INTELLECTUAL PROPERTY OFFICE

2007 ANNUAL REPORT

GROWING INVENTION

Children's Hospital Boston

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LETTER FROM THE DIRECTOR

Children's Hospital Boston initiated a number of changes in FY07 that demonstrate its ongoing commitment to translate our world class laboratory and clinical research into products that can positively impact patient care and outcomes. It is with this mission in mind, and with the retirement of Brenda Manning, PhD, former director of licensing, that I accepted the position of Director of Technology and Business Development at Children's in September 2007. By bringing in new resources, services and expertise around business development and technology development to complement patenting and licensing activity—Children's is actively addressing the changes in the commercial sector and the challenges they pose to our mission of bringing new diagnostics and treatments to patients.

One challenge that we continue to face is the expanding developmental gap between the stage of technology/intellectual property arising from research hospitals and academic institutions and the stage at which companies or investors take on and invest capital in R&D for such programs. Children's has made a commitment to address this gap through new initiatives that will invest in translational research and technology development.

In order to further break down walls between innovation and translation, Children's is on a track to become more proactive and creative in all of its interactions with industry. By increasing collaborations with industry and foundations at all stages of research and development we believe we are serving our mission to bring devices, diagnostics and treatments to patients more rapidly.

Implementing a new organizational structure while continuing to expand and improve resources and expertise around technology and business development will be our focus in 2008.

As 2008 begins with eager anticipation and enthusiasm for the changes ahead—it is tempered by the loss we feel from Dr. Judah Folkman's passing. Dr. Folkman's pioneering work in the field of angiogenesis created a novel modality of treatment for cancer and other non-neoplastic diseases. He appreciated the interplay between clinical observations, laboratory research, intellectual property and commercial collaboration in order to fully develop a product that could benefit patients. It is in that spirit that we will continue to work to bring down barriers and find creative solutions to speed and maximize this process.

Erik Halvorsen, PhD

IPO ACTIVITIES

Invention disclosures

The Intellectual Property Office (IPO) received 94 new invention disclosures from Children's Hospital Boston faculty and staff, a number that has been relatively constant over the last several years.

FY07 DATA SUMMARY

Invention disclosures	94
Patent applications filed	122
Provisional applications filed	47
PCT applications filed	24
US applications filed	33
Foreign applications filed	18
Patents issued	55
US patents issued	16
Foreign patents issued	39
Licenses and options granted	29
Gross revenues ($M)	18.06
Net revenue (total revenue less $ distributed to other institutions; $M)	12.18
Revenue from new licenses and options ($M)	0.38

Patent filings

The IPO oversaw the filing of 122 patent applications over the course of the year. Forty-seven provisional patent applications were filed. Twenty-four applications were filed for US and foreign rights under the Patent Cooperative Treaty (PCT) mechanism. Thirty-three applications were filed in the US and 18 patent applications were filed in individual foreign countries.

Patent issuances

Children's was granted 16 patents by the US Patent and Trademark Office and 39 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.

Licensing activity

The IPO negotiated 29 license and option agreements for Children's technologies: seven exclusive licenses, 19 non-exclusive licenses and three options. The revenue recognized from these new license and option agreements was $376,000. The IPO's overall performance and licensing and patenting activities over the past five years are illustrated in Appendices 1 and 2.

Distribution of licensing revenue

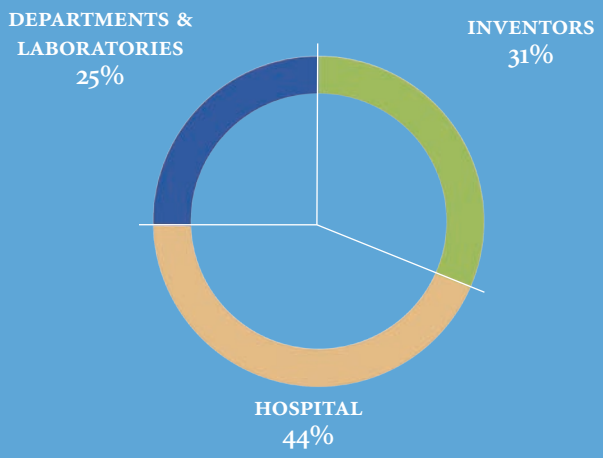
Gross revenue received from all licenses was $18.06 million, a 19 percent decrease from the FY06 revenues of $22.35 million. Of the 179 active license agreements, 66 generated revenue in FY07. Twenty-six of these 66 licenses brought in less than $10,000 each, but four produced over $1 million each. The net revenue received by Children's was $12.18 million, which is $18.06 million in gross revenue less $5.88 million distributed to other institutional co-owners. Of the $12.18 million in net revenue, $3.8 million was

"The Intellectual Property Office at Children's Hospital Boston is responding to the commercial preference for later stage technology in the context of a decreasing research funding environment by increasing business development activity geared towards ***bringing innovation and translation closer together.*** *The addition of a technology development fund to accelerate the development of Children's innovations demonstrates the institutional commitment to bringing new products to the market and impacting the lives of children and their families."*

- Neil Exter, Third Rock Ventures

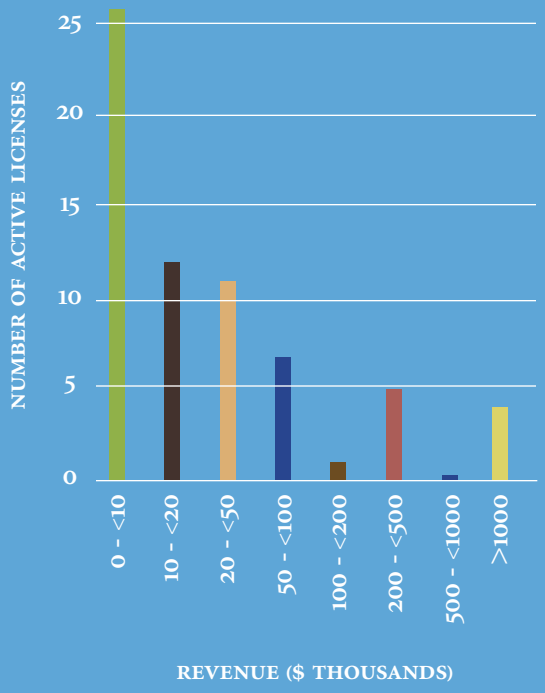
distributed to inventors and $3.0 million was distributed to the inventors' departments and laboratories. The remaining $5.4 million to the hospital was apportioned to the general research endowment, unrecovered legal expenses and the IPO's operations.

NET LICENSING REVENUE DISTRIBUTION FY07: $12.18 MILLION

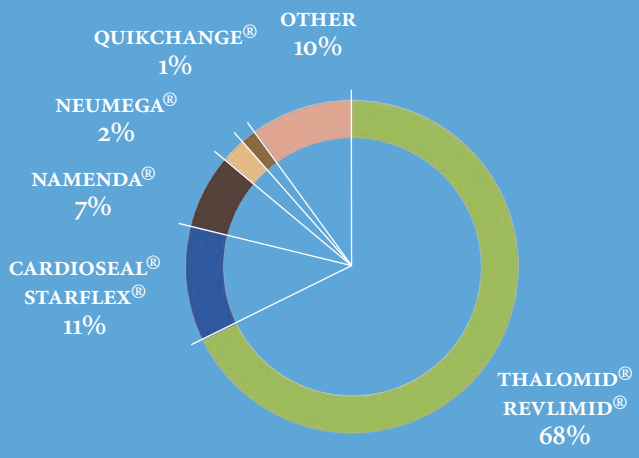


INVENTORS	DEPARTMENTS	HOSPITAL	TOTAL
$3,799,414	$3,002,685	$5,375,473	$12,177,152

REVENUE-GENERATING LICENSES FY07



SOURCES OF LICENSE REVENUE



Significant revenue-generating inventions

Sixty-eight 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; and Neumega®, which stimulates platelet production and is used in combination with chemotherapy by cancer patients.

Invention management activity

At the end of FY07, the IPO had 448 inventions under active management. Working with David Altman, marketing support specialist, 145 of these inventions were in marketing campaigns. Licensing managers monitored 179 ongoing license agreements, and coordinated the activities of outside patent attorneys to manage 1,083 pending patent applications on 246 inventions and maintain 739 issued US and foreign patents.

Inventions under active management	448
Inventions under initial evaluation	47
Inventions in marketing campaigns	145
Inventions in IPO development	13
Inventions with license pending	7
Licensed inventions	181
Inventions with other institute leading	55
Current licenses	179
Issued US patents	365
Issued foreign patents	374

LICENSING HIGHLIGHTS

Alliance between the research group of Judah Folkman, MD, at Children's Hospital Boston and Ortho-Clinical Diagnostics, Inc. (OCD), a Johnson & Johnson company

The relationship, beginning in December 2006, involves a license and sponsored research around the development of the platelet angiogenesis proteome. The Children's team had discovered that the profile of angiogenic and antiangiogenic proteins in blood platelets changes in the presence of microscopic-sized malignant tumors. Results in mice suggested that the analysis of the platelet proteome can be a powerful diagnostic tool to diagnose cancer at a very early stage, before the tumor can be visualized by any presently used clinical imaging method. Dr. Folkman's group and OCD have joined forces to prove the principle in humans, to develop the technology and eventually distribute testing kits for clinical use both in the US and abroad. Since the tests would be based on the detection of angiogenic and antiangiogenic proteins, similar tests could be developed for other angiogenic diseases besides cancer, including diabetic retinopathy, macular degeneration and endometriosis. Dr. Folkman was the director of Children's Vascular Biology Program until his recent passing. Robert D'Amato, MD, PhD, is continuing with the development of the project. The role of the IPO has been to do the management of the intellectual property portfolio and the execution and monitoring of the license. The IPO has been collaborating with the Clinical Trials Office at Children's to execute the sponsored research agreement, monitor compliance with that agreement and to do the ancillary agreements necessary for the development of the project.

New antiangiogenic drugs: Caplostatin™ and Lodamin™

The intellectual property portfolios for Caplostatin™ and Lodamin™ were optioned in September 2007 to SynDevRx™, Inc., a Cambridge-based start-up company. Caplostatin™ and Lodamin™ are two new drugs developed in the laboratory of Dr. Judah Folkman, based on the conjugation of an analog of the compound TNP-470 attached to tumor targeting nano-particles.

TNP-470, based on a discovery by Donald Ingber, MD, PhD, new interim co-director of the Vascular Biology Program, and developed by Takeda Chemical Industries Ltd in the 1990s, is a semi-synthetic analogue of an antibiotic isolated from fungal cultures. TNP-470 is very effective against a broad spectrum of cancers and showed significant effects in previous

clinical trials, including complete tumor remissions. However, its clinical use was abandoned after some reversible neurotoxicity was observed.

In order to eliminate TNP-470's neurotoxicity, Ronit Satchi-Fainaro, PhD, a former postdoctoral fellow in Dr. Folkman's laboratory and currently a faculty member at the Sackler School of Medicine, Tel Aviv University, developed Caplostatin™ by combining an analog of TNP-470 with the co-polymer HPMA (N-(2-hydroxypropyl) methacrylamide) and published the first results in 2004. More recently, Ofra Benny, PhD, also a member of Dr. Folkman's laboratory, developed Lodamin™ as the first oral formulation of TNP-470 and a first in its class polymeric-antiangiogenic oral drug. Lodamin™ is based on the conjugation of TNP-470 with another polymer, polyethylene glycol-polylactic acid (PEG-PLA). The researchers have shown that in mice, both Lodamin™ and Caplostatin™ have kept the original anticancer properties of TNP-470, without any observed neurotoxicity.

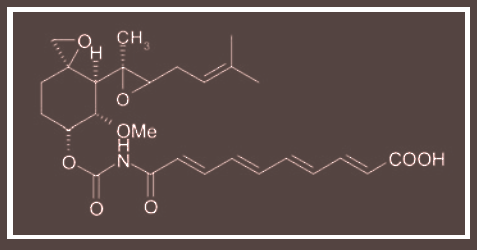
Dr. Benny and Ofer Fainaru, MD, PhD, another investigator in Dr. Folkman's group, are developing synergistic combinations of Lodamin™ and other anticancer drugs, opening up a promising clinical avenue based on prevention of vascular permeability.

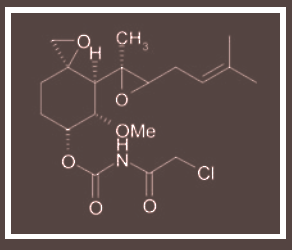
SynDevRx™ is planning to develop both compounds and start clinical trials in 18 to 24 months. A team composed of clinical oncologists with first-hand experience in administering TNP-470 to patients and scientists from Dr. Folkman's laboratory are working with SynDevRx™ on designing the protocols for the upcoming clinical trials.

Donald Ingber, MD, PhD, interim co-director of the Vascular Biology Program, discovered Fumagillin's role in blocking angiogenesis, the basis for Caplostatin™ and Lodamin™.

Endostatin and angiostatin genes for cancer therapy to Oxford BioMedica

Children's signed an exclusive gene therapy license in July 2007 with Oxford BioMedica for the rights to endostatin and angiostatin for the treatment of cancer. Oxford BioMedica, based in the United Kingdom, specializes in the development of innovative gene-based medicines. Solid tumor growth is dependent upon angiogenesis, the formation of new blood vessels. Endostatin and angiostatin are naturally occurring anti-angiogenic proteins that were discovered in Dr. Folkman's laboratory. The proteins have been shown to be effective in preventing the formation of new blood vessels and reducing solid tumors in numerous animal studies. Both proteins were tested in





Obese mouse (front) with wild type counterpart (back), used by Maria Rupnick, MD, PhD, Robert Langer, ScD, of MIT and Judah Folkman, MD, to show that obesity can be mitigated by anti-angiogenic compounds.

human phase I clinical trials and demonstrated to be extremely safe. These anti-angiogenic proteins have different mechanisms of action, which may have synergistic effects in a combination therapy and potentially prevent the development of drug resistance.

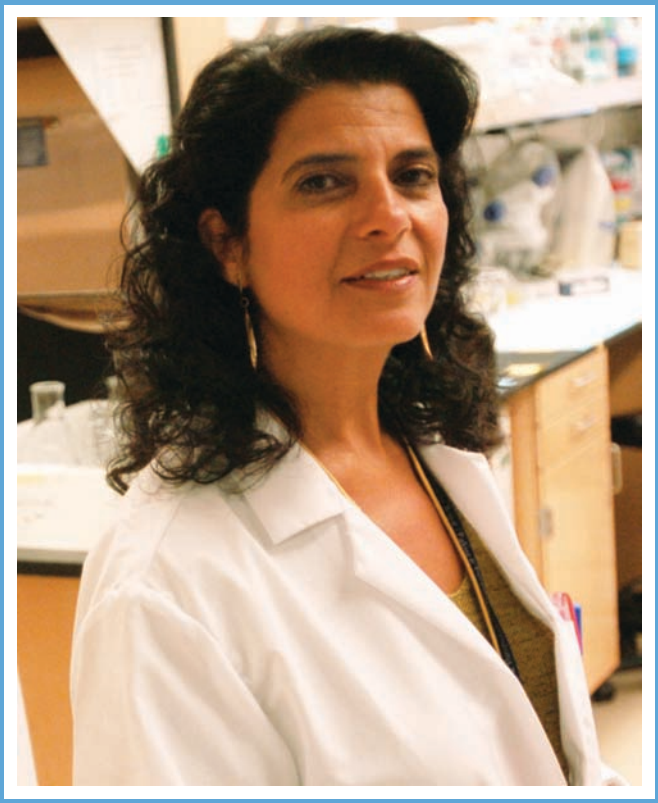
Children's Hospital Boston normal Z-score dataset for pediatric echocardiography licensed to academic institutions and hospitals

For over 10 years, Steven Colan, MD, chief of Non-Invasive Cardiology, has gathered cardiac measurements on pediatric patients with normal heart structure and function. He performed statistical analysis on the data and developed a set of Z-scores that can be applied to the analysis of cardiac structures in pediatric patients of any age. The strength of the Z-score dataset is based on the depth of the data from which it was derived: over 1100 patients with normal heart structures were analyzed, ranging in age from fetal to 20 years. The Z-scores are particularly useful when incorporated into a standard echocardiography reporting system used by cardiologists, as this allows comparison of a patient of any age to the normal standard and shows whether the patient's measurement falls into the normal range.

This year we non-exclusively licensed the Z-score dataset to seven institutions internationally for incorporation into their echocardiography reporting software. We are pleased to provide

"Children's Hospital Boston has been an ideal partner as our company translates the groundbreaking research of its researchers into a clinical and commercial reality. The team in the Intellectual Property Office understands the needs of a start-up like Zafgen, and the aligned interest of ***bringing breakthrough medicines to patients in need*** *facilitates a seamless licensing process."*

- Stuart Chaffee, PhD, director of Business Development, Zafgen



Marsha Moses, PhD, interim co-director of the Vascular Biology Program (left) and Bruce Zetter, PhD, Charles Nowiszewski Professor of Cancer Biology (right) built a portfolio of cancer biomarkers that is expected to lead to non-invasive cancer diagnosis and personalized therapeutic management.

a standard framework for licensing this resource and facilitate access to the information by the pediatric cardiology community.

Four start-up companies formed around Children's technologies

Children's helped start four new companies willing to assume more risk for the opportunity to develop a technology in its infancy. Through such licensing efforts, the entrepreneurs involved in these companies can raise the initial capital needed to begin advancing the science through translational or developmental stages on the way to becoming products available to the public. The technologies around which the start-up companies were formed cover a broad spectrum: obesity, diagnostics for cancer, therapeutic devices for spinal cord injuries and treatment of lead poisoning in children.

Zafgen takes aim at obesity based on Children's platform technology

The platform technology developed by Maria Rupnick, MD, PhD, Robert Langer, ScD, of MIT and Judah Folkman, MD, was licensed in January 2007 as one of the founding technologies of Zafgen, Inc. The company will focus on the use of anti-angiogenic agents for regulating new blood vessel formation to prevent the growth of adipose tissue and thereby provide a treatment to reduce obesity. Currently there is no medical or surgical treatment for obesity that is directed at the vascular compartment of the adipose tissue. "Children's has been an ideal partner as our company translates the groundbreaking research of its researchers into a clinical and commercial reality," says Stuart Chaffee, PhD, Zafgen's director of Business Development. "The team in the Intellectual Property Office understands the needs of a start-up like Zafgen, and the aligned interest of bringing breakthrough medicines to patients in need facilitates a seamless licensing process."

Unique biomarkers of cancer licensed to Predictive Biosciences Inc.

In October 2006, Children's entered into an exclusive license agreement with Predictive Biosciences Inc., a molecular cancer diagnostics company headquartered in Lexington, Mass., which was co-founded by two investigators from the Vascular Biology Program,

Michael Shannon, MD, MPH, director of Clinical Pharmacology is developing a palatable lead poisoning treatment for children.

Marsha Moses, PhD, interim co-director of the Vascular Biology Program, and Bruce Zetter, PhD. The company was formed around an extensive patent portfolio of approximately 13 cancer biomarkers that were discovered in the laboratories of Drs. Moses and Zetter over the course of 15 years of research. Some of these biomarkers are secreted proteins that can be detected in the urine of patients with cancer—bladder cancer, breast cancer, even brain cancer—and can provide a simple, non-invasive approach to cancer diagnosis and prognosis.

Predictive Biosciences has indicated its first tests will be based on detecting matrix metalloproteinases (MMPs) and/or a disintegrin and metalloproteinase (ADAM 12), combined with proprietary clinical algorithms for cost-effective monitoring and personalized management of bladder cancer survivors.

The biomarkers, licensed exclusively from Children's Hospital Boston, are applicable across multiple types of epithelial cancer, and Predictive Biosciences is initially focusing on diagnostic applications in bladder, breast and colorectal cancer, which together comprise more than five million cancer survivors. The assays that are being developed with these biomarkers and Predictive's proprietary algorithms will provide physicians with the information to manage patients in a timelier and more personalized manner, resulting in improved patient outcomes.

New devices for spinal cord injury

InVivo Therapeutics was founded based on research of Yang (Ted) Teng, MD, PhD, from the Department of Neurosurgery, working in collaboration with Robert Langer, ScD, of MIT and Eric Woodard, MD, of New England Baptist Hospital. The company is focused on developing therapeutic options that combine biomaterials and cell therapies to treat spinal cord injuries (SCI) and other central nervous system (CNS) disorders and improve the quality of life for people living with SCI and other CNS conditions. Several implantable devices are under development to treat different forms of SCI and spinal cord tumors.

Treatment for lead poisoning in children

Bezoloven Inc. was created as a virtual company by Angel investor Roger Kitterman to sponsor a clinical trial of a lead poisoning treatment for children. The treatment, a reformulated d-penicillamine, was developed by Michael Shannon, MD, MPH, director of Clinical Pharmacology, in collaboration with Tedor Pharma Inc., to be an effective treatment for low-level lead poisoning in children. If the clinical trial is successful d-penicillamine will become one of the few available treatment options for lead-poisoned children.

SIGNIFICANT MILESTONES ON LICENSED AGREEMENTS

Tengion launches Phase II clinical trials for its first product

Children's Hospital Boston licensee Tengion Inc., a leader in regenerative medicine, reached several important milestones in FY07 for its first product. In January 2007, Tengion announced the launch of its first Phase II multicenter clinical trial for its Neo-Bladder Augment™, a replacement bladder constructed in part from a patient's own bladder cells. The clinical trial is being conducted in pediatric patients with neurogenic bladder due to spina bifida, a neural tube defect that happens in the first month of pregnancy when the spinal column does not close completely. Bladder function diminishes over time in these patients,

"We very much appreciate the diligence and support of the Children's Hospital Boston Intellectual Property Office over the years. Their efforts on our behalf have played a major role in the establishment of a new diagnostic company whose goal is to develop ***non-invasive biomarkers for cancer*** *based on our patent portfolio."*

- Marsha Moses, PhD, interim co-director of the Vascular Biology Program, Children's Hospital Boston

and without correction, there can be significant kidney damage and even kidney failure. A second Phase II clinical trial was initiated in September 2007 for adult patients with neurogenic bladder due to spinal cord injuries. Both studies are evaluating the safety and efficacy of the Neo-Bladder Augment™ in patients who have failing bladders that predispose them to a risk of kidney failure and incontinence despite receiving optimal medical treatment. Tengion has also completed two neo-organ production facilities: the first is a Good Manufacturing Practice (GMP) pilot manufacturing operation that is making Neo-Bladders for the company's Phase II clinical trials, and the second is a full-scale commercial manufacturing center being readied for Phase III clinical trials and the initial demand after the product is launched. Tengion was formed in 2003 around the regenerative medicine platform developed by former Children's researcher Anthony Atala, MD.

Audrey Marshall, MD, associate in Cardiology, designed a device for fetal cardiac surgery with James Lock, MD, cardiologist-in-chief, that is now FDA approved.

Syntonix Pharmaceuticals acquired by Biogen IDEC

Syntonix Pharmaceuticals was founded in 1997 based on the work of Wayne Lencer, MD, PhD, chief of Children's Division of Gastroenterology/Nutrition, and his collaborator Richard Blumberg, MD, chief of Gastroenterology at Brigham and Women's Hospital. Syntonix has focused on discovering and developing long-acting therapeutic products that may improve treatment regimens for chronic diseases such as hemophilia and multiple sclerosis. In February 2007, Syntonix was acquired by publicly held Biogen IDEC, which hoped to enhance its pipeline and expand into additional specialized markets. This marks the sixth start-up company from Children's to be acquired.

ATC Technologies receives regulatory approval for fetal interventional cannula

In June 2007, Children's licensee ATC Technologies of Wilmington, Mass., received FDA approval for a Cannula Needle set. James Lock, MD, chief of Cardiology and physician-in-chief, and Audrey Marshall, MD, from the Department of Cardiology, designed the device for fetal cardiac interventional procedures. Despite a reduction in the mortality rate of infants born with rare congenital heart defects, Drs. Lock and Marshall wanted to prevent the defects from developing by treating the

"Tengion continues to ***passionately advance the technology*** *that we licensed from Children's Hospital Boston. The 15 years of tireless work by the scientists at Children's has served as a very solid platform as Tengion seeks to bring significant medical advances to patients in need."*

- George Landau, vice president, Business Development and Marketing Planning, Tengion

fetus while *in utero*. This device enables interventional cardiologists to perform procedures on the fetus more easily than with available devices.

The cannula, a hollow surgical tube, is inserted through maternal and fetal tissue until it reaches the fetal heart. The cannula must be straight and inflexible during insertion but flexible once the cardiologist reaches the intended fetal heart structure. Drs. Lock and Marshall collaborated with ATC Technologies to develop a unique prototype cannula with a tip that can bend once it is in position. When the cannula is rotated, the bend at its distal tip permits the entry angle of the therapeutic device to be different from the initial entry angle of the cannula. The lumen of the cannula is then used to introduce a therapeutic device, for example, a balloon for dilation procedures. While the initial application is for fetal interventions, the cannula could be used in other types of surgical procedures. Following the collaboration, ATC Technologies licensed the technology from Children's in 2006.

Celgene receives regulatory approval for cancer therapy

In June 2007, Celgene Corporation announced that its REVLIMID® brand drug (which relates to an agreement between Children's and Celgene) had been granted full marketing authorization by the European Medicines Agency (EMEA) for use in combination with dexamethasone as a treatment for patients with multiple myeloma (MM) who have received at least one prior therapy. This approval represents the first regulatory approval for Celgene in Europe, and REVLIMID® represents the first breakthrough oral cancer therapy in Europe for MM patients in more than 40 years. In August 2007, REVLIMID® was also approved by Swissmedic for the use indicated above. REVLIMID® is also approved in the US in combination with dexamethasone for the treatment of MM patients who have received at least one prior therapy and for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1–risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

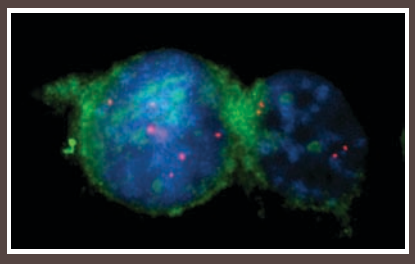
REVLIMID® brand drug has also obtained Orphan Drug designation for MDS in the European Union (EU), US, and Australia, Orphan Drug designation for MM in the EU, US, Australia and Switzerland, and Orphan Drug designation for chronic lymphocytic leukemia (CLL) in the EU.

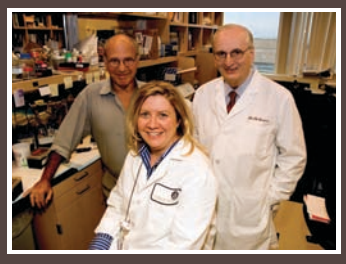
TECHNOLOGY HIGHLIGHTS

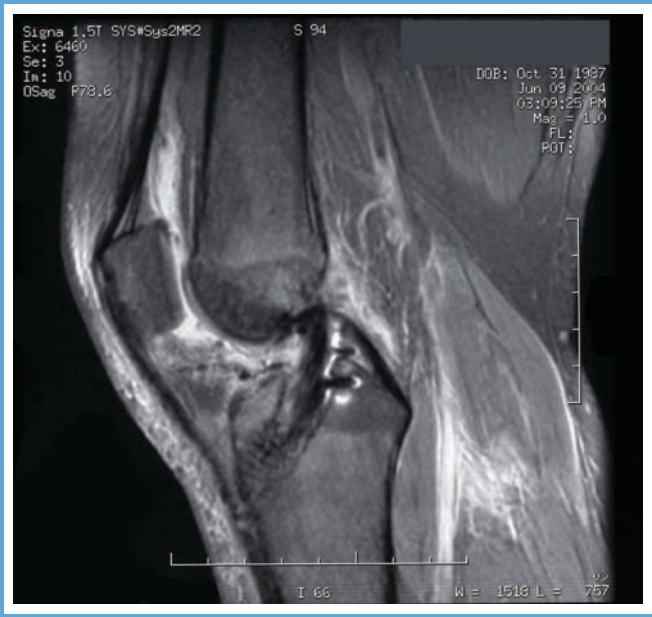
Healing joint tissues from the inside out

Martha Murray, MD, an orthopedic surgeon in Children's Hospital Boston's Division of Sports Medicine, is developing a collagen hydrogel material that facilitates the healing of injured tissues inside joints. Her laboratory research has focused on tears of the anterior cruciate ligament (ACL), an injury that affects over 200,000 individuals annually in the US alone. The ACL is one of the four main ligaments of the knee, and is notorious for not healing after being torn. The current technique for treating ACL tears is surgical reconstruction, which involves complete removal of the torn ligament and replacement with a graft of tendon taken from elsewhere in the body. While this treatment is successful at maintaining the physical stability of the knee, it is associated with high rates of premature arthritis, potentially due to the removal of the native ACL, which has a different anatomy that may help guide the knee's normal biomechanics.

Dr. Murray's goal is to develop a minimally invasive procedure that would stimulate healing of the two ends of a torn ACL, as opposed







MRI of a knee joint.

to removal and replacement; this should ideally decrease recovery time and give athletes a knee with more normal function. Dr. Murray and her colleagues have found that despite the ACL's low rate of healing, cells in the ACL, if provided with the appropriate environment, can proliferate, produce extra-cellular matrix and migrate, and therefore have great potential for natural healing after injury. These researchers have determined that the ACL's inability to heal in its native environment likely results from the degradation of fibrin clot - which facilitates wound healing elsewhere in the body - by the synovial fluid in the joint environment.

Utilizing their deep understanding of the biology of the intra-articular environment, Dr. Murray and her colleagues have developed a collagen-platelet-rich plasma material that resists degradation by synovial fluid and can stabilize the healing process in the joint environment. They have demonstrated the effectiveness of this matrix in both a canine and porcine model of ACL injury, and the most recent results were published in the August 2007 issue of the *Journal of Orthopedic Research*.

Fish oil enables babies to survive and thrive

Last year, a new treatment developed by Mark Puder, MD, PhD, in the Department of Surgery, and Kathleen Gura, PharmD, in Children's Pharmacy, permitted over 60 children with liver damage to be successfully treated with an alternative intravenous lipid (fat) source called Omegaven®. These children, unable to take food orally due to their underlying medical condition, had developed liver damage as a result of receiving the standard plant-derived intravenous fat emulsions for a prolonged period of time. Omegaven® is an omega-3 based fat derived from fish oil. It is given as a supplemental fat source only to adult patients in Europe who require intravenous nutritional support. However, it is not used as a sole source of intravenous fat, as Drs. Puder and Gura have been using it for the care of extremely ill patients at Children's.

They have made considerable clinical progress with this new use of Omegaven®. Their ongoing Phase II treatment study, now with over 70 participants, continues to demonstrate that liver damage can be reversed in infants and is a safe source of essential fat nutrition. The children have not experienced essential fatty acid deficiency, which was a major concern initially because Omegaven® doesn't contain the plant-derived fat. The study further demonstrates that Omegaven®, in lieu of the standard of care, diminishes the need for liver transplants, results in fewer central line infections and permits normal growth. A second trial investigating its use in the prevention of this often fatal condition began in July 2007. Drs. Puder and Gura are working closely with the FDA to gain their approval. The IPO is actively focused on engaging a company that will bring Omegaven® to the US and worldwide markets as the standard pediatric intravenous lipid source for nutritional support.

New treatments aimed at cancer metastasis

Randolph Watnick, PhD, from the Vascular Biology Program, is interested in studying tumor stroma interactions. He has discovered what is thought to be the first naturally occurring protein primarily involved in the protection against cancer metastasis. This discovery has important practical applications, since it is well accepted that the vast majority of cancer-related deaths are caused by the development of cancer metastasis, not by the primary tumor. A sophisticated companion test to indicate the likelihood of metastasis in different tissues in the body is also being developed. Dr. Watnick has developed powerful screening systems, which could be platforms for the discovery of other such proteins. The role of the IPO has been to protect the intellectual property, with the goal of developing a strong patent position. The IPO has also been looking for appropriate partners to establish relationships centered around the development of the technologies from this laboratory.

Bumetanide and topiramate for neonatal seizures

Frances Jensen, MD, director of Epilepsy Research, has been leading research on specific types of brain injuries to premature and full-term infants. Newborns who suffer from oxygen deprivation *in utero* or during delivery are vulnerable to seizures that can lead to lasting brain damage and epilepsy. While there are anticonvulsant drugs that work well in adults and older pediatric patients to control seizures, newborns respond poorly to anticonvulsants because their brain physiology differs from that of adults. Based on her understanding of the biology of the developing brain, Dr. Jensen has determined that certain drugs, given at the right time, can ameliorate brain injury in vulnerable newborns.

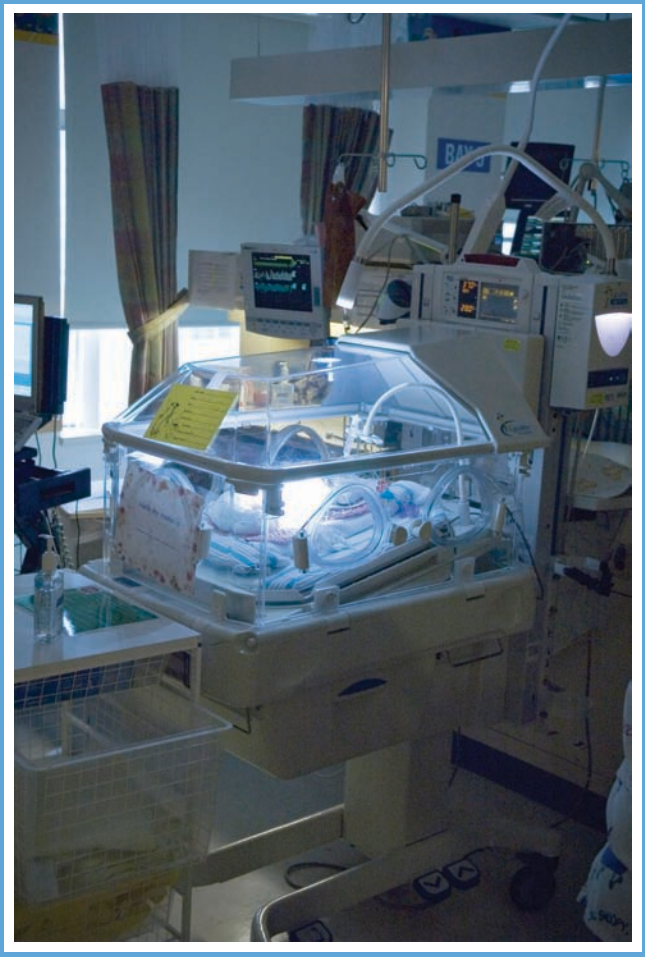
Past work in Dr. Jensen's laboratory showed that an FDA-approved drug, topiramate, may prevent long-term seizure disorders in newborns who have suffered oxygen deprivation. This drug acts by blocking a receptor, known as the AMPA glutamate receptor, which is highly expressed in the brains of newborns. More recent work by Dr. Jensen and colleagues has shown in a rat model that adding bumetanide (an FDA-approved diuretic that has been safely used in newborns) to anticonvulsant treatment had a calming effect that significantly reduced seizure time. Like topiramate, bumetanide targets proteins that are uniquely expressed in the neonatal brain, in this case, the NKCC1 receptor. Bumetanide's activity on neurons changes neuronal chemistry such that traditional anticonvulsant therapy can be effective. Dr. Jensen and her colleagues are now preparing to conduct a phase I clinical study of bumetanide in newborns. A clinical trial is promising, since the drug is FDA-approved and has been used in newborns for other indications; it would be added to the conventional anticonvulsant therapy, which is currently the standard of care. Developing successful treatments and preventive measures against neonatal seizures has the potential to prevent long-term neurologic impairments in the thousands of babies who are born each year with these injuries.

Frances Jensen, MD, director of Epilepsy Research, with colleagues Thao Huynh and Neil Marya. Dr. Jensen's team is finding treatments for neonatal seizures based on understanding of brain development.

Potential new therapy to prevent and reverse vision loss in premature infants

Lois Smith, MD, PhD, in the Department of Ophthalmology, has spent more than 20 years treating eye conditions of children while working in her laboratory to find better treatments for those same eye conditions. This work has led to a potential breakthrough in the treatment of retinopathy of prematurity (ROP), utilizing omega-3 fatty acids. ROP is a condition that results in abnormal growth of the tiny blood vessels in the retinas of premature or low birth weight babies and can result in retinal detachments and bleeding. ROP is severe enough to cause blindness in 400 to 600 infants each year because the current treatment options are not always successful in preventing or reversing the vision loss.

In her latest studies, Dr. Smith utilized a diet-based approach, instead of a growth factor-based approach. Premature infants are missing many factors normally provided by the mother in the third trimester of pregnancy, including omega-3 fatty acids, which are building blocks of healthy retinal tissue. These are essential dietary lipids that cannot be synthesized by the child. By providing dietary omega-3 fatty acids to mice at risk for ROP, she demonstrated that the onset of abnormal blood vessel growth leading to ROP could be prevented. Further, retinal damage could be reversed by giving omega-3 fatty acids later on. It is hoped that a diet-based approach would make this potentially vision-saving therapy accessible to premature infants worldwide because it would be less expensive and more accessible than a drug therapy. Since the underlying problems resulting in ROP are similar to those associated with diabetic retinopathy and age-related macular degeneration, two of the leading causes of blindness in adults, this breakthrough discovery has the potential to prevent and treat vision loss in an enormous number of people.



The omega-3-based therapy being developed by Lois Smith, MD, PhD, professor in Ophthalmology holds promise as a treatment for retinopathy of prematurity, a complication of premature birth.

Stem cell technology moves from the aquarium to the clinic

A novel treatment to stimulate patients' hematopoietic stems cells discovered in the laboratory of Leonard Zon, MD, director of the Stem Cell Program, has moved from the fish tanks to the clinic within just a few years. Dr. Zon's research has focused on using zebrafish as a whole animal model system to study hematopoietic stem cells and cancer. Hematopoietic stem cells give rise to all the blood cell types. This small population of cells is found in the bone marrow of adults, and is continuously renewing in order to generate new blood cells. For laboratory research, there are several features of the zebrafish that make it an ideal animal model to study the human blood system and diseases. Dr. Zon's goal is to improve the therapeutic potential of hematopoietic stem cells, which have been used in treatments for decades, most notably in bone marrow transplants for such diseases as leukemias.

Alternatives to bone marrow transplantation have become more common in recent years, including transplants with peripheral blood hematopoietic stem cells, which are collected after the mobilization of bone marrow stem cells into the peripheral blood stream; this type of treatment has surpassed bone marrow transplants as the standard of care for many diseases. Hematopoietic stem cell transplants using umbilical cord blood as the source, although still rare, are also happening more frequently due to favorable factors such as ease of collection, no risk to the donor and decreased risk of adverse effects. However, since adults usually require blood from at least two cords

to receive enough stem cells, the need for multiple cord blood units per transplant increases the costs and the risks of complications when two separate stem cell populations are brought together.

A drug screen in zebrafish embryos, initiated by postdoctoral fellow Trista North, PhD, and continued with postdoctoral fellow Wolfram Goessling, MD, PhD, tested more than 2,500 known chemicals for their ability to increase or decrease hematopoietic stem cell numbers. The most potent stimulation of these cells in zebrafish was with prostaglandin E2, and the stimulatory effects were further optimized with a more stable derivative, known as 16,16-dimethyl PGE2 (dmPGE2). Prostaglandins are a class of naturally occurring signaling compounds known to have broad physiological effects. The researchers also confirmed that dmPGE2 can stimulate hematopoietic stems cells from mice and improve the engraftment of human umbilical cord blood stem cells transplanted into mice. Dr. Zon is now ready to move the research from his laboratory to the clinic. He has assembled a team from Children's and neighboring institutions to initiate a clinical trial for the treatment of donated umbilical cord blood with dmPGE2; this work is expected to begin in 2008. Use of prostaglandins to increase the number of hematopoietic stems cells prior to transplantation also has promise for bone marrow or peripheral blood-derived hematopoietic stem cells, and to increase their patients' endogenous stem cell populations to help them recover from treatments like chemotherapy or radiation. Initial description of the Zon group's prostaglandin research was published last June in the journal *Nature*.

New methods to promote neovascularization for tissue engineering and therapeutic neovascularization

Tissue engineering and therapeutic neovascularization hold great promise as new approaches to repair congenital defects or diseased tissue or create new replacement tissues. For most engineered tissues to be successfully implanted in the human body, they require a microvascular (or blood vessel) network, just as normal tissues do, for the efficient delivery of oxygen and nutrients and removal of waste materials. Therefore the search for clinically relevant sources

Casper, the transparent zebrafish, bred by clinical fellow Richard White, MD, PhD.

of human cells that can form a vascular network (i.e., vasculogenic cells) is of utmost importance. Joyce Bischoff, PhD, in the Vascular Biology Program, has developed methods to obtain highly purified vasculogenic cells from human blood and bone marrow. Dr. Bischoff and her group have demonstrated that these vasculogenic human cells form new, functional vascular networks *in vivo* in a short period of time. The precursor cells are of two types, endothelial cells that line the interior of all of the blood vessels of the body and mesenchymal progenitor cells that surround the vessels and take on the role of pericytes/smooth muscle cells. The identification of precursor cells in peripheral blood and bone marrow and the development of methods to collect and utilize the precursor cells from peripheral blood and bone marrow are breakthroughs that will allow Dr. Bischoff and other researchers to create patient-specific engineered tissues.

Transilluminating catheter for infants

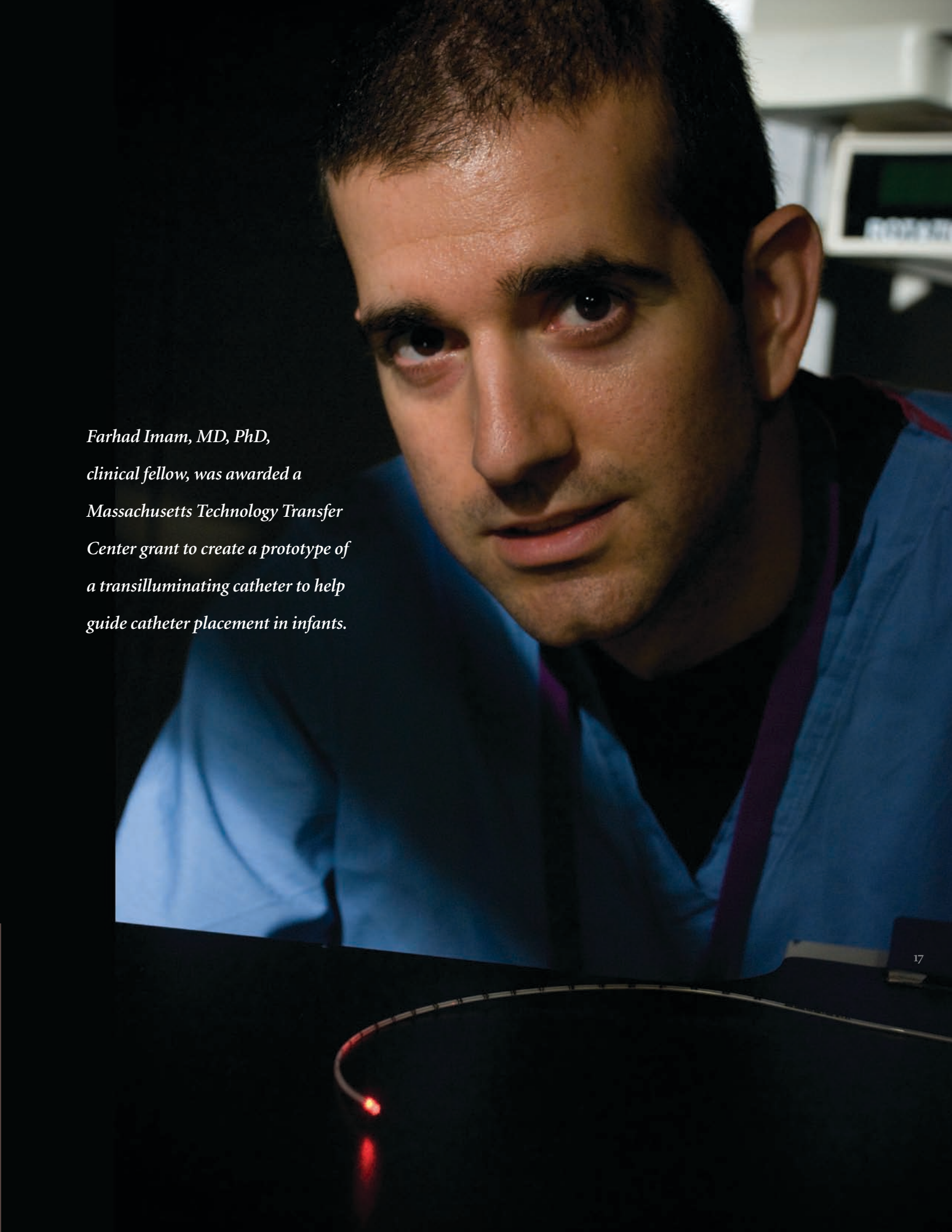
Care of premature babies often requires the insertion of catheters into the venous or arterial system to introduce anesthetics, therapeutics, or nourishment. The challenge, even for the skilled practitioner, is accurately inserting the catheter into a tiny vein or artery of an infant who may weigh less than 1,000 g (2.2 lbs) and guiding it to precise locations inside the body near the heart. Unfortunately, they are often inserted incorrectly and need to be removed and reinserted through a new puncture site. The complications associated with errant catheter placement are sadly a significant cause of morbidity and/or mortality, and because the insertion procedure is performed blindly, placement errors are often not detected until an X-ray is viewed almost an hour later.

While an intern at Children's, Farhad Imam MD, PhD, now a newborn intensive care clinical fellow at Children's, had the idea of developing a catheter fitted with an internal light that can be seen through the patient's skin. He figured this would help clinicians determine in real time if the catheter had been guided to the correct location. Dr. Imam built and tested simple prototypes during residency using internal funding from the Fred Lovejoy Resident Research Award. Last spring he received additional funding from the Massachusetts Technology Transfer Center to develop more sophisticated prototypes that are currently under construction and testing. Dr. Imam will optimize these prototypes in rabbits before beginning human testing in the near future.

Periostin and cardiac regeneration

Bernhard Kuhn, MD, in the Department of Cardiology, demonstrated a way to get injured heart tissue to regrow and regain pumping ability. In an animal model, Dr. Kuhn and colleagues used a naturally occurring protein called periostin to stimulate growth pathways that are normally switched off in heart cells after embryonic development.

The researchers found that 12 weeks after inducing heart attacks in rats, those treated with periostin had improved cardiac pumping ability and decreased left-ventricular wall stress. They also had less scarring of heart tissue, a reduction in infarct size and a denser network of blood vessels feeding the area. In contrast, the untreated rats showed little if any improvement. It is hoped that periostin could be developed as a therapeutic protein that would be given at the time of or soon after a heart attack to both prevent damage to the heart muscle and facilitate its healing and regeneration. His work was published in the August 13 issue of *Nature Medicine*.



Farhad Imam, MD, PhD, clinical fellow, was awarded a Massachusetts Technology Transfer Center grant to create a prototype of a transilluminating catheter to help guide catheter placement in infants.

Stem cell program

In the past year, Children's Hospital Boston researchers and the IPO have expanded their participation in the Harvard Stem Cell Institute (HSCI), established by a group of Harvard-affiliated hospitals and research institutions that have formed a community for stem cell research and technology development. The HSCI provides a core facility for local stem cell researchers and coordinates research programs in the various areas of stem cell research. An important component of HSCI support is Seed Grants, which provide early funding for innovative projects. In 2007, from a pool of about 70 applications, 10 HSCI Seed Grants were awarded, including three to Children's investigators. Richard Gregory, PhD, in the Stem Cell Program, was awarded a grant to study promoting stem cell expansion through chemical inhibition of microRNA-mediated cell differentiation, Carla Kim, PhD, also in the Stem Cell Program, received an award to study lineage tracing of lung stem cells *in vivo* and *in vitro*, and Stuart Orkin, MD, in the Department of Hematology/Oncology, received an award to study Down syndrome, somatic mutation of GATA-1 and acute megakaryoblastic leukemia.

The IPO continued its participation in the HSCI Intellectual Property Committee, which oversees the marketing and licensing of intellectual property arising from HSCI projects and coordinates stem cell related intellectual property among the participating institutions to identify synergies and potential for multi-institutional technology packages. The committee has benefited greatly from the participation of Brenda Manning, PhD, the former director of licensing from the IPO, and John Counts, JD, from Children's Clinical Trials Office, especially for their help in forging the Standing Agreement for participation in HSCI and in providing summaries of Children's stem cell technologies for the HSCI community. Going forward, Children's will be represented on the committee by case managers Peter Hodges, PhD, and Abbie Meyer, PhD.

MARKETING PROGRAMS & FACULTY & STAFF EDUCATION

The IPO marketing team is comprised of a group of licensing managers, coordinated by Senior Licensing Manager, Christine P. Nogueira, PhD, MBA, and Marketing Support Specialist, David Altman. Responsibilities include the design and execution of strategies for bringing Children's Hospital Boston's collaboration, licensing and alliance opportunities to the attention of industry. On the internal side, the focus is on educating Children's investigators about intellectual property and promoting the IPO's services to the Children's community.

Outreach to industry

The IPO actively participates in the main trade events of the pharmaceutical and biotechnology communities in order to showcase Children's technologies and provide the IPO staff with professional development opportunities. Marketing coordinates and provides all the logistical support for our participation.

Last year, the IPO participated in the BIO International Convention, the main conference for the biopharmaceutical industry, for the third straight year. The IPO co-sponsored an exhibition booth with Children's Clinical Trials Office and joined other Massachusetts technology transfer entities in the Massachusetts Association of Technology Transfer Offices (MATTO) cluster located in the Massachusetts Pavilion.

The IPO had an exhibitor's booth at the 2007 Licensing Executive Society's annual meeting in Vancouver, as in past years.

IPO staff also attended a number of other conferences targeted to specific areas of interest. Our office hosted a number of visits from

industry representatives and venture capital groups, which we used to present opportunities for licensing and sponsored research at Children's.

Education and service to the Children's community

The marketing team has designed and coordinated a number of educational presentations and events, some of which are new, and others that have been running continuously for several years now.

New education programs and events in FY07

On September 24, 2007, the marketing team supported "Inventor's Day," which was organized by the IPO's Technology Development team to showcase medical device inventors and promote interaction between inventors, investors and product development experts. Additional details about the event can be found in the Technology Development team section of this report.

Two networking events were held to build awareness of intellectual property and give Children's investigators an opportunity to meet in person with the IPO licensing managers. The first one was a "Crepe Day" in the Enders Building lobby. The second one was a luncheon for the Children's Fellows Association. Both events were well attended.

Ongoing education programs

Presentations to the newly hired Children's research laboratory personnel: This is a biweekly presentation about basic concepts in intellectual property, such as patentability of an invention, basic pathways for getting a patent, problems with premature public disclosures and the proper handling of research materials. All newly hired laboratory personnel are expected to attend, and the IPO licensing managers take turns covering such presentations.

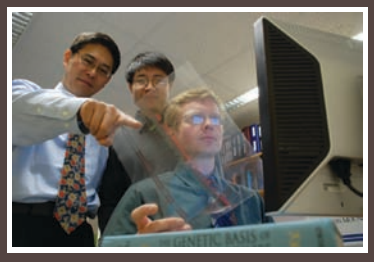
Last year was the fifth consecutive year that this presentation was given, with a total of 24 presentations in the year.

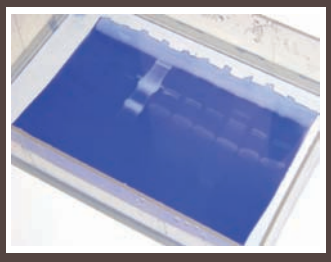
Presentations to Children's research administrative personnel: The IPO designed this presentation for administrative personnel who interface with investigators and may have contact with intellectual property. The presentation also covers basic principles and handling of intellectual property as above, but for a different audience. This effort is done in collaboration with Children's Research Administration. One presentation was made in November 2006.

Poster in Children's annual research day: For the fifth year in a row, the IPO has participated at this scientific event with a poster that promotes our services to Children's investigators. Our participation in this event also opened the door for our participation in other similar events such as the Surgical Research Symposium poster session in November 2007. Our goal is to educate our investigators that science and intellectual property go hand in hand.

Online presence

The IPO website serves as a portal for online access by potential industry partners and the Children's community. For those partners, we offer a look inside the Children's research laboratories, inventions available for licensing, recent news and information about our office. Our website is also an important service tool for Children's investigators because it is a source of information on intellectual property related policies, such as the distribution of licensing revenues to the inventors, and it facilitates basic operations such as the execution of material transfer agreements and disclosures of inventions to the office. In 2007, we added a new feature for frequently asked questions to our site. Children's technologies are also posted on three external





technology exchanges: The MassTech Portal (www.masstechportal.org), TechEx (www.techex.com) and BirchBob (www.birchbob.com).

Marketing materials

The IPO produced and published its first annual report, prepared by the entire IPO team. Three hundred copies of the finished report were distributed to Children's researchers, industry collaborators and peer technology transfer offices. The IPO also worked with an outside vendor to design branded chipboard notebooks and leather business card holders for promotional use.

Internal assessment of the marketing activities of the IPO

We believe that efficient marketing is essential, not only to try to find potential licensees for a particular technology, but also as a powerful tool for high quality business decisions to justify investment in a particular technology. Licensing managers in the IPO keep records of how frequently the cases disclosed to us are being marketed, and how frequently this information is shared with the inventors. A marketing plan is sent to the investigators usually within three months from the date we receive the disclosure, outlining the planned marketing activities for this case. A marketing report is sent approximately six months later, detailing which activities were pursued and the results of those efforts.

TECHNOLOGY DEVELOPMENT TEAM

The Technology Development team within the IPO continued its efforts to accelerate product development by securing new partnerships and funding opportunities. Through these efforts, three investigators were successful in obtaining grant funding from the Massachusetts

"The Intellectual Property Office has been an invaluable service guiding me step by step through a number of different projects. The ***initiative, interest and expertise provided has made a real difference*** *in our ability to keep making progress towards our goal of bringing new cardiac instruments and tools to the clinical world. A tremendous resource!"*

- Pedro del Nido, MD, chief of Cardiac Surgery, Children's Hospital Boston

Technology Transfer Center. Pedro del Nido, MD, chief of Cardiac Surgery, and Nikolay Vasilyev, MD, in the Department of Cardiac Surgery, were granted $40,000 to fund prototype development of an instrument port to facilitate beating heart surgery. The device is being developed in collaboration with engineering partners at Symmetry-TNCO.

Farhad Imam, MD, PhD, in the Division of Newborn Medicine was granted $40,000 to develop a working prototype of the illuminated catheter described on page 16. TDC Medical and Optimum Technologies are working with Dr. Imam on the device.

Small Business Innovation Research (SBIR) federal grants continued to be a good source of funding for Children's investigators. Joseph Madsen, MD, in the Department of Neurosurgery, and a team of eight surgeons at Children's are working with Infoscitex on a Phase II grant to design robotic endoscopic tools. The $730,000 Phase II SBIR grant was awarded in January 2007 and will continue to support the project until 2009. In addition, Infoscitex and Dr. Madsen were awarded three Phase I SBIR grants and a total of $308,000 to develop an "intracranial sensor array," a "bipolar coagulator" and a "device for monitoring intracranial pressure."

The Technology Development team held its first "Inventor's Day" on September 24, 2007 to showcase Children's medical device inventors and provide an opportunity for Children's clinicians to interact with engineering resource teams, commercial partners, representatives from various state and institutional funding sources, and other Children's device inventors. Professor Ed Marram, director of the Arthur D. Blank Center on Entrepreneurship at Babson College, moderated a panel discussion on innovation that featured three clinical innovators from Children's, Dr. James Lock, Dr. Martha Murray and Dr. Farhad Imam (all of whom are mentioned in this report), as well as Professor Jean Luc Boulnois, CEO of Microline Pentax. Fourteen Children's inventors were featured in a poster session. The event was an outstanding success, with more than 100 people in attendance.

James Mandell, MD, president and CEO of Children's Hospital Boston (center) at Inventor's Day with (from left to right) Farhad Imam, MD, PhD, James Lock, MD, Professor Edward Marram, Martha Murray, MD, and Professor Jean Luc Boulnois. Professor Edward Marram is director of the Arthur D. Blank Center on Entrepreneurship at Babson College and Professor Jean Luc Boulnois is the CEO of Microline Pentax. Drs. Imam, Lock and Murray are from Children's.

APPENDIX 1
SUMMARY OF TECHNOLOGY TRANSFER ACTIVITY
(FISCAL YEAR 2003 THROUGH FISCAL YEAR 2007)

INVENTION DISCLOSURES

	2003	2004	2005	2006	2007
TOTAL	111	118	98	98	94

PATENT APPLICATIONS

	2003	2004	2005	2006	2007
Provisionals filed	29	54	54	49	47
PCTs filed	30	14	30	25	24
Foreign filed	83	33	31	27	18
US filed	75	41	50	49	33

GROSS REVENUES ($M)

	2003	2004	2005	2006	2007
TOTAL	13.2	14.1	17.6	22.4	18.1

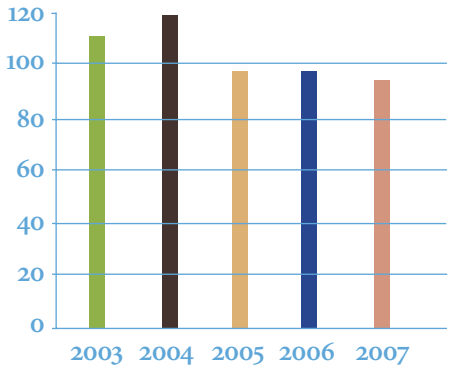
ALL AGREEMENTS NEGOTIATED

	2003	2004	2005	2006	2007
Exclusive Licenses	9	7	5	8	7
Non-exclusive Licenses	11	4	13	16	19
Options	8	8	3	3	3
TOTAL	28	19	21	27	29
Agreements Involving the Receipt of Equity	1	1	0	0	1
Amendments	4	4	2	5	4
Research Collaboration*	3	5	11	7	6
Corporate Sponsored Research*	6	5	6	4	12
Material Transfer*	180	203	261	285	398
Confidentiality*	49	75	95	80	64
Inter-institutional Invention Administration	9	11	8	11	11
Other	3	5	12	5	6

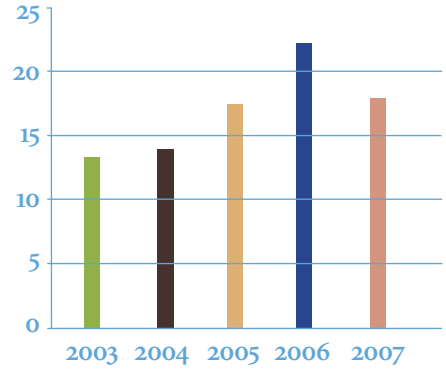
*Corporate Sponsored Research, Confidentiality, Research Collaboration and Material Transfer Agreements are negotiated in collaboration with the Clinical Trials Office.

APPENDIX 2
FIVE-YEAR TREND OF TECHNOLOGY TRANSFER ACTIVITY
(FISCAL YEAR 2003 THROUGH FISCAL YEAR 2007)

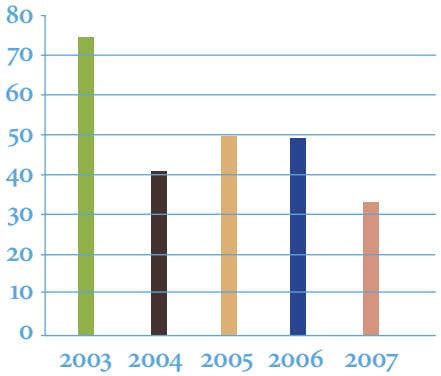
INVENTION DISCLOSURES



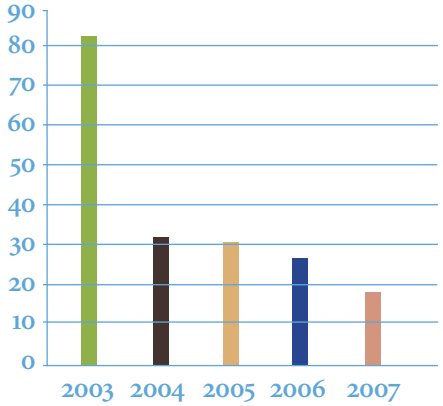
GROSS REVENUES ($M)



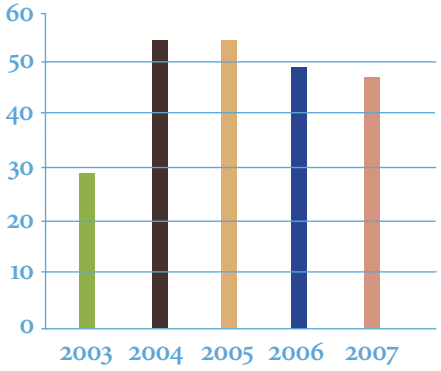
U.S. PATENTS FILED



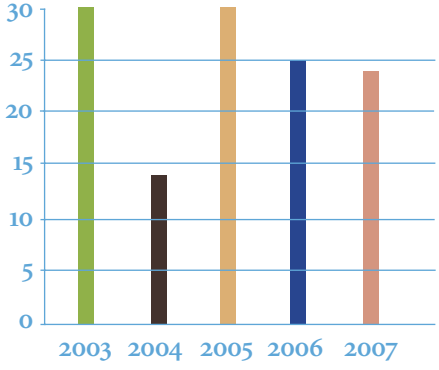
FOREIGN APPLICATIONS FILED



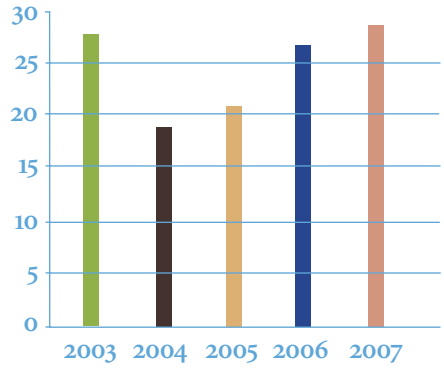
PROVISIONALS FILED



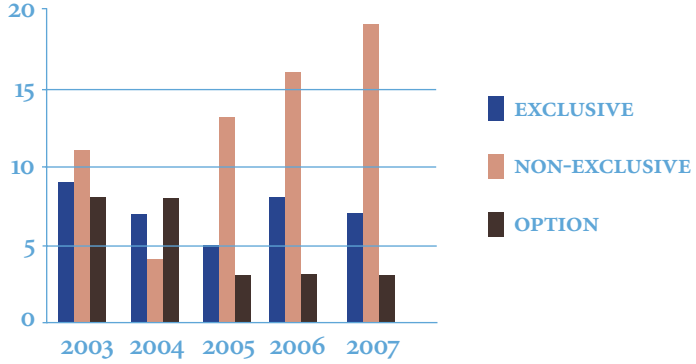
PCTs FILED



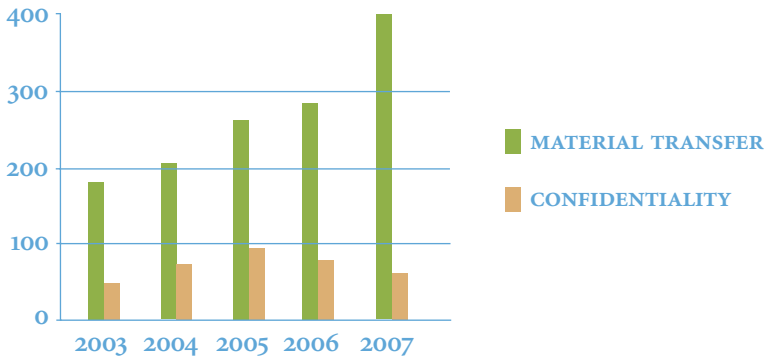
LICENSES & OPTIONS GRANTED



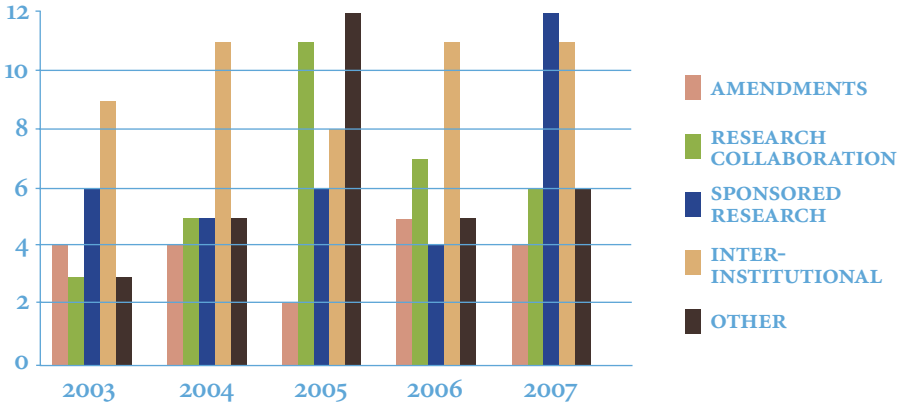
BREAKDOWN OF LICENSE AND OPTION AGREEMENTS



NON-LICENSE AGREEMENTS MATERIAL TRANSFER & CONFIDENTIALITY



NON-LICENSE AGREEMENTS OTHER



APPENDIX 3

US PATENTS ISSUED FY07

LEAD INVENTOR	COUNTRY	ISSUE DATE	PATENT NUMBER	APPLICATION TITLE
Aldovini, Anna	US	10/17/06	7,122,180	DNA vectors containing mutated HIV proviruses
Wright, Dowain	US	11/7/06	7,132,265	Circular site-directed mutagenesis
Smith, Lois	US	12/5/06	7,144,707	Determination of risk and treatment of complications of prematurity
Moses, Marsha	US	12/26/06	7,153,660	Non-invasive enzyme screen for tissue remodelling-associated conditions
D'Amato, Robert	US	12/26/06	7,153,867	Use of nitrogen substituted thalidomide analogs for the treatment of macular degeneration
Folkman, M. Judah	US	1/2/07	7,157,556	Deglycosylated Kringle 1-3 region fragments of plasminogen and methods of use
Zon, Leonard	US	1/23/2007	7,166,448	Ferroportin1 nucleic acids and proteins
Benowitz, Larry	US	2/6/2007	7,172,871	Methods and compositions for modulating axonal outgrowth of central nervous system neurons
O'Reilly, Michael	US	2/20/2007	7,179,608	Therapeutic antiangiogenic compositions and methods
Saunders, Scott	US	2/27/2007	7,183,393	Construction and use of synthetic constructs encoding syndecan
Snyder, Evan	US	3/6/2007	7,186,409	Neural stem cells and use thereof for brain tumor therapy
Benowitz, Larry	US	7/3/2007	7,238,529	Methods and compositions for treating ocular disorders
He, Zhigang	US	7/3/2007	7,238,659	Reducing axon degeneration with proteasome inhibitors
Wiley, Don	US	8/28/2007	7,262,270	Fusion protein construct and method for inducing HIV-specific serum IgG and secretory IgA antibodies in-vivo
Klagsbrun, Michael	US	9/25/2007	7,273,612	Soluble inhibitors of vascular endothelial growth factor and use thereof
Lock, James	US	12/5/2006	D533270	Introducer cannula and cannula straightener

APPENDIX 4

FOREIGN PATENTS ISSUED IN FY07

COUNTRY	SERIAL NUMBER	ISSUE DATE	PATENT NUMBER	APPLICATION TITLE
Australia	2001247442	11/9/2006	60189720	Systemic gene delivery vehicles for the treatment of tumors
Australia	2002301263	12/7/2006	2002301263	Engraftable neural progenitor and stem cells for brain tumor therapy
Australia	2002249922	3/5/2007	2002249922	Method for identifying genes involved in cell proliferation
Australia	2001292787	5/11/2007	2001292787	Differential treatment of selected parts of a single cell with different fluid components
Canada	2,395,674	2/6/2007	2,395,674	Methods and compositions for reconstruction of multilayered tissue structures
Canada	2,203,151	5/29/2007	2,203,151	Systems and methods for promoting tissue growth
Canada	2,307,792	6/26/2007	2,307,792	Method for regulating size and growth of vascularized normal tissue
China	2827224.2	1/17/2007	ZL 02827224.2	Creation of tissue engineered female productive organs
China	95193293.4	4/11/2007	ZL 95193293.4	Angiostatin and method of use for inhibition of angiogenesis
Germany	96942905.9	10/24/2006	871778	Improved circular site-directed mutagenesis
UK	96942905.9	10/24/2006	871778	Improved circular site-directed mutagenesis
France	96942905.9	10/24/2006	871778	Improved circular site-directed mutagenesis
UK	1990050.5	2/14/2007	1343876	Modulators of activity of G-protein-coupled receptor kinases
Ireland	1990050.5	2/14/2007	1343876	Modulators of activity of G-protein-coupled receptor kinases
France	1990050.5	2/14/2007	1343876	Modulators of activity of G-protein-coupled receptor kinases
Germany	1990050.5	2/14/2007	1343876	Modulators of activity of G-protein-coupled receptor kinases
Austria	95918854.1	2/28/2007	758390	Angiostatin and method of use for inhibition of angiogenesis
Belgium	95918854.1	2/28/2007	758390	Angiostatin and method of use for inhibition of angiogenesis
France	95918854.1	2/28/2007	758390	Angiostatin and method of use for inhibition of angiogenesis
Germany	95918854.1	2/28/2007	758390	Angiostatin and method of use for inhibition of angiogenesis
Hong Kong	95918854.1	2/28/2007	758390	Angiostatin and method of use for inhibition of angiogenesis
Ireland	95918854.1	2/28/2007	758390	Angiostatin and method of use for inhibition of angiogenesis
Switzerland	95918854.1	2/28/2007	758390	Angiostatin and method of use for inhibition of angiogenesis
UK	95918854.1	2/28/2007	758390	Angiostatin and method of use for inhibition of angiogenesis
France	908590.3	4/18/2007	1153125	Deglycosylated Kringle 1-5 region fragments of plasminogen & methods of use
Germany	908590.3	4/18/2007	1153125	Deglycosylated Kringle 1-5 region fragments of plasminogen & methods of use
Ireland	908590.3	4/18/2007	1153125	Deglycosylated Kringle 1-5 region fragments of plasminogen & methods of use
UK	908590.3	4/18/2007	1153125	Deglycosylated Kringle 1-5 region fragments of plasminogen & methods of use
Japan	2004-228253	11/17/2006	3880593	Angiostatin and method of use for inhibition of angiogenesis
Japan	7-527831	7/25/2007	3880064	Angiostatin and method of use for inhibition of angiogenesis
Austria	96913208.3	7/25/2007	824546	Angiostatin fragments and aggregate angiostatin and method of use
Belgium	96913208.3	7/25/2007	824546	Angiostatin fragments and aggregate angiostatin and method of use
France	96913208.3	7/25/2007	824546	Angiostatin fragments and aggregate angiostatin and method of use
Germany	96913208.3	7/25/2007	824546	Angiostatin fragments and aggregate angiostatin and method of use
Ireland	96913208.3	7/25/2007	824546	Angiostatin fragments and aggregate angiostatin and method of use
Italy	96913208.3	7/24/2007	824546	Angiostatin fragments and aggregate angiostatin and method of use
Spain	96913208.3	7/25/2007	824546	Angiostatin fragments and aggregate angiostatin and method of use
Switzerland	96913208.3	7/25/2007	824546	Angiostatin fragments and aggregate angiostatin and method of use
UK	96913208.3	7/25/2007	824546	Angiostatin fragments and aggregate angiostatin and method of use

M. JUDAH FOLKMAN, MD

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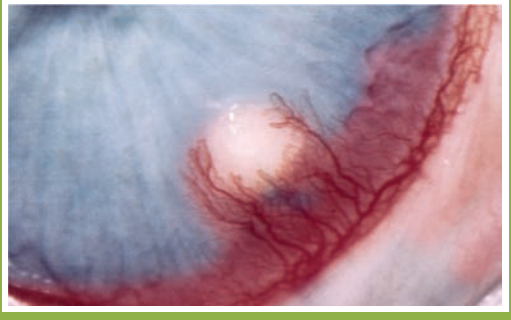
Our office joins the scientific community in mourning the passing of Dr. Judah Folkman earlier this year. We are truly honored to have been part of Dr. Folkman's tireless mission to bring the benefits of anti-angiogenic agents to patients, having worked closely with him for over 15 years to manage intellectual property arising from his research and industry collaborations. Dr. Folkman was ahead of his time, in his appreciation of the importance of developing strong intellectual property and transferring discoveries to industry through licensing and collaboration, in order to achieve the translation of research into potential life saving treatments. As a prolific and innovative researcher, his work resulted in more than 300 patents and pending patent applications and spanned areas as diverse as cancer, complications of premature birth and pre-eclampsia, endometriosis, obesity, hydrocephalus, hypertension and lymphangioleiomyomatosis.

Dr. Folkman's vision of anti-angiogenesis therapies is currently being realized. There are more than 12 angiogenesis-inhibiting drugs currently approved for over 20 indications and this class of therapeutics will help millions of patients worldwide. We will miss Dr. Folkman, not only as a visionary inventor, but as a friend and a supporter of our office. We look forward to continuing our work with the world class researchers of the Vascular Biology Program at Children's as they continue their research in the field pioneered by Dr. Folkman.



A classic angiogenesis assay. A pellet releasing a proangiogenesis factor is implanted into the eye of a mouse where it recruits blood vessels and induces their proliferation.

Intellectual Property Office

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