SHAPING IDEAS – FURTHERING INNOVATION – ADVANCING CARE

TECHNOLOGY & INNOVATION DEVELOPMENT OFFICE

2008 ANNUAL REPORT

Children's Hospital Boston

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MESSAGE FROM THE DIRECTOR

Fiscal year 2008 was filled with challenges and change. The economic downturn that affected so many Americans caused many companies—to which we license patents and technology—to focus their restricted resources on existing products in development or set their sights on late stage technology. While the shift this past year was a dramatic one, the commercial sector had been trending over the past decade towards the acquisition of fully validated and de-risked technology. The challenge for academic and non-profit research institutions working to translate their innovations into products has never been greater—and the cost of doing business (patent expenses and attorney fees, information management systems, Web site and marketing) has not decreased—as a result . . . the pressure is on.

One of the hallmarks of Children's Hospital Boston is its commitment to improving the lives of its patients and children everywhere. This is directly demonstrated in the world-class clinical care delivered at Children's and indirectly through the groundbreaking research that has translated into nine major clinical products that are improving the lives of children and adults worldwide. With the support of the administration, chiefs and researchers at Children's, the office formerly known as the Intellectual Property Office, or IPO, implemented an aggressive reorganization to meet the challenges head on.

The restructuring over the course of 2008 and into 2009 focused on allocating the office's resources and expertise in a way that helps support research at Children's Hospital Boston and advance the stage of development of resulting innovations. Reflecting the shift away from the "tech transfer" model and towards a full service operation focused on adding value throughout the lifecycle of an innovation, the office reformed as the Technology & Innovation Development Office (TIDO). The creation of new roles in Business Development, Technology Development and Technology Marketing allows TIDO to increase responsible research collaborations with industry, invest in and develop Children's technologies directly, and communicate credibly the value of the innovative technology within the marketplace.

While 2008 was filled with numerous challenges—it was a year to be proud of as the institution and TIDO implemented the long-term changes necessary to deal with a dynamic marketplace and struggling economy. With an updated organizational structure and integration of new functions, TIDO is positioned for 2009 and beyond to better support the mission of translating Children's Hospital research into products for the public benefit.

Erik Halvorsen, PhD

TECHNOLOGY & INNOVATION DEVELOPMENT OFFICE'S REORGANIZATION

Like our counterparts throughout the nation, Children's Hospital Boston has been facing growing challenges in bringing new 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 when you consider the cost of developing new drugs and medical devices—the average expense to bring a drug to market is estimated at over $1 billion[1]—it has added tremendous pressure on the academic institutions that typically lack adequate facilities and capabilities to move ideas for new medications, treatments and technologies from research to development.

Addressing the changes in the commercial sector and the challenges they pose, the Technology & Innovation Development Office (TIDO, formerly the Intellectual Property Office) at Children's Hospital Boston is working to advance promising innovations in order to increase the likelihood of licensing, and support Children's researchers and thought leaders by attracting collaboration opportunities with industry.

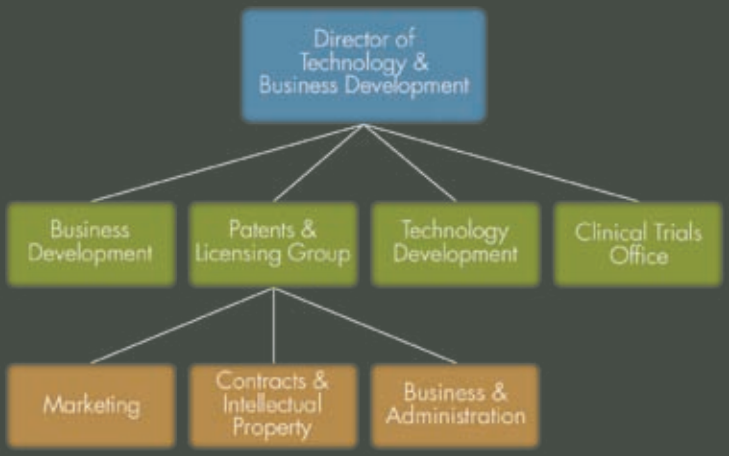
Based upon internal reviews and assessments, as well as discussions with external company executives, TIDO has changed its office structure to provide a broader array of services. This new structure consists of four main functional groups, all working together to support the mission.

- The Business Development function identifies collaboration opportunities and facilitates partnerships with companies with the goal of supporting innovations at all stages, from initial ideas to technology portfolios with multiple patents.

- The Technology Development function helps speed the translation of Children's laboratory and clinical research excellence into products. To go along with the new function, the Children's Technology Development Fund was launched in March of 2009. The fund uses a three-pronged approach, providing the funding, technical support and business acumen necessary to develop commercially viable technologies.

- The Clinical Trials Office (CTO), which had been a separate department, became part of TIDO in February 2009. The move was a natural fit as the CTO and TIDO both work to translate technologies into products for patient care. The office consists of experienced contract specialists who negotiate industry-sponsored research, material transfer and clinical trial agreements.

- The core function of the office remains within the Patents and Licensing Group, which was restructured to increase efficiency and enhance customer service. Licensing managers with expertise in various life sciences handle technology assessments, patent prosecution, technology marketing and contract negotiation. A primary licensing manager is assigned to each hospital department/program and manages all technologies reported to our office from that department. The list of licensing managers and the departments they cover is found on TIDO's new Web site at **www.childrensinnovations.org**.



To assist the licensing managers with their varied responsibilities, a number of specialized support functions have been created.

- The Contracts and Intellectual Property group works with outside patent counsel to protect Children's intellectual property and manage patent-related documents and correspondence. They also draft, review and negotiate various industry agreements.

- The Marketing group was expanded to increase all aspects of specific and broad marketing for Children's technologies. In addition to the traditional marketing activities they engaged in, the group now conducts in-depth market research to guide an innovation's

path to market, creates and disseminates promotional materials and supports communications with potential partners.

Along with the organizational changes comes a new Web site at **www.childrensinnovations.org**. It highlights TIDO's expanded services and provides industry with a glimpse into our current research efforts, technologies we've developed or are developing and partnership opportunities. TIDO anticipates that with their new streamlined technology evaluation and marketing approach, increased resources to advance a technology's stage and increased collaborations with industry, Children's will increase the dissemination of its innovations to have an impact on patients of all ages around the world.

1. Pharmaceutical Manufacturers Association/Tufts Center for the Study of Drug Development http://www.phrma.org/files/2008%20Profile.pdf

THE TIDO TEAM

TIDO ACTIVITIES

Children's Hospital Boston, the primary pediatric teaching affiliate of Harvard Medical School and a Howard Hughes Medical Institute-affiliated institution, is the world's leading pediatric research enterprise, with annual funding of over $194 million. In the laboratories and clinics, our researchers seek to identify factors that contribute to both childhood and adult diseases, and develop effective treatments. Children's 740 scientists are experts in many fields, including oncology, cardiovascular, neuroscience, stem cells, genomics, vascular biology and informatics.

Invention Management Activity

At the end of FY08, the Technology & Innovation Development Office (TIDO) had 493 inventions under active management. Working with David Altman, the marketing communications specialist, 174 of these inventions were marketed. Licensing managers monitored 184 ongoing license agreements, and coordinated the activities of outside patent attorneys to manage 1,087 pending patent applications on 377 inventions, and maintain 775 issued US and foreign patents.

INVENTION MANAGEMENT ACTIVITY

Inventions under active management	493
Inventions under initial evaluation	42
Inventions in marketing campaigns	174
Inventions under development	14
Inventions with licenses pending	9
Licensed inventions	191
Inventions with other institute leading	70
Current licenses	188
Issued US patents	385
Issued foreign patents	407

Invention Disclosures

TIDO received 116 new invention disclosures from Children's faculty and staff, which is an increase of about 20 percent over last year.

FISCAL YEAR 2008 DATA SUMMARY

Invention disclosures	116
Patent applications filed	147
Provisional applications filed	69
PCT applications filed	26
US applications filed	30
Foreign applications filed	22
Patents issued	54
US patents issued	21
Foreign patents issued	33
Licenses and options granted	22
Gross revenues ($M)	16.3
Net revenue (less external institutes; $M)	11.3
Revenue from new licenses and options	0.14

Patent Filings

TIDO oversaw the filing of 147 patent applications over the course of the year. Sixty-nine provisional patent applications were filed. Twenty-six applications were filed for US and foreign rights under the Patent Cooperative Treaty mechanism. Thirty applications were filed in the US and 22 were filed in individual foreign countries.

Patent Issuances

Children's was granted 21 patents by the US Patent and Trademark Office and 33 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

TIDO negotiated end executed 22 license and option agreements for Children's technologies: five exclusive licenses, 14 non-exclusive licenses and three options. The revenue recognized from these new license and option agreements was $136,703. TIDO'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 $16.3 million, an amount on par with previous years. Of the 184 active license agreements, 65 generated revenue in FY08. Thirty-eight of these 65 licenses brought in less than $10,000 each, but three produced over $1 million each. The net revenue received by Children's was $11.3 million, which is $16.3 million in gross revenue less $5 million distributed to other institutional co-owners. Of the $11.3 million in net revenue, $3.5 million was distributed to the inventors and $2.7 million was distributed to the inventors' departments and laboratories. The remaining $5.1 million to the hospital was apportioned to the general research endowment, unrecovered legal expenses and TIDO's operations.

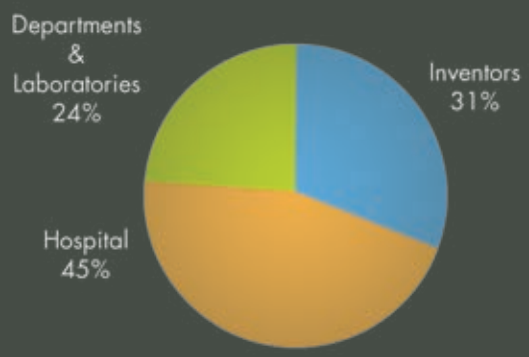
RECIPIENTS OF DISTRIBUTED LICENSING REVENUE

Inventors	$3,459,306
Departments	$2,676,770
Hospital	$5,121,711
TOTAL	$11,257,787

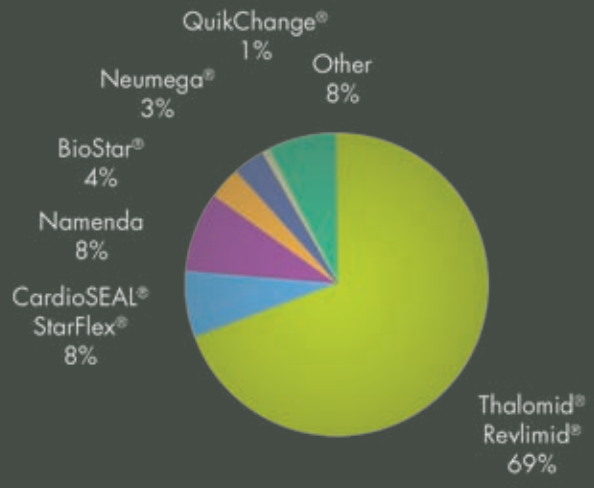
Significant Revenue-Generating Inventions

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

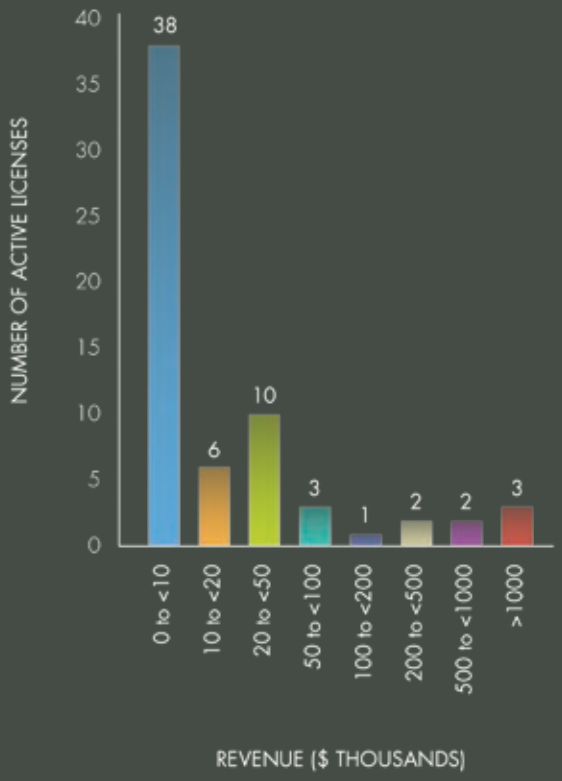
NET LICENSING REVENUE DISTRIBUTION FY08: $11.3 MILLION



SOURCES OF LICENSE REVENUE



REVENUE-GENERATING LICENSES FY08



LICENSING AND COLLABORATION HIGHLIGHTS

Technology to Prevent Blindness in Premature Infants Licensed to Premacure AB

Children's Hospital Boston entered into an exclusive license agreement with Premacure AB, based in Uppsala, Sweden, for the use of insulin-like growth factor (IGF-1) to prevent and treat retinopathy of prematurity (ROP). ROP is one of several potential complications of preterm birth. In premature or low birth weight infants, there may be abnormal growth of the tiny blood vessels of the retinas, which may in serious cases result in retinal detachment and blindness. Lois Smith, MD, PhD, associate professor of Ophthalmology, and long-time collaborator Ann Hellström, MD, have spent several years studying ROP and potential treatments for the disease. Their key discovery was that IGF-1 is critical for normal development of retinal vasculature, and its level falls in premature infants after birth since it is no longer being provided by the maternal environment. This finding suggested that increasing the level of IGF-1 in the premature infant soon after birth would allow the retinal vasculature to develop normally and ROP would not occur. In addition, measuring the level of IGF-1 in premature infants could help assess the infant's risk of developing ROP. The company has started clinical studies in very low birth weight infants, with initial results demonstrating increased serum levels of IGF-1 without any acute adverse events.

Anesthetic Combinations with Tetrodotoxin Licensed to WEX Pharmaceuticals Inc.

Children's signed an exclusive license and sponsored research agreement with WEX Pharmaceuticals Inc. for the development of long-acting anesthetics using a combination of various agents with Tetrodotoxin, a sodium channel blocker. Tetrodotoxin is WEX Pharmaceutical's lead compound and is currently being tested in two Phase III clinical trials as a single agent to reduce moderate to severe pain associated with cancer. Charles Berde, MD, PhD, chief of the Pain Medicine Division, in collaboration with colleagues at Children's and elsewhere discovered that the safety, specificity and duration of pain relief of local anesthetics can be improved by combining them with sodium channel blockers like Tetrodotoxin. The sponsorship and collaboration with WEX will support the continuation of this research and help move the combination technology closer to clinical trials.

Developing Better Vaccines for Pneumococcal Disease with PATH

Pneumococcus is the leading vaccine-preventable cause of death in children under age five in the world. Since 2000, US infants have been routinely immunized against pneumococcal (Streptococcus pneumoniae) infection, while in developing countries, almost one million children die from pneumococcal infections each year. Supported by a Children's Translational Research Grant and funding from PATH, an international nonprofit organization that creates sustainable, culturally relevant solutions, enabling communities worldwide to break longstanding cycles of poor health, and traditional NIH funding, Richard Malley, MD, of Children's Division of Infectious Diseases, is working on pneumococcal vaccine technologies addressing immunogenicity and delivery. The goal is to make a vaccine with broad protection that can be used worldwide, made cheaply and withstand high temperatures without refrigeration. Additionally, the vaccine can be given without needles, avoiding the need for a sterile environment and medical professionals to administer it.

LOIS SMITH, MD, PHD

CHARLES BERDE, MD, PHD

Identification of New Non-Serotype-Specific Vaccine Targets with Genocea Biosciences: The Next Generation Pneumococcal Vaccines

Due to the complexity of assembling the serotype-specific, multivalent vaccine, existing life-saving serotype-specific pneumococcal vaccines are too expensive for most developing countries. In addition, clinically significant pneumococcal serotypes vary around the world. To address both of these significant barriers, PATH is funding a collaboration between Dr. Malley and a local vaccine development company, Genocea Biosciences Inc., to identify a novel multivalent, protein-subunit pneumococcal vaccine based on Genocea's antigen-discovery technology platform. The goal is to create affordable common protein vaccines that could provide broader protection to children worldwide. As with other PATH-funded projects, the structure of the agreement is designed to give PATH the rights to provide the product to impoverished populations, while allowing the company to protect its opportunities in the private market.

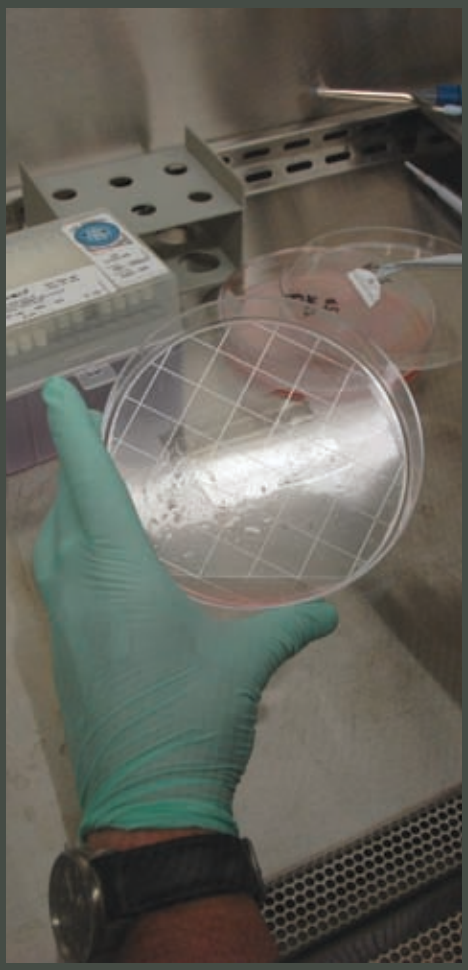
RICHARD MALLEY, MD

Vaccine Delivery Technology Research Collaboration with Intercell USA

Richard Malley, MD and his team began a collaboration with Intercell USA to test a whole cell pneumococcal vaccine administered by a heat-stable skin patch developed by Intercell USA in animal studies. Although the first studies will be in animals, the product in development is a patch placed on infants' backs for several hours, immunizing them transdermally. Because the vaccine is based on a whole-cell Pneumococci vaccine and adjuvant, this technology could provide protection against proteins common to virtually all of the 91 pneumococcal serotypes that infect people worldwide. Similarly, patches could feasibly be developed for many other vaccines.

Sanofi-aventis Educational Grant Supports Cancer Stem Cell Research

In October 2007, Children's clinician and researcher Scott Armstrong, MD, PhD, in the Department of Hematology and Oncology, began a collaboration with researchers at sanofi-aventis using a model created by Dr. Armstrong to further understand leukemia stem cells and to search for drugs that target the cancer stem cell. Dr. Armstrong has created a model system of acute myelogenous leukemia (AML) and used this model to identify leukemia stem cells. When transduced into granulocyte macrophage progenitor cells (GMP) from mice, the MLL-AF9 translocation product (one of the most frequent gene rearrangements found in infantile and therapy-related leukemias) transforms the GMPs into a cell that can efficiently transfer leukemia to a healthy recipient. Sanofi-aventis's grant aids in the development of a model using human cells and provides a means to test potential therapeutics on the elusive leukemia stem cell. They are interested in moving the research area forward in their search for new and effective cancer therapies.



Collaboration with Microfabrica Inc. for New Tools for Minimally Invasive Cardiac Surgery

Pedro del Nido, MD, chief of Cardiac Surgery, is collaborating with Boston University and Microfabrica Inc. to develop a robotic needle that can extend into the heart through needle-sized incisions in the chest and heart walls. The goal is to enable complex surgical repairs while the heart is still beating in a manner that is as minimally invasive as catheter interventions. At the end of the robotic needle are millimeter-sized metal tools for removing and suturing tissue. Using medical imaging technology to guide the robotic needle to the surgical site within the heart, the tiny tools could be used to repair heart valves and close leaks. A surgical procedure that can be done using these instruments while the heart is still beating would eliminate the risks of putting patients on cardiopulmonary bypass. The collaboration is funded by a five year, $5 million grant from the National Institutes of Health Bioengineering Research Partnership.

STARTUP ACTIVITIES

TIDO continually explores opportunities to develop Children's technologies through the creation of new businesses. Depending on the opportunity, TIDO's role has ranged from licensing core technology platforms to active solicitation of initial funding and recruiting key management leaders. Below are highlights of last year's developments in new businesses formed through Children's innovations.

Fate Therapeutics, Inc. Options Stem Cell Stimulation Technology

In May 2008, Children's signed an exclusive option agreement with Fate Therapeutics, Inc., for the rights to methods of stimulating hematopoietic stem cells discovered in the laboratory of Leonard Zon, MD, director of Children's Stem Cell Research Program. Fate is a new company, formed at the end of 2007 with Dr. Zon serving as one of five founding scientists. It is focused on developing medicines that stimulate adult stem cells resident within the body to fight disease and regenerate damaged cells and tissue. A license to Children's innovations can supply an integral cornerstone to Fate's strategic development.

Dr. Zon's group has found that chemically stabilized derivatives of the naturally occurring inflammatory signal Prostaglandin E2 are potent stimulators of hematopoietic stem cells. Treatment of bone marrow, peripheral blood stem cells or umbilical cord blood before transplantation into a recipient speeds the recovery of the hematopoietic system and reduces the amount of material needed for a successful transplant. So far, the treatments have been demonstrated in zebrafish and mice, but not in humans. However, the treatments work on human umbilical cord blood cells when transplanted into mice.

The option agreement is expected to lead to an exclusive license.

LEONARD ZON, MD

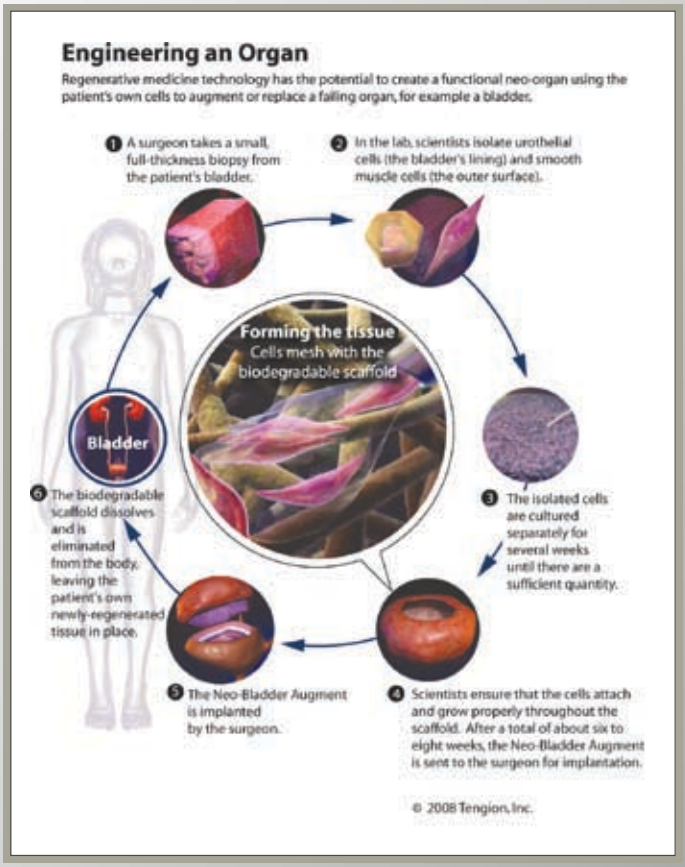
GROWING ORGANS FROM PATIENTS' OWN CELLS: SCIENCE FICTION?

Tengion, Inc., a company formed from groundbreaking basic and clinical research at Children's Hospital Boston, is turning the regenerative medicine dream into a reality

Dr. Anthony Atala's pioneering work

When Dr. Anthony Atala, MD, joined Children's Hospital Boston in the late 1980s, little did he know that he would spend 15 years here (Dr. Atala is currently the director of the Wake Forest Institute for Regenerative Medicine), conducting groundbreaking research that has since revolutionized the field of regenerative medicine and that his work would become the basis for a company able to regenerate diseased and failing organs and tissues.

At that time, the standard procedure for treating patients with neurogenic bladder (due to spina bifida, spinal cord injuries, multiple sclerosis, Parkinson's and other diseases) as well as bladder cancer was to surgically augment or remove the bladder and replace it with a section of the patient's bowel. This highly dangerous and complex surgery practiced since the 1800's has serious and well-documented limitations, mainly due to the intestine's physiological function, which is to absorb urine and excrete mucus. Performing the bowel-for-bladder augmentation on children bothered Dr. Atala. It did not make sense to him to perform a surgery that was bound to create problems in a child with a 70 or 80 year life expectancy. Thus began Dr. Atala's quest for a way to grow new bladders for his patients.



Dr. Atala decided to explore tissue engineering, which could use the patients' own (autologous) cells, and therefore avoid many of the problems associated with organ transplant, including rejection. His idea was to grow the autologous cells on a scaffold in the shape of the desired organ.

In 1999, Dr. Atala reported that these autologous bladders functioned well in large mammals for a full year—and that same year he inserted the bladder scaffold seeded with cells into the first of seven children with spina bifida. This clinical trial was the first to study a regenerated human organ. The successful implantation and multi-year follow-up data were reported in the prestigious medical journal *The Lancet* in 2006. The publication prompted worldwide media coverage about scientists' ability to grow organs from a patient's own cells. In addition, Dr. Atala's group had expanded its work to growing other autologous organs and tissues such as urethras, skeletal muscle, blood vessels and cartilage.

A startup company: the best way to develop Dr. Atala's technology

During this time, TIDO at Children's protected the technology by actively filing patents and building a large worldwide intellectual property portfolio to cover all aspects of this complex work. The best route to successfully commercialize the technology was a subject of debate at TIDO. While former Director, Don Lombardi, favored the strategy of a startup company that would give the broad technology the attention it needed, the former Director, Dr. Brenda Manning, was rooting for a deal with a large pharmaceutical company that would have the necessary infrastructure and financial resources. They finally agreed to seek a venture capital firm with solid backing from leading investors, including a pharmaceutical company, partly to ensure that Dr. Atala would closely participate in the evolution of his technology.

A few months later they began discussions about an exclusive license agreement with Scheer & Company, a life sciences advisory firm that had a track record of building a series of successful companies and a network of institutional and corporate venture capital groups, including a long-standing relationship with Johnson & Johnson. Johnson & Johnson was and continues to be a tremendous supporter of Tengion and its involvement, along with that of Tengion's other investors, has significantly contributed to the success of this technology. David Scheer, president of Scheer & Company, has served as the company's chairman of the Board of Directors since inception.

After one year of ongoing talks with TIDO, the worldwide exclusive license agreement to form a startup called Tengion was signed in 2003. At the time of the deal, forty-eight patent applications had been filed by TIDO and close to $500,000 spent on the intellectual property portfolio. Scheer & Company recruited an experienced management team, with Dr. Atala as a member of the Board of Directors and the chairman of its Scientific Advisory Board, and established headquarters in Philadelphia.

Tengion: achievements to date

Tengion has made remarkable progress since its foundation in 2003. The company has had to overcome a number of challenges, including building the world's first facilities to grow human organs, and advancing the technology of non-traditional personalized therapeutic products to produce them efficiently and safely with guidance from the US Food and Drug Administration and European medical regulators. Despite these scientific, manufacturing and regulatory difficulties, it is now a high-profile clinical stage biotechnology company focused on the development of neo-organs and of neo-tissues. Tengion was named a model of venture capital-backed innovation and success at the 35th Anniversary Celebration of the National Venture Capital Association.

Today, approximately 100 employees are working at Tengion's headquarters and research laboratories—both of which house their neo-organ production facilities. Tengion's management team has raised approximately $150M from top biotech equity investors in four rounds of financing in August 2004, June 2006, September 2007, and October 2008 to support the company's pioneering work.

Currently, the company's lead product candidate, the Tengion Neo-Bladder Augment™, based on Dr. Atala's basic and clinical research at Children's, is in Phase II clinical trials in pediatric patients with spina bifida, and adult patients with spinal cord injury. The European Medicines Agency has designated the Neo-Bladder Augment as an orphan medical product for the treatment of spina bifida and for the treatment of neurogenic bladder associated with spinal cord injury. In the next year, Tengion expects to begin Phase II clinical trials with its Neo-Urinary Conduit – a product designed to treat patients whose bladders are removed due to bladder cancer and who today have their replacement bladders rebuilt using bowel or intestinal tissue.

In addition to the Neo-Bladder Augment, Tengion is researching and developing additional cutting-edge product candidates: Neo-Bladder Replacement™, Neo-Vessel™ and Neo-Kidney™.

SIGNIFICANT MILESTONES ON LICENSED AGREEMENTS

Entremed, Inc. Received IND Approval for 2-Methoxyestradiol to Treat Rheumatoid Arthritis

At the end of 2007, Children's licensee EntreMed, Inc. received IND approval for 2-methoxyestradiol (2ME2 or Panzem®) to treat rheumatoid arthritis. The company plans to conduct standard safety studies in human subjects as required by the FDA. Additional pre-clinical data showing the efficacy of 2ME2 in an animal model was published in late 2008 (*J Rheumatol* 2008;35:2119-28).

RESEARCH HIGHLIGHTS

THE CHILDREN'S HOSPITAL INFORMATICS PROGRAM (CHIP)

The Children's Hospital Informatics Program (CHIP) is a multidisciplinary applied research and education program at Children's Hospital Boston. Under the direction of Isaac Kohane, MD, PhD, 22 CHIP faculty investigators work at the intersection of information science and clinical and biomedical discovery. CHIP's faculty include distinguished leaders in the fields of personally controlled medical records; coordination and analysis of dispersed medical record information; and the aggregation, analysis and display of large, complex datasets. Two of the CHIP projects are highlighted here.

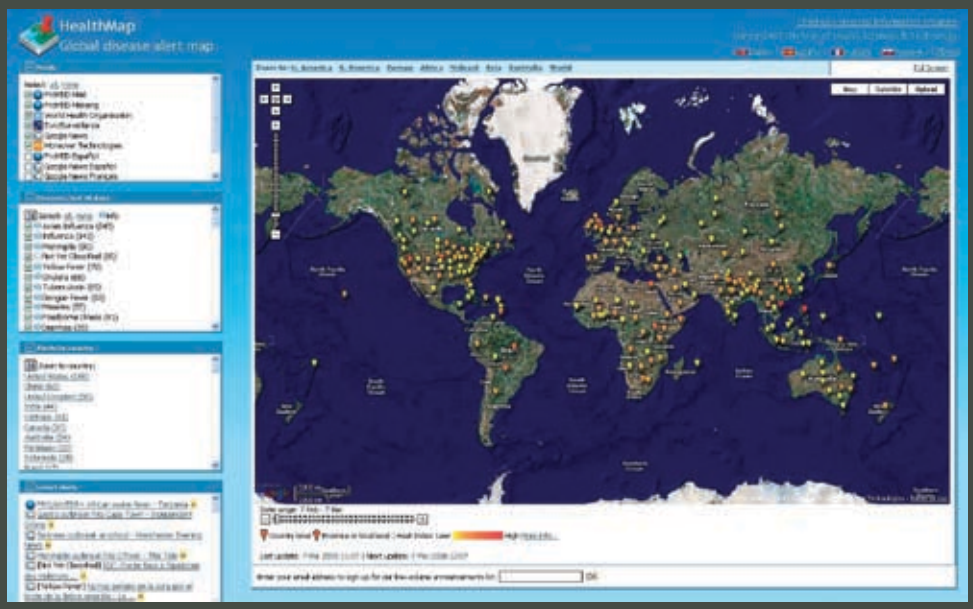
IndivoHealth™

More than a decade of work, by Dr. Kohane, Kenneth Mandl, MD, MPH, Division of Emergency Medicine, Dan Nigrin, MD, MS, chief information officer and many others, has built the foundation for the realistic application of Personally Controlled Health Records (PCHRs), enabling patients to own complete and secure copies of their medical records and to integrate their health information across sites of care and over time. IndivoHealth™, a development project within CHIP, has created a software application platform for PCHR, built to public standards and made available as open source code for wide adoption. Using this platform, IndivoHealth has already developed and deployed PCHR systems in real-life settings. The MyChildren's patient portal (**http://MyChildrens.org**) provides a secure Web site for patients and families to interact with Children's. It allows them the ability to view a patient's personally controlled health record, manage ambulatory appointments, send secure HIPAA-compliant messages to clinicians within Children's, view and pay bills online and update demographics. MyChildren's has been piloted in several clinics and will be deployed to all outpatient clinics in 2009.

By far the largest deployment of the IndivoHealth-based PCHR system is in collaboration with Dossia, which is a consortium of large employers united in their goal of providing employees, their dependents, retirees and others in their communities with an independent, lifelong health record. As announced in September 2008, Walmart has rolled out an IndivoHealth-based PCHR system to all of its 1.4 million employees and their dependents as part of the company's benefits package. TIDO is working with the CHIP researchers to enable the Indivo platform to power the growing revolution in health record accessibility.

HealthMap

Developed by CHIP investigators John Brownstein, PhD, associate professor, Division of Emergency Medicine and Clark Freifeld, MS, reseach software developer with CHIP, HealthMap provides a unified and comprehensive view of the current global state of infectious diseases and their effects on human and animal health. It filters and synthesizes data from a variety of Internet sources, ranging from conventional news media reports to blogs, in multiple languages, then extracts the relevant disease-specific information tied to its location in the world. In essence, HealthMap provides a bird's-eye view of global health, with interactive maps and color-coded alerts of infectious "hot spots," and is able to sound warnings about outbreaks well before they are reported by public health sources. "We've traced the earliest reports of the SARS virus back to Internet chat rooms where people were talking about a problem going on in Guangdong Province in China," notes Brownstein.



HEALTHMAP.ORG, GLOBAL DISEASE ALERT MAP

Additional development of HealthMap is funded through a $3 million grant from Google.org to combine HealthMap with the ProMED-mail global alert system for health specialists run by the International Society of Infectious Diseases. Together, ProMed-mail and HealthMap aim to identify infectious disease hot spots, detect outbreaks earlier, and initiate quick responses. A view of HealthMap is freely available at **HealthMap.org**, integrated into Google's GoogleMap viewer. Access to raw data feeds of the HealthMap content for customized use is available through a licensing agreement through TIDO. Also, applications are in development for the intelligent extraction of relevant information from diverse Internet sources, and the display of geopositional data correlated with a wide array of other extracted intelligence.

KENNETH MANDL, MD, MPH, AND JOHN BROWNSTEIN, PHD

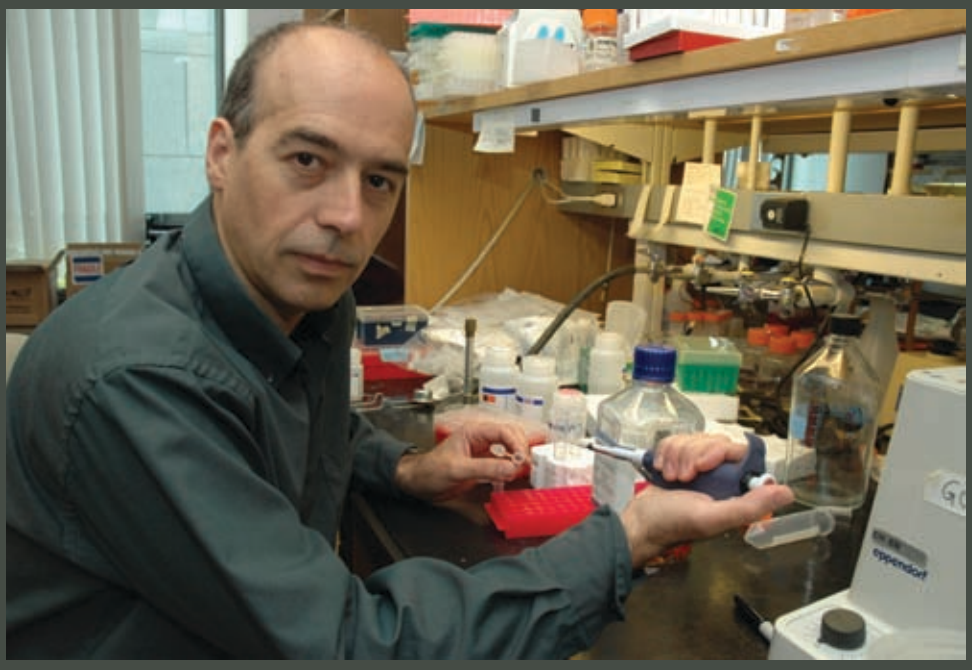
NEUROBIOLOGY PROGRAM

The Neurobiology Program at Children's Hospital Boston is a multidisciplinary program that includes faculty members studying essential aspects of neurological development at all levels, from the single neuron to small neural networks to neurological systems to the brain. The group's investigation of complex genetic disorders that impact neurological development has led to a deeper understanding of how the brain develops and functions, opening up new possibilities for the treatment of a variety of neurological diseases. Scientists studying biological questions as well as clinical specialists who treat patients and perform research are both well represented in the program, facilitating the performance of translational research projects focused on efficient development of cures for patients.

The research includes studies of molecular mechanisms controlling neuronal regeneration, differentiation and synapse formation; studies of disorders such as Rett syndrome, congenital strabismus, tuberous sclerosis, autism, complications of premature birth, hypoxic injury and epilepsy; and studies of early childhood brain development, including the wiring of visual circuits, processing of images and interpretation of emotion. Two specific projects on which TIDO has filed patent applications are highlighted below.

Promising Treatment for Peripheral Neuropathy—a Devastating Disease

Gabriel Corfas, PhD, professor of the F.M. Kirby Neurobiology Center at Children's, and Departments of Neurology and Otolaryngology at Harvard Medical School, and his former postdoctoral fellow, Joshua Murtie, PhD, have made a promising discovery to cure peripheral neuropathy, a disease that afflicts millions of patients. The disease results in dramatic sensory defects, with a variety of symptoms, including loss of sensation or chronic pain. It commonly affects the extremities of patients with diabetes, AIDS, alcoholism and those with cancer who are undergoing chemotherapy. Because of the loss of sensation, the



GABRIEL CORFAS, PHD

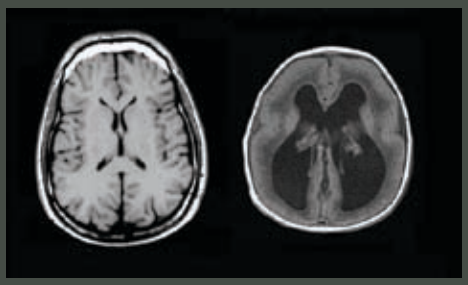
extremities often suffer from injuries caused by agents such as heat and sharp edges, leading to wounds that are difficult to heal. Currently, there is no cure for peripheral neuropathy and the existing treatments only address the symptoms of the disease. Dr. Corfas and Dr. Murtie have discovered a compound that can not only cure neuropathy, but also prevent it from developing. Results in well-established neuropathy mouse models are very convincing. They show that the compound produces not only anatomic improvement in the abnormal nerve fibers, but even more importantly, the recovery of the nerve function. Furthermore, investigators have designed a topical application for the drug, aimed at a safe and convenient delivery system for patients.

"We are very hopeful that this cream cannot only treat the patients who have already developed nerve damage and pain because of the neuropathy, but also prevent the nerve damage and the pain from developing in the patients at risk," says Dr. Corfas. The manuscript detailing the scientific results has been submitted. TIDO has filed for patent protection, an essential step for future commercialization of the technology. The discovery has sparked interest among the investment community because it is relatively advanced and close to commercialization for an academic technology. TIDO is talking to contract research organizations to define the best, quickest and most efficient path to the safe use of this compound in humans. The Office is also talking to potential partners that can diligently bring this technology to the market.

Stopping Epilepsy Before it Starts

Seizures shortly after birth can have long-term detrimental effects on brain development. Every seizure event increases the likelihood that a person will have recurring seizures and develop epilepsy. As a clinician, Frances Jensen, MD, director of Epilepsy Research, is keenly aware of the treatment options faced by these patients as well as the prognosis for their long-term outcome. Dr. Jensen's research has shown that several FDA-approved drugs, including topiramate and bumetanide, may prevent seizures in newborns, and Children's has filed patents on both of these treatments to support their ultimate development into products. She is currently conducting a Phase I clinical trial testing the addition of bumetanide to the current standard of care for seizures in neonates.

Dr. Jensen's current work examines the mechanism of "epileptogenesis," the process by which seizures change the brain and make neurons more susceptible to future seizures. Results published by Dr. Jensen's group in 2008 in the *Journal of Neuroscience* show that seizures cause modifications of AMPA receptors present on the neuron's surface, which make them more sensitive and likely to suffer the overstimulation that results in a seizure event. Dr. Jensen was one of 12 investigators in the country to receive an NIH Pioneer grant, awarded for highly innovative, potentially transformative approaches that address major challenges in biomedical research. This funding is supporting further elucidation of the cascade of post-seizure molecular events that results in cognitive and behavioral impairment, learning disorders or autism. Using this increased understanding, Dr. Jensen is developing new treatments for seizures that address these downstream consequences. Children's has filed patents describing these treatment regimens.



RARE BRAIN MALFORMATIONS

FRANCES JENSEN, MD

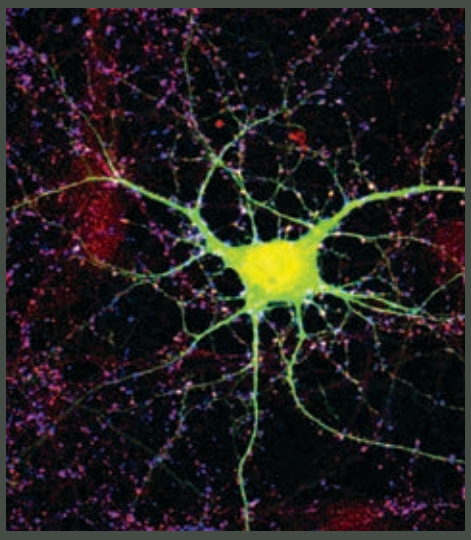
AUTISM INTERDEPARTMENTAL COLLABORATION

Genetic Origins of Autism Spectrum Disorders and Developmental Delay

Autism spectrum disorders (ASDs) affect as much as 0.6 percent of the population. Although autism appears to have a strong genetic basis, no commonly occurring causative mutations have been discovered. Instead, more than a dozen mutations (single gene mutations, DNA deletions and duplications) have been associated with the disorder. No individual mutation accounts for more than 1 percent of the total number of cases, and a genetic cause has been found for only about 15 percent of cases. Children's has a strong multidisciplinary clinical and basic science research effort aimed at investigating the causes, diagnosis and possible treatments for autism. TIDO is exploring opportunities to help bring these research discoveries into clinical practice.

The lab of Bai-Lin Wu, PhD, in the Genetics Diagnostic Laboratory, within the Department of Laboratory Medicine, has developed a simple, rapid and cost-effective whole-genome analysis that uses both commercial DNA arrays and custom-designed arrays developed for clinical use to detect deletions or duplications among children with developmental delay and ASDs. In a collaboration between researchers from Laboratory Medicine and the Division of Genetics, 512 patients referred for developmental delay and/or suspected ASDs were screened for genetic copy-number variants (duplications or deletions of genomic regions). The study revealed that in some of the patients a section of chromosome 16 is deleted, and in others it is duplicated. The findings were published in the *New England Journal of Medicine* in February 2008, in combination with similar findings from other institutions in the nationwide Autism Consortium, which is a collaboration of 14 leading universities and medical centers, including Children's. The Consortium makes DNA samples available from a national research repository known as the Autism Genome Research Exchange. The same chromosome 16 deletions were detected in patient DNA samples from that repository, as well as in patients studied by deCODE Genetics, Inc. in Iceland. Combining these studies, it is estimated that the chromosome 16 deletion/duplication accounts for about 1 percent of all autism cases, meaning it is one of the most prevalent genetic causes of autism yet reported.

The Genetic Diagnostics Laboratory continues to use the whole genome analysis to detect deletions or duplications among children with developmental delay and ASDs. An updated study, published this year in the *Journal of Medical Genetics* by Dr. Wu and collaborators, describes a deletion/duplication on chromosome 15, discovered in several of the 1,445 patients screened, and in those from the Autism Consortium repository samples. Unfortunately, after screening so many patients, no frequently occurring deletions or duplications have been detected, reenforcing the idea that autism represents the common symptoms resulting from extremely heterogeneous causes. However, this genome analysis allows clinicians to subtype the autism spectrum disorders, identify distinct clinical presentations associated with this specific genetic variation and hopefully to tailor treatments to specific subsets of autism patients.



DR. GREENBERG'S LAB GENERATED THIS IMAGE OF A NEURON, HIGHLIGHTING ITS SYNAPSES

Taking a dramatically different approach, a collaboration led by Christopher Walsh, MD, PhD, chief of Genetics at Children's, has identified several new genes associated with ASDs and helped define their role in the development of the brain. The study, published in *Science* in July 2008, looked at large families with multiple children with autism whose parents were related. The study

CHRISTOPHER WALSH, MD, PHD

looked for any DNA deletions/duplications as well as markers of chromosome blocks inherited with autism, and within these regions individual genes were sequenced to detect single nucleotide mutations.

Just over 6 percent of the 88 families showed rare, inherited deletions within DNA regions linked to autism. These affected DNA regions varied among families, which is further indication of the many genetic causes of autism. In all, the technique identified five chromosome deletions affecting at least six identifiable genes (C3orf58, NHE9, PCDH10, contactin-3 [CNTN3], RNF8 and genes encoding a cluster of cellular sodium channels). NHE9 was also found to be mutated in children with autism from unrelated parents (particularly those with both autism and seizures).

Working independently of Dr. Walsh, Michael Greenberg, PhD, then the director of the Neurobiology Program at Children's, and his colleagues had already identified three of the same genes (c3orf58, NHE9 and PCDH10) while looking for genes that turn on or off in response to synaptic activity. Dr. Greenberg had mapped at least 300 genes that are regulated in neurons in response to synaptic changes, and may underlie the physiological basis of learning. His *Science* paper, combining genetic etiology with clues to the mechanism of abnormal neuronal development, heralds a new direction in research to understand autism.

THE VASCULAR BIOLOGY PROGRAM

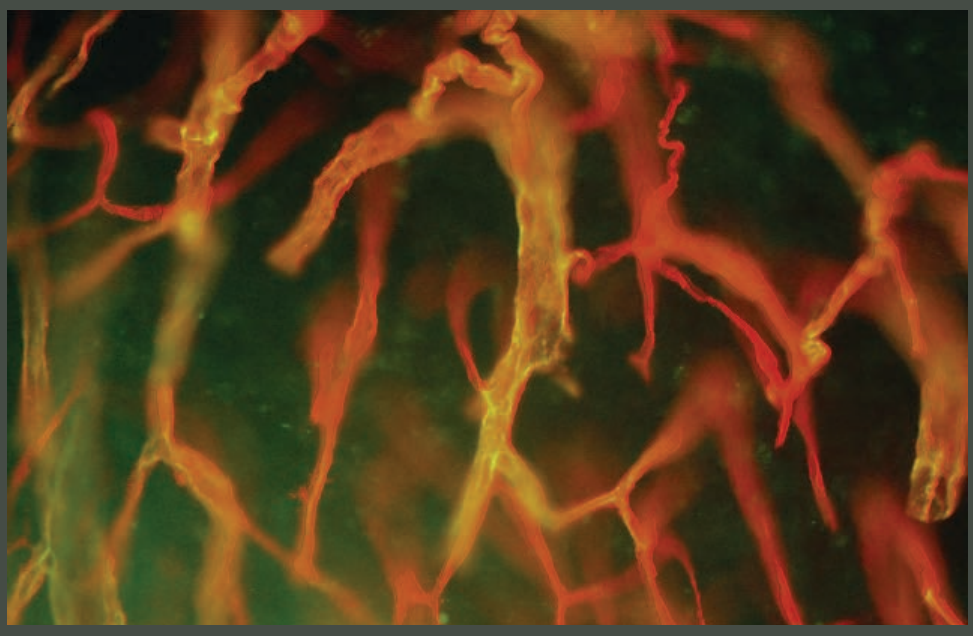
The Vascular Biology Program (VBP) was founded by the late Dr. Judah Folkman, MD, centered around the area of angiogenesis as it relates to cancer. The program now has expanded into other areas with angiogenic components such as heart and eye diseases, metastasis, obesity and stem cells. A number of new anti-cancer drugs that target the process of angiogenesis have been discovered in the VBP. To learn more about the VBP at Children's, see the feature interview with Marsha Moses, PhD, the interim director of the VBP, on page 28.

Treatment to Make Organs Refractory to Metastasis

Most cancer patients do not die from the primary cancer tumor, but from metastasis—cells that migrate from the primary tumor, land in distant organs and start new tumors. Physicians have known for years that tumors seem to select where their metastases will grow: lung cancer often metastasizes to bone, for example. But no one knows what guides this site selection, or the likelihood that the metastasis will actually develop.

Randolph Watnick, PhD, assistant professor in the Department of Surgery, Vascular Biology Program, works in the important area of tumor and stroma interactions. He has been studying thrombospondin, a natural angiogenesis inhibitor, for many years. More recently, he discovered an important link between this angiogenesis inhibitor and the phenomenon of metastasis. He and his team discovered a common property among several types of tumors known to be metastatic in humans: they all had the ability to turn off thrombospondin. Cells from primary tumors that did not metastasize actually stimulated the thrombospondin production in the distant organs, which could otherwise be the target of metastasis.

Using this information, Dr. Watnick has identified a novel suppressor, a protein that reduced metastasis in mice by as much as 20-fold. The use of this protein has been shown to



ELECTRON MICROGRAPH OF BLOOD VESSELS

prevent metastasis in preferential metastatic sites such as bone, lung, liver and lymph node. A companion diagnostic, to identify organs most likely to develop metastasis from a particular tumor, has also been developed. This is a new approach to cancer management, and supports Dr. Folkman's idea of managing cancer as a chronic disease, a dramatic shift in the current oncology paradigm.

The research is ongoing, attempting to further develop this protein into a drug. Dr. Watnick now plans to expand his original findings to identify other types of tumors whose metastasis may be inhibited by this protein. His team is also actively exploring the mechanism of action of this protein with the goal of identifying new targets or pathways for anti-metastatic therapy. They have also developed a powerful screening system which allows for the discovery of other similar proteins. TIDO sees great potential in this technology and has filed patent applications to protect it. The Office has been actively talking to potential partners to develop the technology.

RANDOLPH WATNICK, PHD

STEM CELL PROGRAM

Science magazine named Reprogramming Cells as the 2008 Breakthrough of the Year (and runner-up in 2007), citing George Daley, MD, PhD, associate director of Children's Stem Cell Research Program, along with colleagues at other institutions for groundbreaking discoveries in reprogramming adult cells into induced pluripotent stem (iPS) cells, and creation of disease-specific iPS cell lines from patients carrying genetic disorders. For several years, Dr. Daley has focused his laboratory's efforts on reprogramming adult tissue cells from an individual patient so they revert to an embryonic state, creating induced pluripotent stem cells. Once in this more primitive, pluripotent state, the adult-derived cells can theoretically be coaxed into developing as healthy cells of many types so they can be used to replace damaged, diseased cells and tissues. Dr. Daley and others are refining and testing several genetic and chemical strategies to make reprogramming more efficient.

Dr. Daley's lab has also created iPS lines from cells derived from patients carrying mutations causing neurological, muscular, metabolic and other disorders. These lines will be a valuable resource to create specific differentiated cells to study disease processes. For instance, researchers have an unlimited source of neurons from Alzheimer's patients and can screen for therapies that act on the specific affected cells. Children's is working closely with the Harvard Stem Cell Institute, a collaborative network of Harvard and Harvard-affiliated stem cell researchers working to establish a core facility for the creation, propagation and distribution of iPS cell lines; Dr. Daley's cell lines will help establish their iPS cell repository.

Although iPS cells closely resemble stem cells derived from human embryos, Dr. Daley is studying the subtle differences between them and the ramification these differences may have in the utility of iPS and embryonic stem cells. He is quick to point out that the iPS cells have not replaced the

LEONARD ZON, MD, AND GEORGE DALEY, MD, PHD

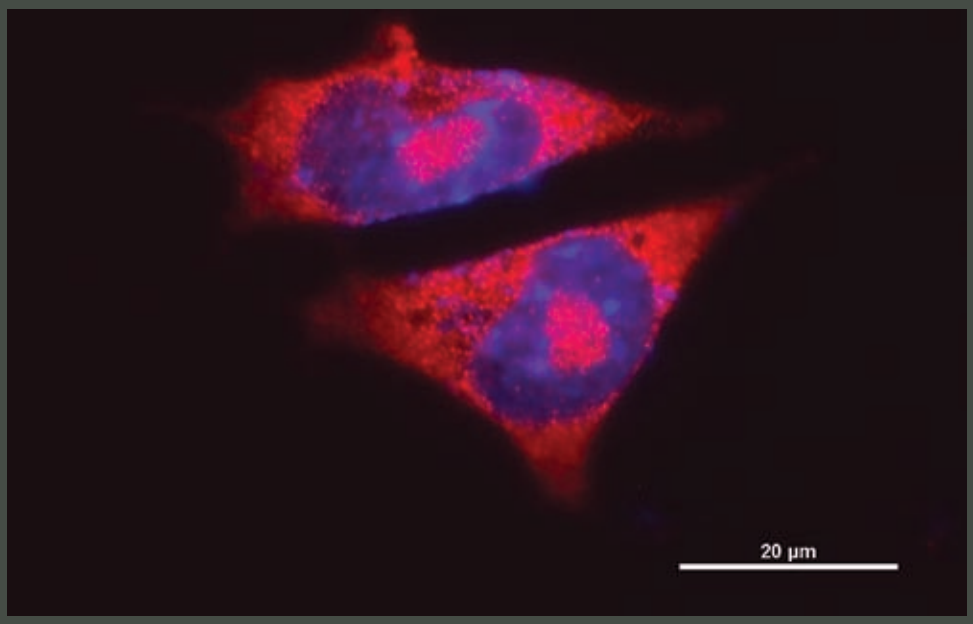
need to study human embryonic stem cells, and he has welcomed the executive order by President Obama on March 9th, 2009 "Removing Barriers to Responsible Scientific Research Involving Human Stem Cells". This change in government policy will certainly speed discovery and broaden opportunities for researchers to utilize techniques and tools developed in the Children's Hospital stem cell research community.

Dr. Daley's lab continues to pursue another approach to reprogram adult cells into the stem cell state that relies on a technique called nuclear transfer (NT), in which the nucleus of an adult cell is placed into an egg cell that has had its original nucleus removed, but still contains natural embryonic factors that reprogram the nucleus, creating a new embryo. Embryonic stem cells created from the NT-derived embryo are then grown in culture, where they can be manipulated to correct genetic mutations or induced to form specific, differentiated cells. In mouse models with a genetic blood disorder, the Daley group has created NT-derived embryonic stem cells from the adult mouse, repaired the mutation in culture, induced the cells to partially differentiate into hematopoietic stem cells (HSCs) and transplanted the HSCs to regenerate a healthy blood system in a recipient mouse, curing the disorder in the mouse. The process is extremely inefficient, but it shows potential for human therapies one day.

Another powerful technique developed in the Daley Lab to create pluripotent cells is based on parthenogenesis, which allows scientists to derive embryonic stem cells from an unfertilized egg—avoiding the need to use viable embryos. Eggs, or unfertilized oocytes, are artificially stimulated to duplicate their chromosomes, resulting in an embryo for cell regeneration therapy that can be tailored to be immunologically compatible with any recipient. These cells can be induced to create heart, skin, blood, liver, spleen, brain, thymus and hair. Dr. Daley ultimately envisions "banks" of master cells and tissues for matching to specific patients, but the transplantation work is currently in a basic modeling stage in animals.

A discovery from Richard Gregory, PhD, a principal investigator in Children's Stem Cell Program, provides a missing link between stem cell generation and carcinogenesis, and points to new approaches to blocking certain cancers. Collaborating with graduate student Srinivas Viswanathan from Dr. Daley's lab, Dr. Gregory showed that the protein Lin-28 regulates an important family of microRNAs called Let-7. Lin-28 is abundant in embryonic stem cells and inhibits them from differentiating into specific cell types, but it is not normally found in healthy adult tissues. It has been used in a cocktail of genes to reprogram fully differentiated cells into induced pluripotent stem cells. As the team reported in *Science* in April 2008, increasing the level of Lin-28 protein in a cell blocked the production of mature Let-7 microRNAs, making them unavailable to regulate cell activity. Conversely, inhibiting Lin-28 production led to an increase in mature Let-7. This is important because low levels of Let-7 microRNAs make a cell more prone to de-differentiate and are associated with breast and lung cancer. Let-7 microRNAs have been shown by other groups to control the expression of certain oncogenes. "We are actively seeking both drugs that mimic the effect of Lin-28 on microRNAs to enhance stem cell generation, and drugs that block Lin-28 to inhibit cancers," says Dr. Gregory.

Today, Dr. Gregory is conducting large-scale chemical screening to find such compounds. He also hopes to find other microRNAs involved in stem cell self-renewal and differentiation—as well as compounds that target them.



LIN-28 IN MOUSE EMBRYONIC STEM CELLS

In a very practical application of stem cell technology, Dario Fauza, MD, associate in Surgery, is pioneering fetal tissue engineering to produce tissue to repair congenital anomalies. He has developed a method to harvest and purify fetal cells from the amniotic fluid surrounding a fetus *in utero*. He found that, like stem cells, some of these cells have the extraordinary power to grow into many tissue types in the body.

Dr. Fauza combined these cells with scaffolding materials to grow new tissues and organs for surgical reconstruction in large animals and is planning clinical trials in newborn patients with prenatally diagnosed birth defects. Fetal cells are immature and not yet fully specialized and could be used to generate a variety of tissues. Dr. Fauza has had success in building and implanting engineered diaphragm, trachea and bone material in sheep. Because these grafts are made using the recipient's own fetal cells that have been shed into the amniotic fluid, there would be no risk of the immune system rejecting the grafts.

DARIO FAUZA, MD

CLINICAL RESEARCH HIGHLIGHTS

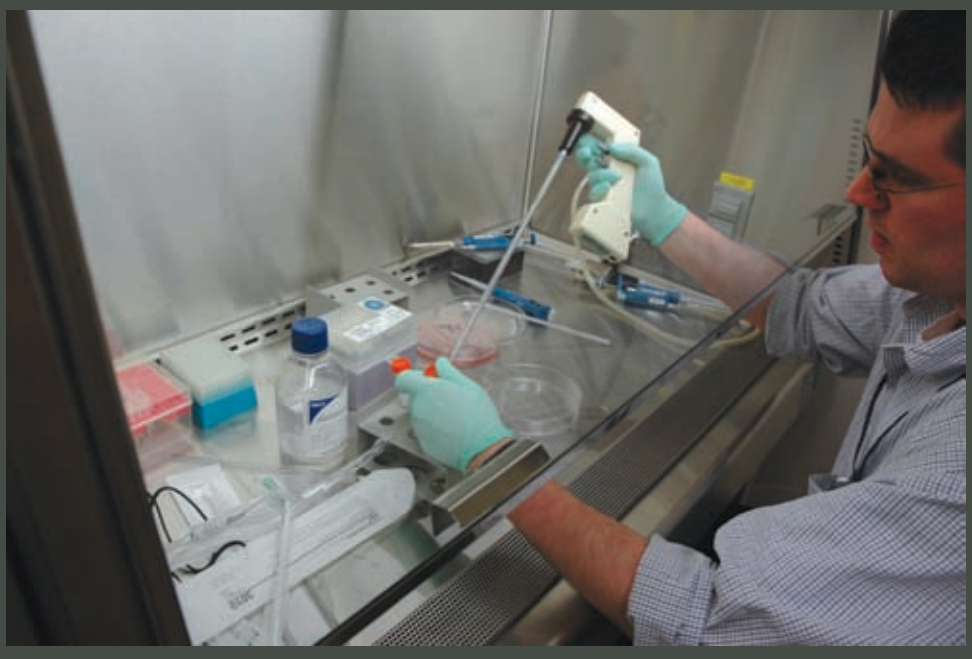
While the basic research efforts in the various laboratories at Children's are searching for the cures of tomorrow, other researchers focus on applied technology addressing critical challenges in clinical care. Clinical research innovations at Children's cover a broad spectrum of technologies, from novel therapeutic devices to diagnostic tools, and in a variety of departments and programs such as Cardiology, Medicine and Neurology. Overall, the results from Children's clinical research projects have been encouraging and continue to have a significant impact on the development of the next generation of clinical innovation.

Transcranial Magnetic Stimulation for Treatment of Seizures

Alexander Rotenberg, MD, PhD, from the Department of Neurology, is working towards a treatment for epileptic seizures in adults and children using Transcranial Magnetic Stimulation (TMS). Repetitive TMS (rTMS) is a technique for noninvasive focal brain stimulation by which small intracranial electrical currents, which excite the neurons, are generated by a fluctuating extracranial magnetic field.

Rather than reducing seizure frequency in established epilepsy, an approach taken by other researchers, Dr. Rotenberg uses EEG-guided rTMS to interrupt ongoing seizures, a method that was proven effective in a rat epilepsy model. He has also carried out a promising trial in a number of adult patients treating ongoing seizures caused by *epilepsia partialis continua*. The treatment's effects in adults last from minutes to a few months. He hopes to find that higher neuroplasticity of the developing brain will enable longer-lasting treatment effects in children.

TIDO is supporting Dr. Rotenberg's research by managing collaborations with other institutions and industrial partners to



HANNO STEEN, PHD

develop hardware and software and license to a TMS equipment manufacturer.

Acute Appendicitis Diagnostic

Rapid differential diagnosis of acute appendicitis remains a severe, unmet medical need. Diagnosis is confounded by the indistinct symptoms of appendicitis and made urgent by its typical emergency room presentation. Despite increasingly expensive standards of diagnostic care associated with ultrasound and CT scans, 3 to 30 percent of suspected cases lead to unnecessary surgeries for non-appendicitis ailments, and 30 to 45 percent of appropriate surgeries are delayed until after the appendix has ruptured.

Alex Kentsis, MD, PhD, and Richard Bachur, MD, both of Children's Emergency Medicine Department, are collaborating with Hanno Stein, PhD, director of Children's Proteomics Center, to find markers in patients' urine that will better distinguish acute appendicitis from a wide range of mimicking conditions. These candidate markers were validated in a study of 67 patients presenting at Children's Emergency Department with possible appendicitis. One protein was found to clearly differentiate appendicitis from other conditions. Immunological detection methods were used to confirm the elevated levels of the marker and its histological association with the inflamed appendix. Drs. Kentsis and Bachur hope to have this biomarker developed into a simple point-of-care test, such as the dipstick test used for pregnancy tests. Having such a rapid, sensitive and specific diagnostic available in clinics and emergency rooms could reduce unnecessary surgeries and speed true appendicitis cases into the operating room.

Beating-heart Cardiac Surgery

Pedro del Nido, MD, chief of Cardiac Surgery, is working on tools and methods that will allow for repair of septal defects and mitral valve prolapses in the heart without having to open the patient's chest or put the patient on bypass. The specialized devices he's developing will enable minimally-invasive repairs inside the beating heart that are not possible with the current minimally-invasive techniques and transcatheter procedures. The specialized instruments in development are:

1) A cardioport that permits the safe introduction of surgical instruments into the cardiac chambers without the risk of significant blood loss or air emboli. It also provides optical visualization in the presence of blood. Initial prototyping has been done with funding from the Massachusetts Technology Transfer Center and Center for Integration of Medicine and Innovative Technology. The prototype has been tested in a porcine model.

2) A deployment system for the introduction of bioprosthetic and synthetic patches to repair septal defects. The deployment system, developed with funding from the National Institutes of Health, successfully delivers a patch to close atrial and ventricular septal defects created in porcine septa.

3) A fixation anchor with a customized delivery device to attach a patch to the septum once the patch has been delivered by the deployment system. Prototyping and animal testing have been funded by the NIH. Studies have demonstrated that the fixation anchor successfully penetrates the patch material and septum to hold the patch in place.

4) A mitral clip with a customized delivery device for the treatment of mitral valve prolapse. Prototyping and testing have been done with funding from the NIH.

Developing specialized instruments, though, is just one component of his extensive research program. Medical imaging is needed to allow the surgeon to manipulate the instruments within the heart without directly visualizing the heart during the surgery. In collaboration with a team of engineers, three-dimensional ultrasound imaging is being enhanced to provide the surgeon with real-time images of the heart tissue and instruments. The devices and imaging together will allow the same types of cardiac repairs to be done in a less invasive manner with fewer potential risks.

PEDRO DEL NIDO, MD

TECHNOLOGY DEVELOPMENT

In 2008, the Technology Development (TD) function of TIDO was redefined and formalized as one of the four functions of the office. Through TD efforts, TIDO aims to advance promising Children's technologies and innovations and increase the probability of translation into products for the public benefit. TD will accomplish this goal in part by providing grants through its new Technology Development Fund.

In 2008, TIDO staff surveyed several universities and hospitals around the country to understand their approach to filling the "gap" between early academic research and late-stage technologies sought by companies and investors. Based on the feedback, and taking into account the portfolio of Children's technologies, Technology Development Manager, Monique Yoakim-Turk, PhD, developed the structure and processes of the Children's TD Fund. The TD Fund is committed to providing the funds necessary to advance a technology; access to product development experts in the form of an advisory board, a network of co-development partners and CROs; and project management of the funded projects under the supervision of a mentor from the advisory board.

MTTC and SBIR Grants

The TD team is also working to accelerate product development by securing new partnerships and funding opportunities. Through these efforts, Carmen Barnes, PhD, of the Vascular Biology Program, was awarded a $40,000 grant from the Massachusetts Technology Transfer Center to develop an ELISA immunoassay to measure blood levels of the naturally occurring steroid hormone, 2-methoxyestradiol (2ME2). Dr. Barnes is collaborating with Prime Organics, Inc. on the early steps of immunoassay development. She presented her project to an audience of investors and entrepreneurs at the Early-Stage Life Sciences Technology Conference in March 2008.

Small Business Innovation Grants (SBIR) grants continue to be a good source of federal funding for Children's investigators. Joseph Madsen, MD, in the Department of Neurosurgery, in collaboration with Infoscitex Corporation (IST), was awarded a Phase II NIH grant to design a robotic endoscopic tool for minimally invasive neurosurgery. The $793,000 grant was awarded in July 2008, and will support work until April 2010. Soon after, Eugene Goldfield, PhD, in the Department of Psychiatry, and IST were awarded a Phase II SBIR NIH grant to continue the development of an active bottle for the home care of dysphagic infants. Half of the $1.5 million grant was awarded in September 2008 and will support work until August 2010.

CARMEN BARNES, PHD

JOSEPH MADSEN, MD

EUGENE GOLDFIELD, PHD

MARKETING & FACULTY EDUCATION PROGRAMS

The role of the marketing and faculty and staff education programs at TIDO was greatly expanded in the past year. These resources include:

- Strategic planning and marketing materials, including online presence, to bring Children's licensing opportunities to the attention of potential licensees and/or investors
- Detailed market analysis for Children's technologies and areas of expertise
- Annual Report
- Web site management
- Faculty and staff education programs aimed at raising the awareness of the Children's community about intellectual property, the processes and resources for translating innovative research into products, and the role of our office in these efforts.
- Logistical support of the Technology Development function and the Business Development function.

Changes in the Marketing Function in the Past Year

Until this year, the TIDO marketing efforts consisted of the work of Marketing Communications Specialist, David Altman, which were coordinated by Senior Licensing Manager, Christine Nogueira, PhD, MBA. This year, however, TIDO created a new position, the Technology Marketing Specialist, and hired Keeley Wray, a market research professional, to fill the position. The creation of this position was based on the recognition that market research is essential to carry out best practices in technology transfer and marketing. In-depth market research allows TIDO to find better potential licensees for Children's technologies so TIDO can focus its resources on the technologies that are most likely to succeed in the marketplace, and to optimize and control patent costs.

In an effort to do better market research, the Marketing group also selected Biopharm Insight, a powerful database and have trained our staff on its use. The Technology Marketing Specialist will also develop and provide quality control for a Customer Relations Management system.

Restructuring the TIDO Web Site

In the past fiscal year, TIDO started an extensive project of developing a new web site, **www.childrensinnovations.org**, which was completed and launched in FY09. The web site is a powerful and effective business tool, to bring not only Children's technologies to the attention of potential commercial partners, but also to feature laboratories and research areas, aimed at developing partnerships with industry.

Outreach to Industry

TIDO actively participates in important trade events of the pharmaceutical, biotechnology and venture capital industries, to showcase Children's research and researchers, and to maintain the collective network of the office, which is an essential piece of the technology transfer and licensing processes. The Marketing team coordinates and supports these efforts, and the licensing managers actively participate. TIDO participated in the Bio International Convention (BIO) for the 4th year in a row, with an exhibitor booth, and in the Bio industry partnering

JOHN COUNTS, JD, ABBIE MEYER, PHD, AND DAVID ALTMAN AT THE BIO 2008 CONFERENCE

event, which allowed TIDO to set up one-on-one meetings with different companies to showcase Children's technologies and research. We routinely attended local events organized by the Massachusetts Biotechnology Council (MBC). The Marketing group and the licensing managers also met with a number of local companies and venture capital groups, to present opportunities for licensing and collaborations. The Marketing group at TIDO held lunch meetings with our marketing counterparts in other local technology transfer offices for exchange of ideas, resources and general networking. We have also strengthened our collaboration with Children's Public Affairs department as a way to exchange ideas and share resources.

Ongoing Education and Services to the Children's Community

The Marketing group has designed and coordinated a number of educational presentations and events for the Children's community, aimed at developing awareness of intellectual property and facilitating interactions with the staff in the office:

Presentations to the New Research Laboratory Personnel

TIDO puts on a required bimonthly presentation during Children's Research Safety training to all new research laboratory personnel. It is aimed at educating researchers about basic concepts in intellectual property and preventing future intellectual property related problems. Topics presented include patentability of inventions, confidentiality, intellectual property restrictions in some research materials and issues with Material Transfer Agreements. Last year was our sixth consecutive year of presenting, with a total of 24 presentations in the year.

Presentations to Children's Research Administrative Staff

TIDO also presents a standard presentation to Children's Research Administrators, upon request of the Office of Research Administration. It educates administrative personnel who interface with inventors about the basic principles of handling intellectual property, including confidentiality, public disclosures and Material Transfer Agreements. One presentation was made in the past fiscal year.

Events with the Children's Community

TIDO held its annual "Cappuccino Event" in June 2008 to promote the contact between investigators and the licensing managers in an informal environment. The event was well attended. TIDO also participated in the Children's Research Day, a scientific annual poster event, for the 6th year in a row. The message we convey to the scientists is that science and intellectual property go hand in hand.

The economy is presenting great challenges to the development of innovation right now, both in the universities and in the industry. TIDO believes that a strong marketing program is essential to address these challenges, by increasing the likelihood that Children's technologies will be licensed, and become a product to benefit society in the future. But the role of marketing in times like these goes beyond that scope. A strong marketing program is a powerful tool for effective decision making regarding investment of existing resources, and indispensable ally to effectively control patent costs.

LEFT TO RIGHT: CHRIS GEEHAN, JD; JOHN COUNTS, JD; MASSACHUSETTS GOVENOR DEVAL PATRICK; ABBIE MEYER, PHD; DAVID ALTMAN

APPENDIX 1
SUMMARY OF TECHNOLOGY TRANSFER ACTIVITY
(FISCAL YEAR 2003 THROUGH FISCAL YEAR 2008)

INVENTION DISCLOSURES

	2003	2004	2005	2006	2007	2008
Total	111	118	98	98	94	116

ALL AGREEMENTS NEGOTIATED

	2003	2004	2005	2006	2007	2008
Exclusive licenses	9	7	5	8	7	5
Non-exclusive licenses	11	4	13	16	19	14
Options	8	8	3	3	3	3
TOTAL	28	19	21	27	29	22
Agreements involving the receipt of equity	1	1	0	0	1	1
Amendments	4	4	2	5	4	9
Research collaborations*	3	5	11	7	6	2
Corporate sponsored research*	6	5	6	4	12	7
Material transfer*	180	203	261	285	398	603
Confidentiality*	49	75	95	80	64	74
Inter-institutional invention administration	9	11	8	11	11	4
Other	3	5	12	5	6	4

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

GROSS REVENUES ($M)

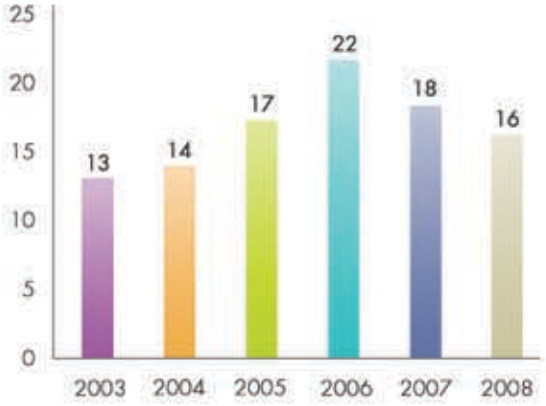
	2003	2004	2005	2006	2007	2008
Total	13.2	14.1	17.6	22.4	18.1	16.3

PATENT APPLICATIONS

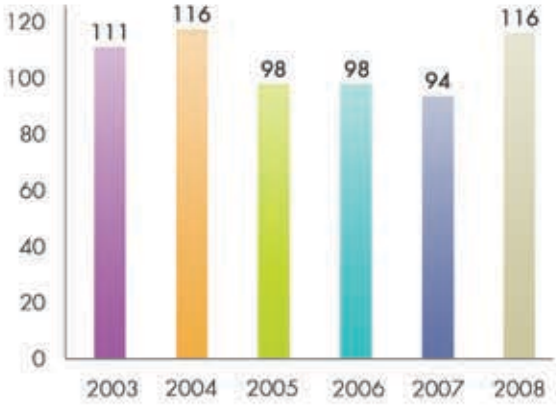
	2003	2004	2005	2006	2007	2008
Provisionals filed	29	54	54	49	47	69
PCTs filed	30	14	30	25	24	26
Foreign filed	83	33	31	27	18	22
US filed	75	41	50	49	33	30

APPENDIX 2
FIVE-YEAR TREND OF TECHNOLOGY TRANSFER ACTIVITY

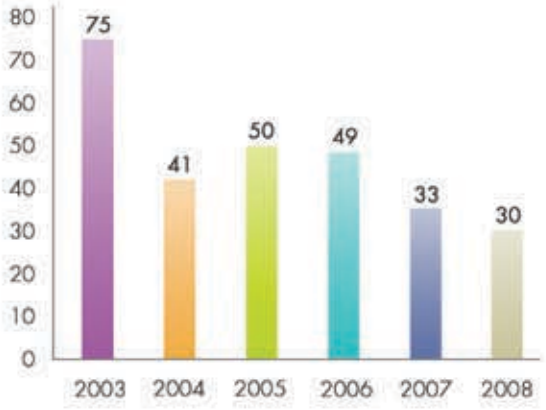
GROSS REVENUES ($M)



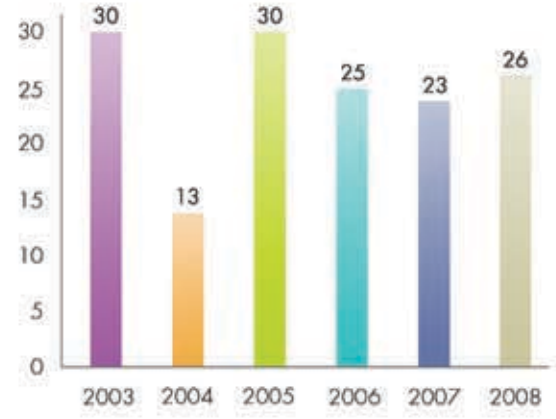
INVENTION DISCLOSURES



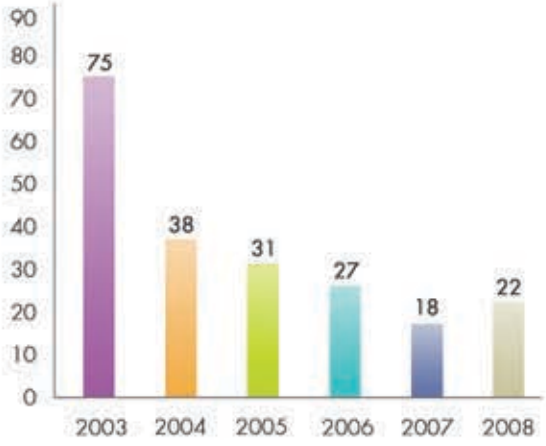
US PATENTS FILED



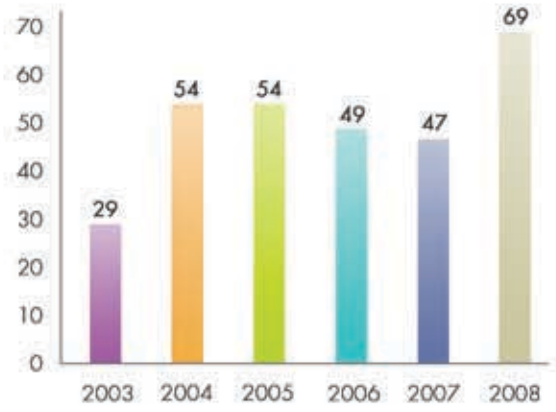
PCTs FILED



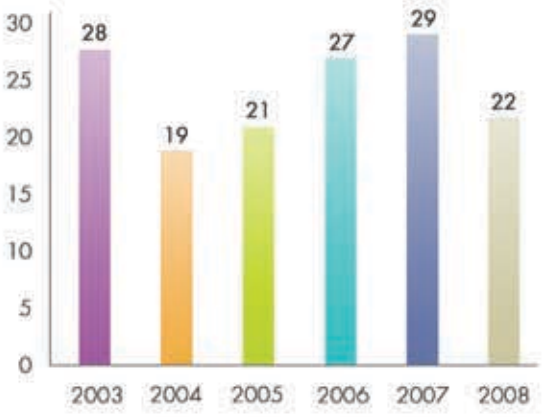
FOREIGN APPLICATIONS FILED



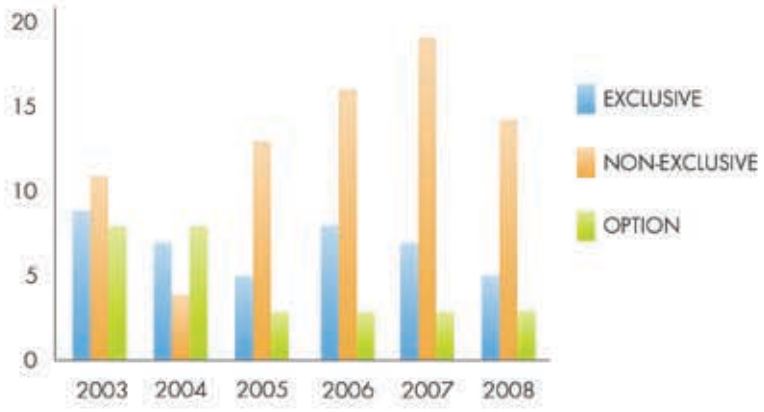
PROVISIONALS FILED



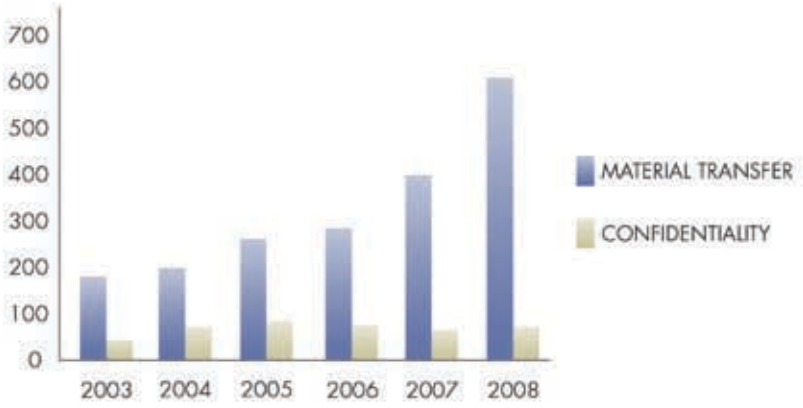
LICENSES & OPTIONS GRANTED



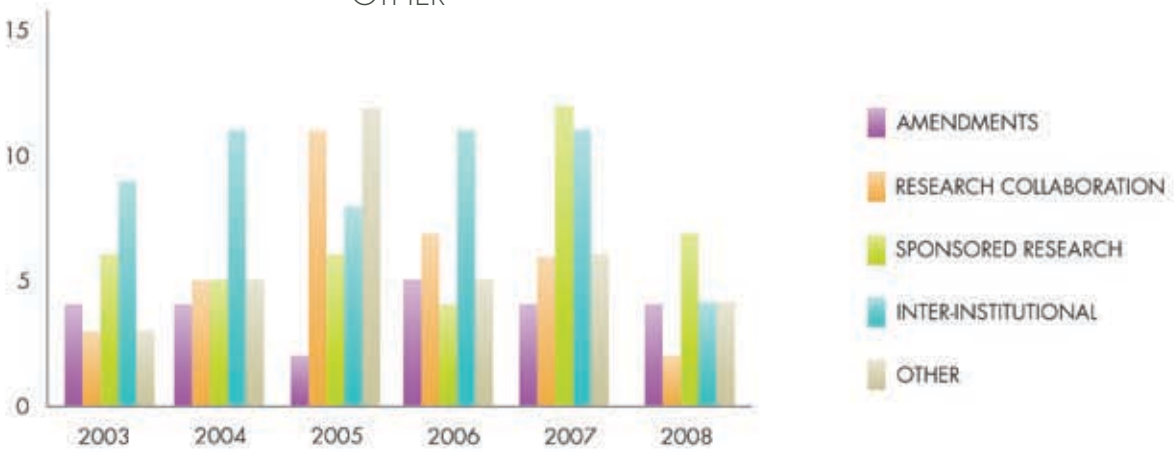
BREAKDOWN OF LICENSE & OPTION AGREEMENTS



NON-LICENSE AGREEMENTS MATERIAL TRANSFER & CONFIDENTIALITY



NON-LICENSE AGREEMENTS OTHER



APPENDIX 3
US PATENTS ISSUED FY08

LEAD INVENTOR	ISSUE DATE	PATENT NUMBER	APPLICATION TITLE
Mulligan, Richard	10/23/2007	7,285,538	Gene repair involving *in vivo* excision of targeting DNA
Ingber, Donald	10/30/2007	7,288,394	Selective deposition of materials on countoured surfaces
D'Amato, Robert	11/6/2007	7,291,610	Estrogenic compounds as anti-mitotic agents
He, Zhigang	12/18/2007	7,309,485	Reducing myelin-mediated inhibition of axon regeneration
Satchi-Fainaro, Ronit	2/19/2008	7,332,523	TNP-470 polymer conjugates and use thereof
Klagsbrun, Michael	2/26/2008	7,335,357	Antagonists of neuropilin receptor function and use thereof
Clapham, David	3/4/2008	7,339,029	Sperm-specific cation channel, CatSper2, and uses therefor
Benowitz, Larry	3/4/2008	7,338,666 B2	Methods for modulating the axonal outgrowth of central nervous system neurons
Folkman, M. Judah	4/29/2008	7,365,159	Angiostatin protein
Moses, Marsha	5/13/2008	7,371,812	Antiangiogenic peptides
D'Amato, Robert	6/3/2008	7,381,848	Estrogenic compounds as anti-mitotic agents
Moses, Marsha	7/1/2008	7,393,829	Pharmaceutical compositions comprising fragments and homologs of troponin subunits
Snyder, Evan	7/1/2008	7,393,526	Systemic gene delivery vehicles for the treatment of tumors
Geha, Raif	7/22/2008	7,402,725	WIP, a WASP-associated protein
Gerard, Craig	7/22/2008	7,402,657	C-C chemokine receptor 3 proteins
Benowitz, Larry	8/5/2008	7,407,937	Therapeutic compositions of oncomodulin
Ingber, Donald	8/12/2008	7,410,791	Device containing cytophilic islands that adhere cells separated by cytophobic regions
Klagsbrun, Michael	8/19/2008	7,414,027	Peptide antagonists of vascular endothelial growth factor
Clapham, David	9/16/2008	7,425,614	Neuroprotective therapeutics preventing ERK/MAPK activation through the NMDA receptor
Zon, Leonard	9/23/2008	7,427,603	Method of enhancing proliferation and/or hematopoietic differentiation of stem cells
Atala, Anthony	9/30/2008	7,429,490	Tissue engineered uterus

APPENDIX 4
FOREIGN PATENTS ISSUED FY08

LEAD INVENTOR	COUNTRY	ISSUE DATE	PATENT No.	APPLICATION TITLE
Atala, Anthony	Canada	12/14/2007	2395336	Methods and compositions for producing artificial fascia
Atala, Anthony	Japan	1/11/2008	4065846	Creation of tissue engineered female reproductive organs
Atala, Anthony	Germany	1/23/2008	1246903	Reconstructing organs from decellularized biomaterial scaffold
Atala, Anthony	France	1/23/2008	1246903	Reconstructing organs from decellularized biomaterial scaffold
Atala, Anthony	UK	1/23/2008	1246903	Reconstructing organs from decellularized biomaterial scaffold

LEAD INVENTOR	COUNTRY	ISSUE DATE	PATENT No.	APPLICATION TITLE
Atala, Anthony	Ireland	1/23/2008	1246903	Reconstructing organs from decellularized biomaterial scaffold
Atala, Anthony	Mexico	2/7/2008	7049057	Creation of tissue engineered female reproductive organs
Folkman, M. Judah	Australia	4/17/2008	2004202593	Therapeutic antiangiogenic endostatin compositions
Mulligan, Richard	Australia	5/8/2008	2004202860	Gene repair involving *in vivo* excision of targeting DNA
Folkman, M. Judah	Israel	6/21/2008	124153	Antiangiogenic endostatin compositions and method of use
Javaherian, Kashi	Germany	7/24/2008	1687426	Antiangiogenic peptides for treating or preventing endometriosis
Javaherian, Kashi	France	7/24/2008	1687426	Antiangiogenic peptides for treating or preventing endometriosis
Javaherian, Kashi	UK	7/24/2008	1687426	Antiangiogenic peptides for treating or preventing endometriosis
Solomon, Keith	Australia	7/31/2008	2003254261	Compositions of ezetimibe and methods for the treatment of cholesterol-associated benign and malignant tumors
Atala, Anthony	Japan	8/1/2008	4162378	Penile reconstruction
Lencer, Wayne	Australia	8/14/2008	2002316574	Central airway administration for systemic delivery of therapeutics
D'Amato, Robert	Austria	8/20/2008	1586322	Compositions comprising thalidomide and dexamethasone for the treatment of cancer
D'Amato, Robert	Belgium	8/20/2008	1586322	Compositions comprising thalidomide and dexamethasone for the treatment of cancer
D'Amato, Robert	Denmark	8/20/2008	1586322	Compositions comprising thalidomide and dexamethasone for the treatment of cancer
D'Amato, Robert	Finland	8/20/2008	158322	Compositions comprising thalidomide and dexamethasone for the treatment of cancer
D'Amato, Robert	France	8/20/2008	1586322	Compositions comprising thalidomide and dexamethasone for the treatment of cancer
D'Amato, Robert	Germany	8/20/2008	1586322	Compositions comprising thalidomide and dexamethasone for the treatment of cancer
D'Amato, Robert	Greece	8/20/2008	1586322	Compositions comprising thalidomide and dexamethasone for the treatment of cancer
D'Amato, Robert	Ireland	8/20/2008	1586322	Compositions comprising thalidomide and dexamethasone for the treatment of cancer
D'Amato, Robert	Italy	8/20/2008	1586322	Compositions comprising thalidomide and dexamethasone for the treatment of cancer
D'Amato, Robert	Luxembourg	8/20/2008	1586322	Compositions comprising thalidomide and dexamethasone for the treatment of cancer
D'Amato, Robert	Monaco	8/20/2008	1586322	Compositions comprising thalidomide and dexamethasone for the treatment of cancer
D'Amato, Robert	Netherlands	8/20/2008	1586322	Compositions comprising thalidomide and dexamethasone for the treatment of cancer
D'Amato, Robert	Portugal	8/20/2008	1586322	Compositions comprising thalidomide and dexamethasone for the treatment of cancer
D'Amato, Robert	Spain	8/20/2008	1586322	Compositions comprising thalidomide and dexamethasone for the treatment of cancer
D'Amato, Robert	Sweden	8/20/2008	1586322	Compositions comprising thalidomide and dexamethasone for the treatment of cancer
D'Amato, Robert	Switzerland	8/20/2008	1586322	Compositions comprising thalidomide and dexamethasone for the treatment of cancer
D'Amato, Robert	UK	8/20/2008	1586322	Compositions comprising thalidomide and dexamethasone for the treatment of cancer

SEVEN QUESTIONS FOR DR. MARSHA MOSES: INTERVIEW WITH MARSHA MOSES, PHD, INTERIM DIRECTOR OF THE CHILDREN'S VASCULAR BIOLOGY PROGRAM

As the Interim Director of the Vascular Biology Program (VBP), what would you like the world to know about the VBP?

This has been a very sad period for the Vascular Biology Program in the wake of the loss of our mentor, Dr. Judah Folkman. Despite his passing, the program is strong, vibrant and vital. Grounded in Dr. Folkman's unique vision and intellectual courage, we have moved forward on a number of important research initiatives. Our faculty, composed of four full professors, five associate professors, six assistant professors, as well as a number of instructors, are highly respected in their fields. In addition to our dedication to the study of human cancers, we continue to do groundbreaking basic and clinical research in the fields of cardiology, ophthalmology, neurology and other disciplines that are linked by the field of vascular biology.

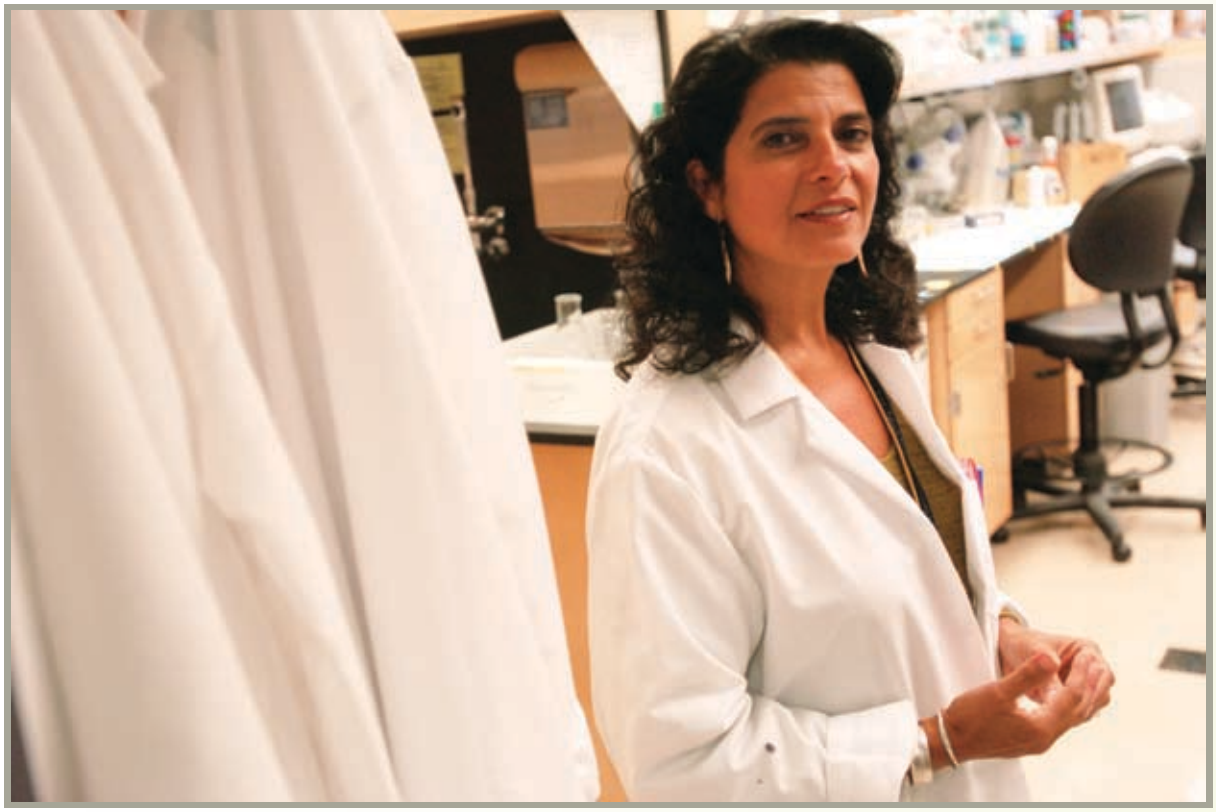
We remain dedicated to translating our basic science findings to the clinic as disease diagnostics and therapeutics.

Dr. Folkman had a great scientific influence on all scientists of the VBP. What about him had a particularly powerful influence on you?

Dr. Folkman was our beloved colleague and mentor, our inspiration both professionally and personally. We were all particularly influenced by his dedication to putting the science, and the patients that it might impact, first. I continue to be inspired by his fiercely original and courageous intelligence and his gift for focusing on big, important questions that could make a positive difference in people's lives.

In your view, what is the role of intellectual property and licensing in helping the Vascular Biology Program achieve its mission?

Intellectual property is an essential requirement for meeting our translational research goals. It has been essential to our significant success



in bringing the drugs and diagnostic tests discovered and validated in the Vascular Biology Program to the clinic, through licenses to established companies as well as to new companies that were started with our technologies. We are very proud of our record in this area: the Vascular Biology Program has over 300 issued patents and more than 250 pending patent applications. We have 39 cases currently licensed and three under option, and have brought approximately $90.3 million in gross licensing revenue to Children's. To my mind, then, intellectual property is a critical asset necessary for meeting our translational goals. These achievements would not have been realized without intellectual property protection.

We also know that this process must begin very early and depends on our willingness and ability to educate our young scientists about the importance of intellectual property. Here in the VBP, we have worked very hard over a number of years to accomplish this. As a result, the VBP has built a close, long-standing relationship with TIDO. Together, I believe we promote a culture of translation, which is synergistic and mutually advantageous.

In addition to a busy life as a faculty member at Children's and Harvard Medical School, Director (Interim) of the Vascular Biology Program, and head of your own laboratory, you are an entrepreneur as a co-founder of Predictive Biosciences, Inc. What have you learned from that experience? If you had to do again (and we hope you do), what would you do differently?

There have been so many positive aspects associated with this experience. I have had the opportunity to meet and work with incredibly smart and motivated people, both on the science and business side. It continues to be gratifying to see a discovery that was made and validated in my laboratory be developed into a technology that may benefit cancer patients around the world. I feel very fortunate.

In answer to your last question, I would definitely consider doing this again, and I would do so earlier in the lifetime of the next discovery.

What advice would you give to other researchers interested in starting a company?

My suggestion to them would be to first develop an extremely strong intellectual property portfolio. Patents are the currency that supports new companies. I would work very hard with the TIDO legal team to develop patents that are as uncontestable as possible. I would then begin to have very frank conversations with TIDO to make one's intentions clear. One should seek an honest and straightforward evaluation from the office, to determine whether the discovery of interest is actually startup material, given that most often, the most interesting scientific results do not always a company make.

You have received several awards because of your work mentoring junior scientists. What do you enjoy most regarding this work? Why do you think it is so important?

It is a privilege to have the opportunity to meet and work with such amazingly smart and dedicated scientists and clinicians. I learn as much from them as they learn from me. In addition to being a pleasure, I believe that to provide advice and counsel is part of one's responsibility as a faculty member and as the head of a lab. This is a difficult moment in time, and there are many challenges facing them, including, but not limited to, financial ones. Whenever the financial landscape changes for the worse, many young scientists find themselves forced to make critically important decisions, sometimes with an urgency that they have not been confronted with before. There is an enormous need for experienced leadership for mentoring young scientists and clinicians at this point in time right now. They may want to remain in academia, but feel that joining a biotech company or going to law or medical school would be a more practical choice under the circumstances. Our program has tried to match younger scientists with a more experienced mentor, based on their common goals and expertise, to help the younger scientists with these kinds of decisions. We take advantage of our collective and significant network of contacts in academia and biopharma to connect the people who seek our advice with those individuals who can actually help them. Essentially, we are trying to open doors at this pivotal point in their careers. This is an honor and a responsibility that I take very seriously.

You were recently elected to the Institute of Medicine (IOM) of the National Academies. This is a great achievement for scientists. What does this recognition mean to you?

To join the ranks of so many preeminent scientists and clinicians from around the world in being elected to this prestigious Institute is a great honor. The fact that IOM membership is determined through election by one's peers is very meaningful to me, and is an equally significant honor.

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