder stretch injury and have shown for the first time, the ability of thrombomodulin to regulate smooth muscle cell migration, a hallmark of smooth muscle remodeling. Their ultimate goal is to identify critical signaling pathways that could be potential targets for therapeutics. Dr. Adam is interested in industry sponsored research with a company working in the field of urology.

CARDIOLOGY

The Department of Cardiology, led by James Lock, MD, cardiologist-in-chief, participates in clinical research activities as well as laboratory research. David Clapham, MD, PhD, is the chief of the Basic Cardiovascular Research Laboratories. Research in the Department of Cardiology involves many focus areas including cardiovascular genetics, electrophysiology, arrhythmias and implantable devices for heart defects. These research areas impact both pediatric and adult patient populations. Featured below are two technologies that illustrate the department's commitment to bringing laboratory discoveries to the patient.

Protein Treatment Repairs Heart Damage

The laboratory of Bernhard Kühn, MD, associate in Cardiology, is developing protein therapies to stimulate the regeneration of adult heart muscle cells. Following a heart attack, healthy heart muscle cells are unable to grow to replace damaged heart muscle cells and there are no existing therapies to regenerate these lost cells. This loss of cardiac muscle cells can lead to heart failure. Dr. Kühn and colleagues have demonstrated that two different proteins, periostin peptide and neuregulin1, can reawaken the heart's dormant regenerative capacity. In their animal studies of induced myocardial infarction, they have shown that hearts treated with periostin peptide or neuregulin1 had enhanced heart muscle cell proliferation and improved heart function (*Nature Medicine* 2007; 13:962-969; *Cell* 2009; 138:257-270). Dr. Kühn's research offers two potential therapies for the heart regeneration toolbox. "Although many efforts have focused on stem cell based strategies, our work suggests that stem cells aren't required and that stimulating differentiated cardiomyocytes to proliferate may be a viable alternative," says Dr. Kühn.


Bernhard Kühn, MD

Diagnosing Heart Failure

The laboratory of William Pu, MD, assistant in Cardiology, is developing improved diagnostic approaches for heart failure. There are different types of heart disease that can lead to heart failure, but diagnosing the various types of these diseases can be a complicated process. Using three types of human heart samples, Dr. Pu studied the expression profile of microRNAs to determine if there is a difference in levels. MicroRNAs are short pieces of RNA whose main function is to downregulate gene expression, and it's known that altered levels of microRNAs are associated with other diseases such as cancer. Dr. Pu's study determined that many microRNAs had a different expression profile in the heart disease samples compared to control samples. Further, the altered expression patterns correctly grouped samples by type of heart disease. Therefore, different types of heart disease are associated with distinct changes in microRNA expression, which may be able to serve as a new approach for diagnosing heart disease.

APPENDIX I SUMMARY OF TECHNOLOGY TRANSFER ACTIVITY FY04–FY09

INVENTION DISCLOSURES

	2004	2005	2006	2007	2008	2009
TOTAL	118	98	98	94	116	128

ALL AGREEMENTS NEGOTIATED

	2004	2005	2006	2007	2008	2009
Exclusive licenses	7	5	8	7	5	10
Non-exclusive licenses	4	13	16	19	14	16
Options	8	3	3	3	3	2
TOTAL	**19**	**21**	**27**	**29**	**22**	**28**
Agreements involving the receipt of equity	1	0	0	1	1	2
Amendments	4	2	5	4	9	9
Corporate sponsored research / collaborations	10	17	11	18	9	8
Material transfer	203	261	285	398	603	617
Confidentiality	75	95	80	64	74	71
Inter-institutional invention administration	11	8	11	11	4	14
Other	5	12	5	6	4	6

GROSS REVENUE ($ MILLIONS)

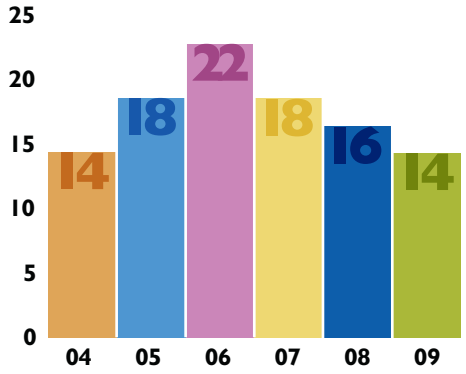
	2004	2005	2006	2007	2008	2009
TOTAL	14.1	17.6	22.4	18.1	16.3	14.3

PATENT APPLICATIONS

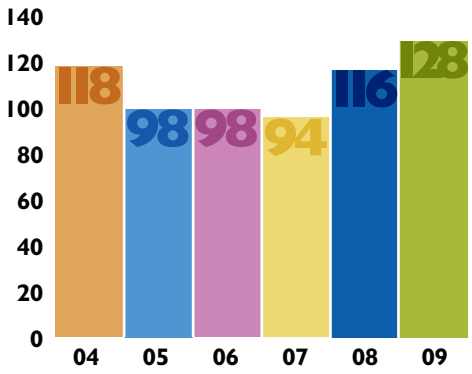
	2004	2005	2006	2007	2008	2009
Provisionals filed	54	54	49	47	69	63
PCTs filed	14	30	25	24	26	33
U.S. filed	41	50	49	33	30	44
Foreign filed	33	31	27	18	22	29

APPENDIX 2 6-YEAR TREND OF TECHNOLOGY TRANSFER ACTIVITY

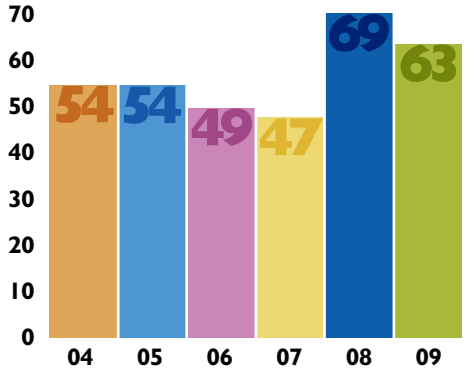
GROSS REVENUE ($ MILLIONS)



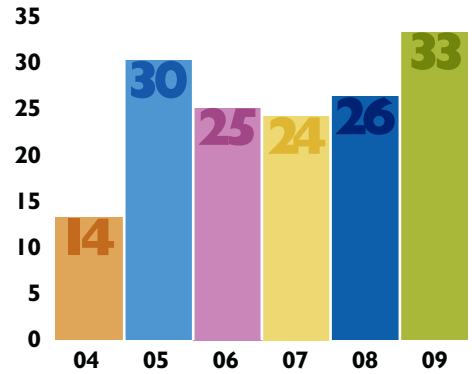
INVENTION DISCLOSURES



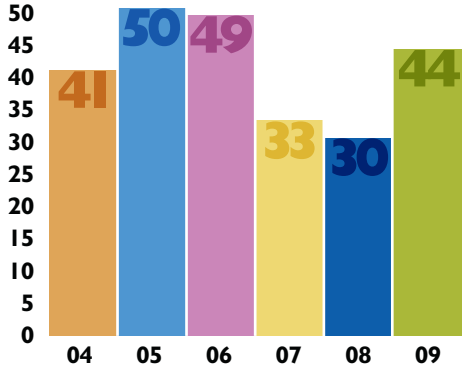
PROVISIONALS FILED



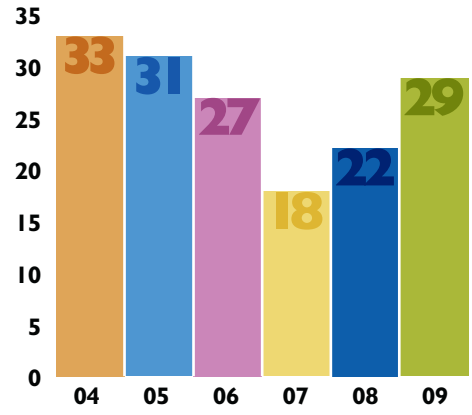
PCTs FILED



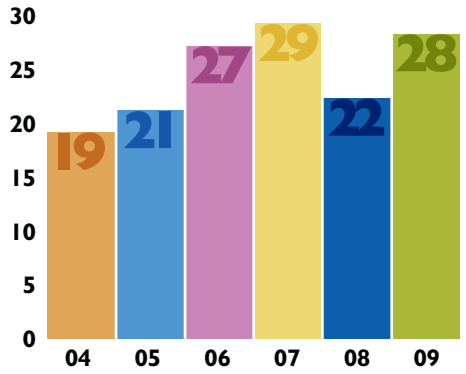
U.S. PATENTS FILED



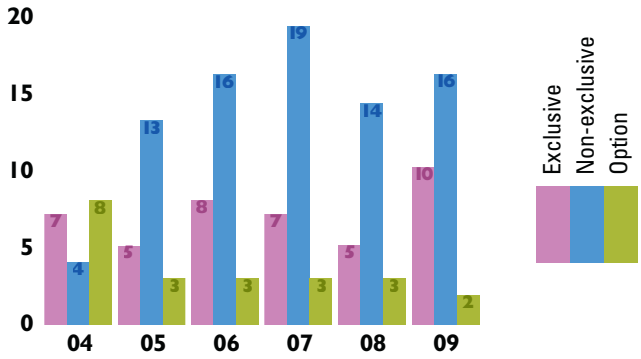
FOREIGN APPLICATIONS FILED



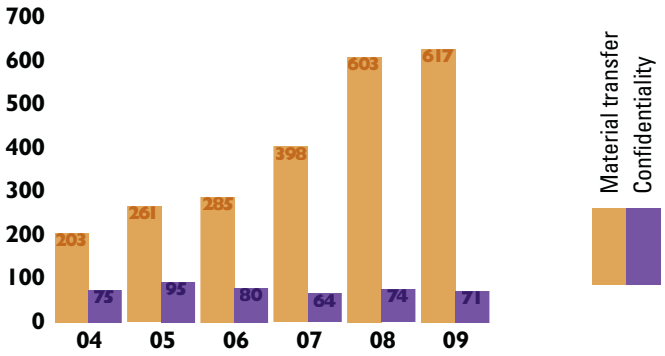
LICENSES & OPTIONS GRANTED



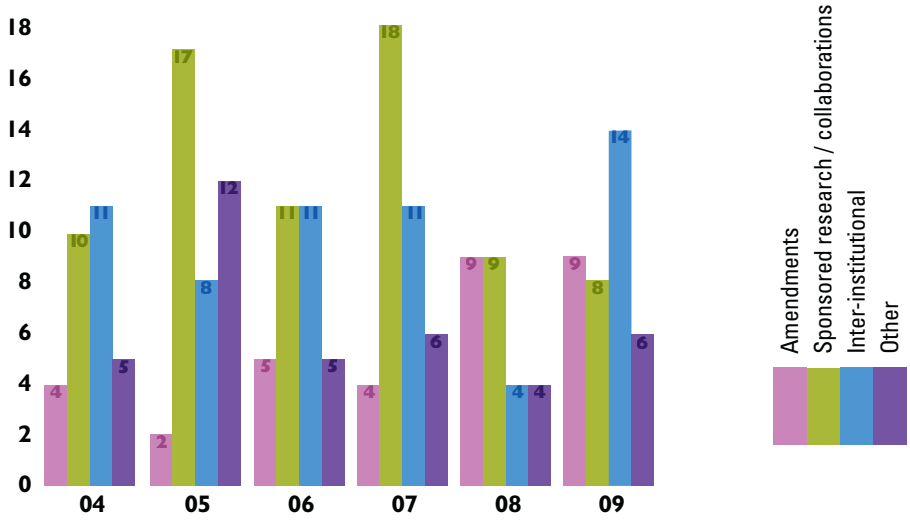
BREAKDOWN OF LICENSE & OPTION AGREEMENTS



NON-LICENSE AGREEMENTS MATERIAL TRANSFER & CONFIDENTIALITY



NON-LICENSE AGREEMENTS OTHER



APPENDIX 3 U.S. PATENTS ISSUED FY09

LEAD INVENTOR	ISSUE DATE	PATENT NUMBER	APPLICATION TITLE
Moses, Marsha	10/07/08	7,432,066	Non-invasive enzyme screen for tissue remodeling associated conditions
D'Amato, Robert	10/14/08	7,435,745	Methods and compositions for inhibition of angiogenesis
He, Zhigang	11/11/08	7,449,442	EGFR inhibitors promote axon regeneration
Solomon, Keith	11/11/08	7,449,453	Compositions of ezetimibe and methods for the treatment of cholesterol-associated benign and malignant tumors
Moses, Marsha	11/18/08	7,452,866	Methods of inhibiting angiogenesis with fragments and homologs of troponin subunit 1
Lock, James	12/30/08	7,470,285	Transcatheter delivery of a replacement heart valve
Vacanti, Joseph	12/30/08	7,470,425	Population of undifferentiated neural, endocrine or neuroendocrine cells in a hydrogel support
Madsen, John	01/13/09	7,476,726	Method of producing and purifying endostatin protein
Folkman, M. Judah	02/03/09	7,485,739	Catalyst system
Ingber, Donald	02/24/09	7,494,482	Methods and apparatus for application of micro-mechanical forces to tissues
Folkman, M. Judah	02/24/09	7,495,089	Therapeutic antiangiogenic endostatin compositions
Zon, Leonard	04/21/09	7,521,055	Ferroportin1 antibodies and methods
Harrison, Stephen	04/28/09	7,524,624	Druggable regions in the dengue virus envelope glycoprotein and methods of using the same
He, Zhigang	04/28/09	7,524,640	Inhibiting Smad2/3 signaling promotes neurite outgrowth in dorsal root ganglia
Folkman, M. Judah	04/28/09	7,524,811	Anti-angiogenic peptides from the N-terminus of endostatin
Puder, Mark	05/05/09	7,527,123	Patient-friendly stethoscope
Brugnara, Carlo	05/12/09	7,531,573	Use of triaryl methane compounds for inhibiting unwanted cellular proliferation
Lencer, Wayne	06/16/09	7,547,436	Receptor specific transepithelial transport of therapeutics
Atala, Anthony	08/04/09	7,569,076	Bladder reconstruction
Atala, Anthony	08/11/09	7,572,221	Reconstructing non-cartilage structural defects
Butte, Atul	08/18/09	7,576,052	Methods and compositions for modulating adipocyte function

APPENDIX 4 FOREIGN PATENTS ISSUED FY09

LEAD INVENTOR	COUNTRY	ISSUE DATE	PATENT NUMBER	APPLICATION TITLE
Atala, Anthony	Canada	10/7/08	2307637	Penile reconstruction
D'Amato, Robert	Canada	10/8/08	2331461	Analogs of 2-phthalimidinoglutaric acid and their use as inhibitors of angiogenesis
Folkman, M. Judah	Mexico	10/10/08	261255	Angiostatin fragments and method of use
D'Amato, Robert	Austria	10/15/08	1640009	Estrogenic compounds as antimitotic agents (2-MOE)
D'Amato, Robert	Belgium	10/15/08	1640009	Estrogenic compounds as antimitotic agents (2-MOE)
D'Amato, Robert	Switzerland	10/15/08	1640009	Estrogenic compounds as antimitotic agents (2-MOE)
D'Amato, Robert	Germany	10/15/08	1640009	Estrogenic compounds as antimitotic agents (2-MOE)
D'Amato, Robert	Denmark	10/15/08	1640009	Estrogenic compounds as antimitotic agents (2-MOE)
D'Amato, Robert	Spain	10/15/08	1640009	Estrogenic compounds as antimitotic agents (2-MOE)
D'Amato, Robert	France	10/15/08	1640009	Estrogenic compounds as antimitotic agents (2-MOE)
D'Amato, Robert	United Kingdom	10/15/08	1640009	Estrogenic compounds as antimitotic agents (2-MOE)

LEAD INVENTOR	COUNTRY	ISSUE DATE	PATENT NUMBER	APPLICATION TITLE
D'Amato, Robert	Greece	10/15/08	1640009	Estrogenic compounds as antimitotic agents (2-MOE)
D'Amato, Robert	Ireland	10/15/08	1640009	Estrogenic compounds as antimitotic agents (2-MOE)
D'Amato, Robert	Italy	10/15/08	1640009	Estrogenic compounds as antimitotic agents (2-MOE)
D'Amato, Robert	Luxembourg	10/15/08	1640009	Estrogenic compounds as antimitotic agents (2-MOE)
D'Amato, Robert	Monaco	10/15/08	1640009	Estrogenic compounds as antimitotic agents (2-MOE)
D'Amato, Robert	Netherlands	10/15/08	1640009	Estrogenic compounds as antimitotic agents (2-MOE)
D'Amato, Robert	Portugal	10/15/08	1640009	Estrogenic compounds as antimitotic agents (2-MOE)
D'Amato, Robert	Sweden	10/15/08	1640009	Estrogenic compounds as antimitotic agents (2-MOE)
Folkman, M. Judah	Australia	10/23/08	2003230852	Polymer therapeutics of angiogenesis inhibitors: HPMA copolymer-TNP 470 conjugate
Folkman, M. Judah	France	10/29/08	1668129	Endostatin peptides: requirements for retention of anti-tumor properties
Folkman, M. Judah	Germany	10/29/08	1668129	Endostatin peptides: requirements for retention of anti-tumor properties
Folkman, M. Judah	Ireland	10/29/08	1668129	Endostatin peptides: requirements for retention of anti-tumor properties
Folkman, M. Judah	Switzerland	10/29/08	1668129	Endostatin peptides: requirements for retention of anti-tumor properties
Folkman, M. Judah	United Kingdom	10/29/08	1668129	Endostatin peptides: requirements for retention of anti-tumor properties
Adamis, Anthony	Germany	11/5/08	1140172	Methods for the prevention and treatment of retinal ischemia and edema
Adamis, Anthony	France	11/5/08	1140172	Methods for the prevention and treatment of retinal ischemia and edema
Adamis, Anthony	Ireland	11/5/08	1140172	Methods for the prevention and treatment of retinal ischemia and edema
Adamis, Anthony	Switzerland	11/5/08	1140172	Methods for the prevention and treatment of retinal ischemia and edema
Adamis, Anthony	United Kingdom	11/5/08	1140172	Methods for the prevention and treatment of retinal ischemia and edema
D'Amato, Robert	Luxembourg	11/6/08	91471	Methods and compositions for inhibition of angiogenesis
Lipton, Stuart	Canada	11/18/08	2143752	Method of preventing NMDA receptor-mediated neuronal damage
D'Amato, Robert	Italy	12/18/08	0688211	Methods and compositions for inhibition of angiogenesis
Atala, Anthony	Australia	1/8/09	2002363659	Human amniotic fetal stem cells
Atala, Anthony	Canada	1/20/09	2307567	*De novo* creation of functional bladders
Zetter, Bruce	United Kingdom	2/4/09	1948213	Methods to predict and prevent resistance to taxoid compounds
Zetter, Bruce	France	2/4/09	1948213	Methods to predict and prevent resistance to taxoid compounds
D'Amato, Robert	Greece	2/18/09	8000289	Methods and compositions for inhibition of angiogenesis
Atala, Anthony	Japan	3/27/09	4282233	Corporal cavernosal tissue for penile reconstruction
D'Amato, Robert	Denmark	3/30/09	0688211	Methods and compositions for inhibition of angiogenesis
Atala, Anthony	Switzerland	4/30/09	1292249B	*Ex vivo* engineered stents for urethral structures
Lencer, Wayne	Australia	5/21/09	2003232081	Receptor specific transepithelial transport of therapeutics
Klagsbrun, Michael	Japan	5/22/09	4312955	Soluble inhibitors of vascular endothelial growth factor and use thereof
Solomon, Keith	New Zealand	6/11/09	538498	Compositions of ezetimibe and methods for the treatment of cholesterol-associated benign and malignant tumors
Atala, Anthony	Japan	6/26/09	4330995	Human amniotic fetal stem cells
Atala, Anthony	Canada	7/14/09	2289038	Systems and methods for promoting tissue growth
D'Amato, Robert	Ireland	8/11/09	1768/92	Methods and compositions for inhibition of angiogenesis

QUESTION AND ANSWER WITH GARY FLEISHER, MD

Gary Fleisher, MD, is the chairman of the Department of Medicine, physician-in-chief and pediatrician-in-chief at Children's Hospital Boston. He treats patients in the Emergency Department and inpatient medical units. Dr. Fleisher graduated from Jefferson Medical College in 1973 and trained in pediatrics and pediatric infectious diseases at the Children's Hospital of Philadelphia until 1979. Subsequently, he achieved board certification in Pediatrics, Emergency Medicine, Pediatric Emergency Medicine and Pediatric Infectious Diseases. He remained on the faculty at the University of Pennsylvania until 1986, at which point he came to Children's Hospital Boston to be the chief of the Division of Emergency Medicine. In 2002, Dr. Fleisher was appointed the chair of the department. We had the rare opportunity to sit down with Dr. Fleisher and ask him a few questions related to innovation at Children's.

Gary Fleisher, MD

How has innovation impacted your own career as a clinician?

I guess I would look at innovation in my career in 2 parts: innovations I have been involved with and then those that have changed my practice. In terms of innovations in which I have played a direct role, I think the major one for me is the fact that I practice pediatric emergency medicine, which was not a specialty when I graduated medical school and was not a specialty when I finished residency. I was privileged to be able to start the first program in emergency pediatric medicine, begin the first fellowship, write the first text book, edit the first journal, work with the American Board of Pediatrics to start the certification process, initiate several lines of research in the field and train many individuals who have gone far beyond me in terms of research and innovation.

If you look at the impact of innovation on a disease specific basis in pediatric emergency medicine, there are a few areas that have changed dramatically. When I started out in the field, I had a lecture I put together on life threatening infections. It covered four infections, three of which for all practical purposes no longer occur, either because we have vaccines to prevent them or we have developed ways to detect them in their incipient stages and prevent the evolution into full blown disease. One is bacterial meningitis, which has gone from 30,000–40,000 cases a year down to 1,000–2,000 cases. Initially through some of the work I did, we were able to identify children who had bacteria in their bloodstream that were at risk for developing meningitis and then brought forth therapies to prevent that process from occurring.

The whole field of single dose therapies for infections has emerged over the last two decades. Some of the studies were my own but many researchers and clinicians have contributed. For a number of the diseases we treated, we had to write a prescription and depend upon the patient to follow a therapeutic regimen for a week to 10 days. Now we have single dose antibiotics that we give orally or intravenously and eradicate some of these diseases within the confines of a single visit.

The whole field of antiviral therapy has grown up in the past 25-30 years. Diseases such as herpes simplex encephalitis, neonatal herpes simplex, and varicella (chicken pox), which were untreatable when I started, are now managed with appropriate antiviral agents. There are a whole group of patients to which we

used to have to say to the parents, "we can only provide supportive therapy," where now we have specific treatments we can offer to them. Some of these drugs are life saving and, if not life saving, at least prevent most major complications.

What are the current trends and future directions that you see in pediatric medicine and what do you think their impact will be on clinical practice?

I think there are several trends going on and they are driven by some very basic factors. One is the explosion of knowledge—no one physician can know everything about pediatrics, and even in a subspecialty—gastroenterology, cardiology, or endocrinology—no one physician can have full command of all the different disease processes and treatments. We are increasingly seeing complex patients with multiple medical problems who are technology dependent—much more than when I began 30 years ago. In order to really care for the full spectrum of children, you have to have a number of subspecialists with varying expertise in each discipline.

The other factor is the increase in technology. More and more imaging modalities and interventional approaches are coming online. These are expensive and you have to have physicians who are trained in utilizing the technology or interpreting the data that comes from its application. In the long term, I think these two factors, the expansion of the knowledge base and the march of technological innovation, are producing a centralization of pediatric care.

In modern medicine, we really depend on the people around us and the milieu. Clinical care has really become much more of a team sport. For instance in my practice, I rely heavily on the nurses, on colleagues in other disciplines, on the facilities, and on additional services such as radiology and the laboratory, and I think Children's provides the ideal environment. Particularly I think the nursing staff is absolutely superb.

How does this team culture inspire discoveries and innovations that improve healthcare?

In a team based environment, collaboration and crosstalk is often a source of innovation. Every individual on a team can bounce ideas off others and sometimes the perspective of an individual in another discipline really stimulates you to think creatively about issues that are more germane to the work that you do.

Children's has committed resources to support technology development and translational research. In your opinion, why are these important to support?

Children's has long supported innovation and all of us, both on the administration and medical/scientific side of the equation, have considered the pursuit of innovation to be paramount. Having said that, it is becoming even more important—actually essential—that we provide the resources. We need to have the proper spectrum of specialists and subspecialists and the right technologies to take care of children with complex diseases. If we are going to do our best job, we have got to be innovative. We are going to continue to be faced with situations for which there are no treatments and with families who have exhausted the resources at other institutions. The onus falls on us to be innovative and provide new forms of care. I think it is a clinical imperative. It is somewhat paradoxical that there have been so many advances in medicine yet so many diseases remain where we have no effective treatments or the treatments are only partially satisfactory. And I think that is our challenge—to try to innovate in those areas and advance the therapies to the next stage.

"If we are going to do our best job, we have got to be innovative."

In addition to licensing inventions at Children's, TIDO works to establish collaborations with company partners around our research and clinics. How does collaborating with corporate partners support Children's mission?

In academic medicine and academic pediatrics, we develop ideas and often perform the initial research and some of the testing in the process of advancing innovations. We seldom, or even perhaps never, bring a product all the way to market. So partnership with industry, with the pharmaceutical companies or medical device makers, is essential for us to fulfill our mission. I have been involved with several stages of that process and found collaboration key to complete all the steps and to offer children new therapies. Moving forward, I think it is an avenue we have to pursue more extensively if we want to innovate to the point of bringing more new treatments to the patients.

What advice would you give to clinicians, particularly those beginning their careers, about the importance of innovation to clinical care?

I would advise trainees and junior faculty not to be satisfied with the status quo. Always be thinking about and looking for new approaches to treat diseases.

TECHNOLOGY & INNOVATION
DEVELOPMENT OFFICE

Children's Hospital Boston
300 Longwood Avenue
Boston, Massachusetts 02115

617.919.3019

TIDO@CHILDRENS.HARVARD.EDU

WWW.CHILDRENSINNOVATIONS.ORG