The Children's Hospital *of* Philadelphia®

RESEARCH INSTITUTE

# 2011

## RESEARCH ANNUAL REPORT

# *Contents*

# I. FOUND IN TRANSLATIONAL RESEARCH

## TODAY'S JOURNEY, TOMORROW'S CURES

Translational Research: it's the essence of our vision at The Children's Hospital of Philadelphia Research Institute. With each research project and program, and with our state-of-the-art resources and critical support staff, we are improving the health and well-being of children everywhere and leading the way worldwide in pediatric research.

We accomplish this through translational research.

But what do we mean by that term? Translational research is far more than experiments in a lab or studies involving patients in a clinical setting. Rather, it's an innovative way of thinking about and performing research, with the aim of quickly and efficiently bringing the results of our discoveries to patients' bedsides.



The path from a research study into medical practice for a pediatric disease or condition is rarely a linear one. Rather, the discoveries from our laboratory and clinical research programs find their way to patients' bedsides in the form of new drugs, techniques and therapeutic approaches. Those treatments and approaches in turn generate new research questions and observations that our investigators bring back to their programs, in the hopes of advancing the health of children even further.

Research is therefore intrinsic to the advancement of healthcare. Without it, there are no new treatments or cures to safely bring to patients.

In this year's annual report, our focus is on translational research and some of the investigators whose endeavors are now – or will soon be – changing the way the patients are treated. Those featured in the report are leading the way in research on spina bifida, a gene therapy approach for treating a rare immunodeficiency, new hope for treating the most common form of hypoclycemia in children, clinical support tools to help premature infants, stem cell research to treat cancer and genetic disorders, and new tools to manage diabetes.

The stories of their research represent only a slight few of the hundreds of ongoing programs at the Children's Hospital Research Institute, which continues its dedication to translating such innovative research findings to outstanding patient care.

# LANDMARK FETAL SURGERY STUDY BRINGS NEW HOPE, BRIGHTER FUTURE TO CHILDREN WITH SPINA BIFIDA

## N. SCOTT ADZICK, MD

The most common birth defect of the central nervous system, spina bifida affects an estimated 1,500 babies born each year in the United States. Myelomeningocele, the most severe and devastating form of spina bifida, occurs when part of the spinal column does not close around the spinal cord, failing to protect it during fetal development.

The conventional treatment for the disabling neurological condition involved surgery on the baby after birth. Despite the postnatal surgical intervention, children born with spina bifida often suffer lifelong disabilities, including paralysis, bladder and bowel problems, excessive fluid pressure in the brain, and cognitive impairments.



However, the future is much brighter now for many children diagnosed with the condition. A landmark clinical study led by Children's Hospital experts has showed that fetal surgery – delicate surgery in a mother's uterus months before a child is born – can significantly improve the outcomes for children diagnosed *in utero* with spina bifida.

Fetal surgery researchers reported long-awaited results from an unprecedented clinical trial that compared outcomes of prenatal surgery versus postnatal surgery, the conventional surgery for this disabling neurological condition. The results of their research was published in the prestigious *New England Journal of Medicine*.

Building upon two decades of research, N. Scott Adzick, MD, Surgeon-in-Chief and director of the Hospital's Center for Fetal Diagnosis and Treatment, led a team that pioneered fetal surgery for spina bifida and set the stage for the groundbreaking clinical study.

The study, called the Management of Myelomeningocele Study (MOMS) trial, showed that two and a half years after fetal surgery, children with spina bifida were better able to walk, when compared to children who received surgery shortly after birth. Patients who received fetal surgery also scored better on tests of motor function. Within a year after fetal surgery, they were less likely to need a shunt, a surgically implanted tube that drains fluid from the brain.

Three fetal surgery centers participated in the trial — CHOP, Vanderbilt University, and the University of California San Francisco. The biostatistics center at George Washington University served as the coordinating center and oversaw data collection and analysis.

The MOMs study proved to be of such importance that other fetal surgery centers in the United States not participating in the trial agreed to perform no fetal surgeries for spina bifida during the study period, which was slated to last seven years. However, the National Institutes of Health ended the trial in December 2010, after 183 of the planned 200 fetal surgeries had taken place, citing the overwhelming evidence that fetal surgery for spina bifida was effective.

"This is the first time in history that we can offer real hope to parents who receive a prenatal diagnosis of spina bifida," says Dr. Adzick. "This is not a cure, but this trial demonstrates scientifically that we can now offer fetal surgery as a standard of care for spina bifida."



Additional research will refine surgical techniques and improve methods to reduce the risks to mothers and fetuses, and the hope is that the success of fetal surgery for spina bifida may broaden its application to other birth defects.

Children's Hospital began performing fetal surgery for spina bifida in 1998, three years after Dr. Adzick launched the Center for Fetal Diagnosis and Treatment. The center's reports of neurological improvements in spina bifida helped lay the groundwork for the MOMS trial.

"It's very gratifying to take this idea forward over 30 years, starting with a concept and now offering hope — to families, mothers, and the children themselves," says Dr. Adzick, who has been working to advance fetal surgery since performing preclinical studies in the early 1980s.

The MOMs trial was sponsored by the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Additional funding for spina bifida research at the CFDT at CHOP was provided by Katherine and Michael Mulligan, the March of Dimes Foundation, and the Spina Bifida Association.

# INTERNATIONAL EFFORT: NEW GENE THERAPY TARGETS RARE IMMUNODEFICIENCY DISEASE

## JORDAN ORANGE, MD, PHD

Some children are born with a genetic inability for their immune system to provide a natural advantage over the environment and held them ward off disease and infection.

Wiskott-Aldrich syndrome (WAS) is one such immunodeficiency. WAS is a rare but often severe X-linked disorder characterized by recurrent infections, eczema and a low platelet count. Mutations in the *WAS* gene disable its ability to produce WAS protein, which plays a crucial role in different types of immune cells. Without this protein, immune cells are disabled and incapable of providing immune defenses, leaving patients susceptible to premature death from infection, cancers or bleeding.



Although WAS has a range of severity, the only current cure is stem cell transplantation, which carries its own risks.

Inspired by the families he sees, Jordan Orange, MD, PhD, Division of Immunology, has been investigating the rare primary immunodeficiency diseases like WAS. Understanding such disease is important because they address scientific concepts that affect common diseases as well.

Dr. Orange performed sophisticated cell imaging and analysis for a study of WAS, led by German researcher Christoph Klein, M.D., Ph.D., of Hannover Medical School. Orange was a senior co-author, and Children's Hospital was the only U.S. institution represented in the study.

*The New England Journal of Medicine* published Dr. Jordan Orange's groundbreaking research as part of an interventional team that could lead to an effective gene therapy treatment for a rare primary immunodeficiency disease. The analytic imaging studies performed by Dr. Orange and his team provided evidence that the gene corrected patient immune cells were functioning normally. "Our highly quantitative imaging studies assessed 'natural killer cells,' a critically disabled immune cell in Wiskott-Aldrich patients, and demonstrated a remarkable return to normality after gene therapy," says Dr. Orange.

Natural killer (NK) cells are white blood cells that are an innate part of the body's immune system. NK cells provide "surveillance" throughout the body for infections and cancer, attaching to those cells and killing them, and are therefore critical to one's survival.

Dr. Orange recently determined that individuals with WAS were missing the structural framework, called actin, between NK and infected or foreign cells and are thus ineffective – leaving patients susceptible to disease. Through gene therapy, the protein missing in these structural frameworks was restored. Individuals with severe forms of WAS who received the treatment experienced no further bleeding or rashes; in effect, the new treatment restored the activity of the NK cells.

For the children participating in the study, the clinical benefits continued three years after the initial gene therapy. Significantly, researchers found that the treatment corrected thrombocytopenia, a particularly hazardous and difficult-to-treat complication of WAS. Based on these encouraging results, the research team recommended the need to expand the study to additional patients, while conducting long-term follow-up and analysis.



Dr. Orange, notes that the gene therapy trial is currently limited to the most severe cases. "Even patients with less severe WAS are at risk for lymphoma and other blood cell cancers, so broadening treatment options would be an important advance in treatment."

In work performed over the past decade, Orange has discovered and developed an immunotherapy for WAS. "If our approach is safe and effective, it may represent a treatment for the full spectrum of WAS patients,"

Dr. Orange's immunotherapy approach bypasses the gene defect in the disease, instead using the cytokine IL-2 to boost immune function. This represents an exciting new potential opportunity for patients more mildly affected by the disease. Orange opened a Phase-I clinical trial of IL-2 at CHOP and published his initial findings in the *Journal of Clinical Investigation*. It is his hope that IL-2 may represent a fundamental component of therapy for children affected with WAS in the future and one which helps prevent the fatal complications of this rare pediatric disease.

Dr. Orange, who was named the Modell Chair in Pediatric Immunology this year, recently received a prestigious award from the American Philosophical Society for his work. Over the past 10 years, Dr. Orange has defined the field of human NK cell deficiencies in various genetic disorders.

# HYPERINSULINEMIC HYPOGLYCEMIA: NEW HOPE FROM A NEW THERAPY

## DIVA D. DE LEÓN, MD

In congenital hyperinsulinism, excessive insulin secretion causes patients to suffer from hypoglycemia, commonly called low blood sugar. Medications, more frequent meals, and sometimes even surgery to remove part of the pancreas can help treat the condition in children. However, those with the most common and severe form of congenital hyperinsulinemic hypoglycemia do not respond to current medical therapies.

Enter Diva D. De León, MD, an assistant professor of pediatrics and a pediatric endocrinologist who treats children with congenital and acquired forms of hyperinsulinemic hypoglycemia, the most common cause of hypoglycemia in children and adults. She is leading research efforts to develop a more effective and innovative therapy for hyperinsulinemic hypoglycemia.

In children, hyperinsulinemic hypoglycemia most commonly stems from genetic defects affecting regulation of insulin secretion. In the last decade, researchers discovered there are focal and diffused forms of congenital hyperinsulinemic hypoglycemia.

Focal forms can be cured through surgery to remove the affected part of the pancreas. For patients with diffused forms, the outcomes are less favorable; at least half of patients continue to have low blood sugar after surgery to remove most of their pancreas and after puberty most patients go on to develop diabetes.

"The biggest obstacle for us is that it's an 'orphan disease.' It's rare — one out of 50,000 live births," Dr. De León explains. "Having a translational focus at CHOP helps everyone because we can focus on treatment and approaches that many for-profit centers may not be interested in."

Dr. De León's research focuses on glucagon-like peptide-1 (GLP-1), a hormone that in healthy states stimulates the secretion of insulin after meals. Dr. De León's findings suggest that the GLP-1 receptor may be a viable therapeutic target for hyperinsulinemic hypoglycemia and that that blocking the effects of the GLP-1 hormone may result in regulating the excess insulin secretion.

Studies are underway to examine the effects of the GLP-1 receptor antagonist, exendin-(9-39), on glucose metabolism and pancreatic islet function in children with hyperinsulinemic hypoglycemia. In a study completed last year involving children and adults with hyperinsulinemic hypoglycemia, Dr. De León and her team discovered that treatment with the investigational product increased fasting glucose levels and decreased insulin secretion with no side effects. The U.S. Food and Drug Administration has approved further studies on children with hyperinsulinemic hypoglycemia who are not responsive to medical therapy.

Hyperinsulinemic hypoglycemia can also result from surgical procedures affecting nutrient delivery to the gastrointestinal tract, including gastric bypass surgery and Nissen fundoplication, a procedure used to treat gastroesophageal reflux disease. In fact, approximately 24 percent of children undergoing a Nissen fundoplication develop hypoglycemia.



"We think that, ultimately, this target therapy will benefit not only kids with genetic forms of hyperinsulinemic hypoglycemia but also children with hypoglycemia as a consequence of reflux surgery," says Dr. De León. "So, a large group of children could potentially benefit from this new therapy."

# NEW CLINICAL SUPPORT TOOL EXPECTED TO IMPROVE PREMATURE INFANT OUTCOMES

## ROBERT GRUNDMEIER, MD

Advances in neonatal care means an increasing number of premature infants are surviving. As a result, however, preemies face myriad medical issues requiring close attention. Some of these issues include failure to thrive, gastro esophageal reflux disease, broncho-pulmonary dysplasia, and apnea.

Yet efforts to ensure high-quality post-discharge care tend to be inconsistently implemented. Those treating premature infants in the outpatient setting must take into consideration a large number of variables that change over time. This challenge is especially difficult for pediatricians who may only have a small number of these vulnerable children in their practices. Inadequate monitoring for early warning signs can result in missed opportunities for effective interventions and undesirable developmental outcomes.



Until recently, no support tools had been designed, implemented or evaluated to handle the complexity of decision-making required for the healthcare of premature infants.

With a grant from the National Library of Medicine, Robert Grundmeier, MD, director of Clinical Informatics for the Center for Biomedical Informatics at CHOP, is developing a system that embeds electronic health records with clinical decision support tools to provide natural and timely opportunities to improve healthcare for thousands of vulnerable infants.

"Our idea is to make the electronic health records work better for high-risk populations, in this case premature infants. A lot of the value is in providing helpful information to families," explains Dr. Grundmeier.

The system will track premature infants up to 23 months (born at less than 35 weeks gestation) in an outpatient setting to assess growth and development. The system alerts care providers about timely blood pressure screenings, immunization for respiratory syncytial virus (RSV), eye exams and hearing exams. Dr. Grundmeier says other tools being developed include a nutrition calculator to help clinicians assess calorie intake and make appropriate recommendations.

"We are trying to move beyond traditional alert and reminder systems [that dictate] 'do this or don't do this' [by] trying to embed guidelines for premature infant support," says Dr. Grundmeier. "For the most part we are targeting the preventive health visits. A lot of the content in our electronic health records assumes that the child's chronological age is the trigger for preventive screenings. But it's often the corrected age of preemies that is most important. The corrected age is the age the child would be if born on their due date," he explains.

At the same time, Dr. Grundmeier says, the system will help improve outcomes by putting new blood pressure screening standards into practice. Preemies are at significant risk for high blood pressure but often do not receive the recommended screening before their first birthday.



Finally, the system will help health care practices proactively manage their premature infant population before a problem arises. For example, in the push to immunize all premature infant patients for RSV, the system will help practices educate families while improving work flow by tracking which patients are due for treatment and whether their insurance company has approved it, Dr. Grundmeier notes.

# GIVING FAMILIES NEW TOOLS TO MANAGE DIABETES

## STEVEN M. WILLI, MD

A diagnosis of diabetes in a child can be an overwhelming prospect for the whole family. It is considered one of the most common chronic diseases in children and adolescents and, although manageable, requires constant care and attention. According to the Centers for Disease Control and Prevention (CDC), approximately 151,000 people younger than 20 years have diabetes.

Steven M. Willi, MD, the medical director of the Hospital's Diabetes Center for Children, is devoted to investigating new therapies for Type 1 diabetes mellitus, also known as juvenile diabetes, as well as Type 2 diabetes, also known as adult-onset diabetes. He is involved in a variety of initiatives, including physiologic studies of the cause and characterization of diabetes in children.



Type 1 diabetes mellitus is a chronic condition in which the pancreas produces little or no insulin. "Insulin helps keep blood glucose levels normal," explains Dr. Willi. Each year, more than 13,000 children and adolescents in the United States are diagnosed with Type 1 diabetes mellitus, the CDC states.

New developments in blood sugar monitoring and insulin delivery have greatly improved the daily management of Type 1 diabetes mellitus in children. Those with Type 1 diabetes mellitus who have the ability to produce at least some of their own insulin may be able to achieve better glucose control than those who produce no insulin at all. Improved glucose control has been shown to reduce the long-term complications of diabetes, Dr. Willi says.

Dr. Willi is seeking to alter the course of Type 1 diabetes mellitus in a four-year study, known as "A Research Trial of Aralast in New Onset Diabetes" (RETAIN), on the effectiveness of the anti-inflammatory drug alpha-1 antitrypsin, or Aralast. The goal of RETAIN, funded by the National Institute of Allergy and Infectious Diseases (NIAID), is to determine whether Aralast can help slow the progression of Type 1 diabetes mellitus by preserving islet cell function in children and adults, he explains.

Dr. Willi is attacking diabetes on several fronts. He is part of a consortium called the Immune Tolerance Network, which was set up by the National Institutes for Health and conducts intervention trials for Type 1 diabetes mellitus. In fact, under Dr. Willi's direction, Children's Hospital has been one of the largest recruiters for the trials under Dr. Willi's direction.

Other noteworthy projects by Dr. Willi and his team include the Type 1 Diabetes Exchange Registry, which will result in the largest national database of information on people with the condition to date. Using the registry, researchers will be able to explore clinical questions with actual patient data and develop optimal evidence-based guidelines for disease management. There are more than 60 diabetes centers participating in the Exchange Registry, which is targeting an enrollment of more than 25,000 patients nationwide. The Diabetes Center for Children at CHOP is currently the second largest site in the United States, with more than 1,000 subjects enrolled.

Dr. Willi recently completed a clinical trial on Lantus, a long-acting insulin, in preschool-age children. The trial was part of a worldwide study with Children's Hospital at the forefront of the initiative as the largest recruiting site in North America. He will soon launch a clinical trial exploring the use of a new extra long-acting insulin analogue called insulin degludec. This therapy represents a significant step in diabetes management as it allows for three-times-a-week dosing of an insulin type that is usually given daily.



Other Type 1 studies by Dr. Willi have involved the use of glucose sensor technology — a device implanted under the skin that measures an individual's blood sugar level and sends a radiofrequency with that information to an insulin pump. This technology "allows those with diabetes to make informed decisions on their management of their disease," notes Dr. Willi.

Dr. Willi co-authored an article in *The New England Journal of Medicine* in July 2010 on the efficacy of sensor-augmented pump therapy. Children and adults with inadequately controlled Type 1 diabetes mellitus participated in the study, which found that the use of the sensor-augmented pump therapy increased a subject's ability to manage the disease compared to injection therapy.

In addition, he leads research efforts targeting Type 2 diabetes, a far more common form of the disease, most frequently manifesting in adolescents and adults when the body becomes resistant to the effects of insulin or stops making enough insulin.

Dr. Willi also participates in the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) initiative, a national research study to determine the best methods to treat adolescents between the ages of 10 and 17 with Type 2 diabetes. Specifically, TODAY researchers are comparing the effectiveness of various treatments, including making changes in eating habits and physical activity, as well as taking different combinations of medicines.

# II. TRAILBLAZERS

## NEW THERAPY BOOSTS CURE RATE OF NEUROBLASTOMA

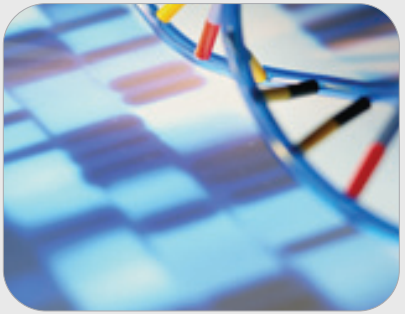
Neuroblastoma, a cancer of the peripheral nervous system, accounts for 7 percent of all childhood cancers, but because it frequently occurs in an aggressive form, it causes 15 percent of all childhood cancer deaths. While low-risk forms of neuroblastoma may spontaneously disappear, in high-risk forms, the cancer tends to return after initial treatment, usually with lethal results. A group of pediatric oncologists, including neuroblastoma expert John Maris, MD, used immunotherapy — biologic agents that stimulate the body's immune system — to achieve the first substantial increase in cure rates for neuroblastoma in more than a decade.

The team assigned 226 high-risk patients to receive either the standard therapy or standard therapy plus immunotherapy. Within two years of follow-up, approximately 54 percent of patients receiving standard treatment suffered a disease relapse, which is almost uniformly fatal. In contrast, 34 percent of patients receiving the experimental immunotherapy regimen had their disease return, a much higher cure rate. Patients receiving immunotherapy experienced a higher rate of pain and other toxic side effects, yet there was evidence of clear benefits from immunotherapy.

The Cancer Center at Children's Hospital has been using this immunotherapy regimen to treat children with high-risk neuroblastoma from around the world following preliminary trial results reported in June 2009. The findings of the current study, published in the *New England Journal of Medicine*, are expected to globally change clinical practice and set a new gold standard of treatment for this often-deadly disease.

Dr. Maris, director of the Hospital's Center for Childhood Cancer Research and chair of the neuroblastoma committee of the Children's Oncology Group (COG), co-authored a second study in the same issue of the journal, reporting on a separate trial that found a substantially reduced dose and duration of chemotherapy achieves a survival rates of 98 percent among children with intermediate-risk neuroblastoma. "Together, these studies report important advances in care for children with this challenging cancer," says Dr. Maris. "We will continue to investigate treatments to further refine the standard of care."

# GENE SITE FOUND FOR CHILDHOOD FOOD ALLERGY



Eosinophilic esophagitis (EoE) is a severe, often painful food allergy that is reported to strike 1 in 10,000 people, but may affect many more. CHOP Research investigators Hakon Hakonarson, MD, PhD, director of the Center for Applied Genomics, and Jonathan Spergel, MD, director of the Center for Pediatric Eosinophilic Disorders conducted the first genome-wide association study on EoE. In collaboration with Marc Rothenberg, MD, PhD, director of the Center for Eosinophilic Disorders at the Cincinnati Children's Hospital Medical Center, the study team found EoE was linked to a region of chromosome 5 that contains the *TSLP* gene.

While two genes are located in the chromosome region identified in the genetic studies, *TSLP* is the plausible candidate because *TSLP* has higher activity levels in children with EoE compared to healthy subjects and has been previously linked to allergic inflammatory diseases such as asthma and the skin inflammation atopic dermatitis. Additionally, *TSLP* has a biological role in allergic inflammation. It holds the genetic code to produce a cytokine, a specific signaling protein that regulates inflammatory responses occurring in allergic diseases.

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Published in *Nature Genetics*, this finding has elucidated a genetic pathway for EoE, which may pave the way for research that intervenes in the pathway and may eventually lead to a new treatment. Study funding was provided by the National Institutes of Health, the Food Allergy Project, the Campaign Urging Research for Eosinophilic Disorders Foundation, the American Partnership for Eosinophilic Disorders, the Chair's Institute at CHOP, the Buckeye Foundation, and the Cotswold Foundation.

# LATEST RECESSION TO HAVE LASTING IMPACT ON CHILDREN

In the largest report reviewing the recent recession's effects on child well being, researchers from PolicyLab at CHOP Research found spells of poverty, even if temporary, may have lifelong health implications for children. The report, *The Effect of Recession on Child Well-Being: A Synthesis of the Evidence*, was commissioned by First Focus and supported by the Foundation for Child Development. The synthesis examines four areas – health, food security, housing stability, and maltreatment – and reviews the relationship of each to the well-being of children during recessions both past and present.

As a result of increased poverty, approximately 43 percent of families with children now report that they are struggling to afford stable housing. The study also found a dramatic increase in the number of households classified as "food insecure" during this recession. Almost a quarter (21 percent) of all households with children fell into this category, and as many as 74 percent of children in some communities rely on food stamps.



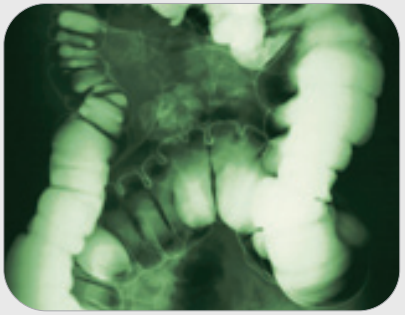
The report also shows the benefit of government programs during times of recession. Children's health insurance programs that were strengthened by Congress and many states before the recession have allowed families to retain coverage for their children even as parents lost jobs and employment-sponsored health insurance. However, in other areas, such as housing, better safety nets still need to be developed. The number of homeless families with children who spent time in a shelter rose by 30 percent between 2007 and 2009.

"The evidence is also strong that those families who entered the recession in poverty will take much longer to rebound, demonstrating that we have a long road ahead even as the economy improves," says David Rubin, MD, MSCE, director of PolicyLab. In addition to Dr. Rubin, study authors include Kathleen Noonan, JD, from the University of Wisconsin School of Law and Katherine Sell, MSSP, and Sarah Zlotnik, MSW, MSPH, from PolicyLab. The study was made possible through support from the Foundation for Child Development.

# MORE CROHN'S DISEASE GENES DISCOVERED

CHOP Research investigators contributed pediatric data to the largest-ever genetic study of Crohn's disease, a type of inflammatory bowel disease (IBD) that causes chronic, painful inflammation of any part of the digestive tract. IBD also includes ulcerative colitis, which is limited to the large intestine. IBD has complex causes, resulting from any of a number of genes that may interact with each other and environmental factors.

In this study, the International IBD Genetic Consortium drew on samples from more than 22,000 patients and 29,000 controls from around the world. The CHOP researchers, including Hakon Hakonarson, MD, PhD, director of the Center for Applied Genomics, Kai Wang, PhD, and Robert N. Baldassano, MD, director of the Center for Pediatric Inflammatory Bowel Disease, contributed genotype data from more than 1,600 pediatric patients with Crohn's disease and 4,000 controls.



The study, which appeared in *Nature Genetics*, identified 30 new locations at which gene variants were associated with a higher risk of having Crohn's disease. When pediatric data was combined with data from adult-onset cases, the joint analysis identified 31 new genetic variants linked to IBD. "In childhood-onset IBD, genetic factors play a stronger role and hence there is early onset of the disease," says Dr. Hakonarson. In adult-onset IBD, by contrast, there is a longer period of time for non-genetic effects to trigger the disease in those with less genetic susceptibility.

Because the variants found in this study are believed not to directly cause IBD, but instead to act as signposts to other gene variants more directly involved, further studies are needed to identify causative genes and understand their biological functions. "Our goal is to use better understanding of how specific genes contribute to IBD to develop more appropriate and effective treatments for the disease," says Dr. Baldassano.

# VACCINE REDUCES PNEUMONIA IN INFANTS

Investigators led by Samir Shah, MD, conducted the first national study to comprehensively examine rates of pneumonia-related complications before and after a vaccine designed to prevent infection with the leading bacterial cause of pneumonia was introduced. The vaccine, known as PCV7, was introduced in the United States 10 years ago. Using data collected from 1997 to 2006, the investigators found that the vaccine appears to reduce hospitalizations for pneumonia by 22 percent in the vaccine's target range, children less than a year old. Conversely, the rate of hospitalization for pneumonia increased in older children, by 22 percent for children ages 6 to 12 years and by more than 40 percent for children older than 13.



The study team also found that the rate of systemic complications such as sepsis and respiratory failure decreased by 9 percent overall and about 35 percent for infants less than 1 year of age. In contrast, rates of hospitalization for lung complications such as empyema increased by more than 70 percent for children between 1 and 18 years of age. The overall decrease in systemic complication rates could be attributed to the decrease in rates for infants, who are the primary recipients of the vaccine. However, the reasons for increased rates of lung complications are unclear.

The vaccine may also disproportionately benefit black children according the study, which was published in *Pediatrics*. Previous studies have shown that black children have a higher frequency of pneumococcal infections, including pneumonia. The current study found that while the rates of pneumonia were higher for black children compared to white children in all years of the study, the difference narrowed from a ratio of 1.98 in 1997 to a ratio of 1.59 in 2006.

Funding support for the study came from the Academic Pediatric Association Young Investigator Award, the National Institute of Allergy and Infectious Diseases, and the Robert Wood Johnson Foundation.

# GRANT SUPPORTS INJURY SCIENCE RESEARCH TRAINING

A three-year grant from the National Science Foundation's Research Experiences for Undergraduates (REU) program will enable eight students to spend 10 weeks conducting research with a faculty mentor at the Center for Injury Research and Prevention (CIRP). Confirming the demand for this training and how competitive the selection of students will be, 120 students submitted an application for the first year of the Injury Science REU and eight exceptionally talented applicants have been selected.

Led by Flaura Koplin Winston, MD, PhD, co-scientific director and founder of CIRP, and Meghan Marsac, PhD, training director of CIRP, the program will increase CIRP's ability to provide research experiences for underrepresented undergraduates, increase student knowledge and interest in science and engineering, and amplify student interest and knowledge in injury science.

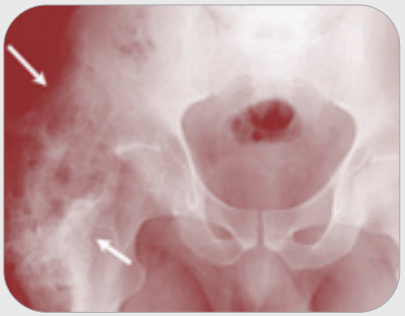
The program also strives to advance individual students' professional development, and provide foundational, hands-on research experience to encourage students to pursue science degrees and careers that integrate injury science. "Part of CIRP's mission is to grow the field of injury scientists and engineers," says Dr. Winston. "We will be able to attract the best and the brightest students at an early enough phase in their academic development that we might inspire them to choose a career in research."

# POTENTIAL TREATMENT FOR DEBILITATING BONE DISEASE

Heterotopic ossification (HO) is a painful and often debilitating abnormal buildup of bone tissue that appears as a congenital form in children or that strikes wounded military personnel and surgery patients following severe injuries and wounds. The bone growths can press against nerves and blood vessels, resulting in chronic pain, limited motion, problems fitting prosthetic limbs, and other complications. There is currently no effective treatment for HO, and surgery to remove the abnormal bone masses may trigger more of the growths.

An animal study led by developmental biologists Masahiro Iwamoto, DDS, PhD, and Maurizio Pacifici, PhD, found that a retinoid agonist called nuclear retinoic acid receptor-γ (RAR-γ) prevented HO from occurring in mice genetically engineered to model both forms of the disorder. The study, published in *Nature Medicine*, found that RAR-γ interrupts a signaling-nuclear protein pathway involved in cartilage formation, an essential step in the development of HO. The protective effect appeared to be permanent, persisting even after drug treatment ended.





"If these animal results are borne out in humans, we may have very potent and effective treatments for both forms of this disease — injury-induced HO and the congenital form," says Dr. Pacifici. While more in-depth preclinical studies must be performed before retinoid agonists are tested in humans with HO, it may be possible for investigators to gain access to a retinoid agonist already in a clinical trial for another disease.

The U.S. Department of the Army and the National Institutes of Health supported this study. Co-authors are from Children's Hospital and Thomas Jefferson University College of Medicine, as well as the University of Michigan, Ann Arbor, and Io Therapeutics Inc., Irvine, California.

# NEW GENE FOR NEUROBLASTOMA DISCOVERED

Neuroblastoma is the most common solid cancer of early childhood, and accounts for 10 percent of childhood cancer deaths. A large team of international pediatric investigators found that common variants in the *LMO1* gene increase the risk of developing an aggressive form of neuroblastoma. The variants also mark the gene for driving the biological changes that make tumors grow and spread throughout the body.

Led by CHOP Research investigators John M. Maris, MD, director of the Center for Childhood Cancer Research, and Hakon Hakonarson, MD, PhD, director of the Center for Applied Genomics, the team published these findings in the prestigious journal *Nature*.

The investigators used a genome-wide association study to look for changes in a single letter within the DNA, called single nucleotide polymorphisms (SNPs), and duplications or deletions of stretches of DNA, known as copy number variations (CNVs). They found a significant association between neuroblastoma and SNPs in the *LMo1* gene, and saw the strongest association among patients with the most aggressive form of the disease. They also found that duplicated sections of DNA in the *LMo1* gene occur in a significant percentage of the tumors.



While using this knowledge to develop treatments will require much further work, Dr. Hakonarson states that, "This is a prime example in which integrative genomics, combining SNP discovery arrays with gene expression arrays and other functional approaches, holds great promise in expanding our knowledge base for translating genetic discovery to clinical uses."

# MAGNETIC FIELDS DELIVER DRUG-LOADED NANOPARTICLES

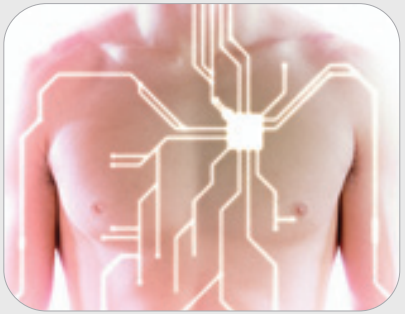
Robert Levy, MD, the William J. Rashkind Endowed Chair in Pediatric Cardiology, led a study published in *Proceedings of the National Academy of Sciences* that introduces a new delivery system to an existing medical technology — catheter-deployed stents.

Patients with heart disease commonly receive stents, narrow metal scaffolds that widen a partly clogged blood vessel. Dr. Levy and his CHOP Research team collaborated with engineers and scientists from Drexel University, Northeastern University, and Duke University to broaden the possibilities for stents, which are often coated with a drug that inhibits obstruction but contain a fixed dose that is not sufficient for addressing reobstruction, which occurs in a significant number of patients.

The team created biodegradable nanoparticles that respond strongly to a magnetic field, and loaded them with drug that inhibits blood vessel obstruction. They then injected the nanoparticles, which are 10 to 100 times smaller than red blood cells, into the arteries of rats with carotid artery stents and magnetized the nanoparticles and stents with a uniform magnetic field comparable to that produced by MRI machines. The rats whose treatment included the magnetic field had more nanoparticles in their stented arteries and significantly lower reobstruction rates 14 days following treatment than the control rats, who received the stents and nanoparticles but were not exposed to the magnetic field.



"This technique is poised to become a new platform for interventional therapies that could be safer and more effective than the current treatments," says Dr. Levy. Magnetic targeting with nanoparticles permits using higher doses, redosing if problems recur, and using more than one type of agent to treat a blood vessel with a stent. Additionally, this study may set the stage for a new medical tool called vascular magnetic intervention that delivers drugs and other agents such as DNA and cells to specific sites where they can produce benefits in diseased or injured blood vessels.



The current study was supported by the National Institutes of Health, the American Heart Association, and the William J. Rashkind Endowment. Dr. Levy expects to collaborate with clinical researchers in the next few years to bring vascular magnetic intervention closer to clinical reality.

# HIV MAKES PROTEIN THAT MAY HELP VIRUS'S RESURGENCE

Viral latency is one of the persistent problems in treating HIV infection. Current combinations of anti-HIV drugs can reduce HIV to undetectable levels, but the virus hides in latently infected cells in a sort of hibernation. If a patient stops taking medication, or is weakened by a different infection, HIV can make a resurgence out of its viral reservoirs, often becoming resistant to previously effective drugs.

Research on human immunodeficiency virus type-1 (HIV-1) led by Terri Finkel, MD, PhD, may shed light on how the virus reactivates after entering latency. The research focused on a protein that HIV-1 produces, called Vif for its role as a viral infectivity factor. Dr. Finkel and colleagues previously discovered that Vif causes HIV-infected cells to stop growing at one phase of the cell cycle, the G2 phase. The current study, published in *Blood*, shows that Vif also acts at an earlier stage in the cell cycle, driving cells out of the G1 phase, a resting phase, and into the more active S phase.

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The investigators also found that two proteins known to regulate the progression of the cell cycle interact with Vif. Identifying these proteins, Brd4 and Cdk9, as Vif's cellular partners may implicate them as potential targets for therapy. Interrupting the activity of Brd4 or Cdk9 may prevent latent infection from becoming active. Harnessing the proteins may make it possible to drive cells out of latency and make the virus susceptible to anti-HIV drugs. Early preclinical testing of inhibitors is getting under way for other conditions, but it is too early to foresee whether, or how soon, these findings will lead to clinical treatments for HIV.

"As we better understand the biological events that revive HIV from latency, we hope to devise ways to eventually intervene in this process with better treatments for people with HIV infection," says Dr. Finkel, who is chief of the Division of Rheumatology and the study's senior author. The first author, also from Children's Hospital, is Jiangfang Wang, MD, PhD. The National Institutes of Health, The Children's Hospital of Philadelphia Research Institute, and the University of Pennsylvania Center for AIDS Research contributed support to this study.

# RESEARCH MAY LEAD TO FIRST TEST FOR IMMUNE DISORDER

A puzzling immune disorder called common variable immunodeficiency disease (CVID) causes a child to have a low level of antibodies, which reduces the body's ability to fight disease and leaves the child vulnerable to recurrent infections. CVID can first occur early or later in life, and the symptoms are highly variable. The great variability of the disease, coupled with the lack of a clear-cut diagnostic test, often causes CVID to go undiagnosed for years before doctors can initiate treatment. During this delay, a child may suffer repeated infections and life-shortening organ damage.

In the first genome-wide, population-based study of CVID, led by the Center for Applied Genomics, the research team searched for genetic variants that might allow physicians to identify genetic patterns found in children with CVID. The researchers found changes in a single base of DNA in an area that codes for a family of proteins involved in immune responses and deleted or repeated sequences in a stretch of DNA in more than a dozen novel genes with direct or potential relevance to the immune system. The study's findings shed light onto the largely unknown biology of how CVID develops and confirmed the genetic complexity of CVID.



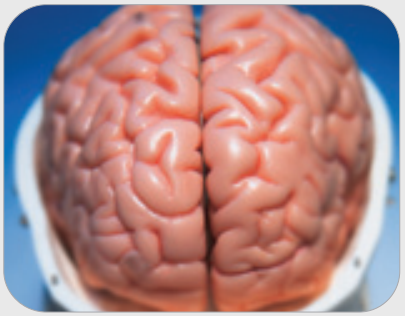
More importantly for clinical application, the researchers were able to use their discoveries to develop a predictive algorithm. When they tested that algorithm on cohorts of CVID cases and controls, they were able to distinguish CVID from healthy controls with 99 percent accuracy. The investigators are now working to refine the algorithm into a standardized diagnostic test for CVID. "This is very exciting," says Jordan S. Orange, MD, PhD, director of the Jeffrey Modell Diagnostic Center. "It suggests that we may be able to use a patient's genetic profile at an early stage to predict whether he or she will develop CVID. Since earlier treatment may greatly improve a child's ability to live with CVID, this research may represent an important advance in managing a complex, puzzling disease."

Dr. Orange collaborated with Hakon Hakonarson, MD, PhD, director of the Center for Applied Genomics at Children's Hospital, Charlotte Cunningham Rundles, MD, of Mt. Sinai School of Medicine, New York City, and researchers from several other institutions. Funded by an Institutional Development Award from Children's Hospital, as well as support from the National Institutes of Health, the Jeffrey Modell Foundation, the Cotswold Foundation, and the NIHR Oxford Biomedical Research Center, the research appeared in the *Journal of Allergy and Clinical Immunology*.

# GENE VARIANTS IN AUTISM LINKED TO BRAIN DEVELOPMENT

A large genetic study led by Xiaowu Gai, PhD, Josephine Elia, MD, and Peter S. White, PhD, director of the Center for Biomedical Informatics, is the first to demonstrate a statistically significant connection between genomic variants in autism and both synaptic function and neurotransmission.

"Prior genomic studies of autism have successfully identified several genes that appear to confer risk for autism, but each gene appears to contribute to only a small percentage of cases," says the lead author, Dr. Gai, who was the current study's lead author. "Our approach considered whether groups of genes with common biological functions collectively accounted for a greater percentage of autism risk."



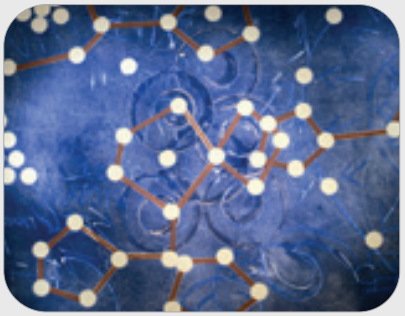
With support from the National Institutes of Health, the Pennsylvania Department of Health, the Seaver Foundation, and Autism Speaks, the team compared the DNA of more than 1,000 children with autism to control sets of healthy participants. They searched for gene variants called copy number variations (CNVs) appearing in the genomes of autistic individuals and their families, but not in healthy controls. Nearly 400 inherited CNVs were exclusive to children with autism in each of two study cohorts. Surprisingly, no single gene was frequently disrupted in either set, and only a few genes harbored CNVs in both sets.

Although there was relatively little overlap between sets of CNVs found in two study groups, the CNVs tended to occur in genes that affected biological processes relevant to autism. Because many genes are possibly involved in autism, researchers face a strong challenge in devising gene-based diagnostic tests and drug treatments. However, the findings strongly suggest functional pathways and gene sets that could be fruitful targets for further investigation.

These findings, published in *Molecular Psychiatry*, were reinforced by data showing that mice with abnormal motor and learning behaviors similar to human autistic behaviors were more likely to have CNVs in genes analogous to human autism genes. Study co-authors are from Children's Hospital and the University of Pennsylvania School of Medicine, Columbia University, Mt. Sinai School of Medicine, and the University of Colorado School of Medicine.

# PROTEINS MAY PROTECT AGAINST DEADLY INFLAMMATION

In children who have juvenile arthritis, lupus, Epstein-Barr virus infection, and other autoimmune diseases, a life-threatening cytokine storm may strike and cause the body's immune system to rage out of control. This complication, called macrophage activation syndrome (MAS) results in overwhelming inflammation, rapid organ failure, and death if not quickly diagnosed and treated.



Investigators led by rheumatologist Edward M. Behrens, MD, developed a variety of mice into the first animal model of MAS and demonstrated that the mechanism of MAS differs importantly from another disease that manifests similar symptoms, called HLH (for hemophagocytic lymphohistiocytosis). While HLH is caused by a genetic mutation, inflammation from rheumatological diseases causes MAS by acting through immunological pathways. In particular, overactive immune system proteins called toll-like receptors interact with the immune system to drive MAS.

"We identified two important molecules in the immune system that control the severity of MAS," says Dr. Behrens. One molecule is interferon-gamma, which makes MAS more severe. The other molecule is interleukin-10 (IL-10), which has a protective effect. "This research strongly suggests that the relative contribution of these molecules can dial up or dial down the severity of a cytokine storm in MAS," says Dr. Behrens.

This study, published in the *Journal of Clinical Investigation*, is a first step toward developing new treatments for MAS. Next studies will investigate whether reducing the action of interferon-gamma, or enhancing the beneficial effects of IL-10, can be used as possible treatments for children who experience this syndrome. Support for the current study came from the National Institutes of Health, an Arthritis Foundation Innovative Research Grant, and a Howard Hughes Medical Institute Early Career Physician Scientist Award to Dr. Behrens.

# ANIMAL STUDY SHEDS LIGHT ON MITOCHONDRIAL DISEASES

Mitochondria are tiny structures that operate as powerhouses within human and animal cells, generating energy from food. Failures of proper mitochondria function impair a wide range of organ systems and contribute to complex disorders. Marni J. Falk, MD, who cares for children in the Mitochondrial-Genetics Disease Clinic, led a study focused on a disease representative of inherited, hard-to-treat mitochondrial diseases called respiratory chain (RC) defects, which share a common cellular failure to properly consume oxygen for the purposes of generating energy.

The current study looked at an inherited genetic deficiency that prevents the production of coenzyme Q, a critical antioxidant and component of the RC. In humans and in the mutant mice used to model this disease, the deficiency results in fatal kidney failure. The current treatment – which consists of providing regular supplements of the missing enzyme product, coenzyme Q10 – is often ineffective.

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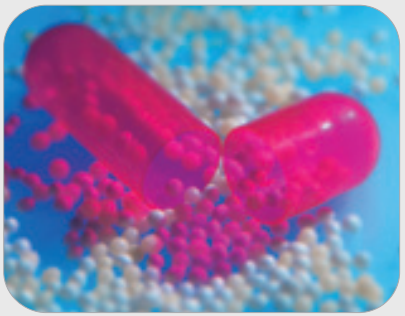
Dr. Falk's team fed the mutant mice probucol, an oral drug formerly used to treat people with high cholesterol (since replaced for that purpose by statin drugs). Probucol showed remarkable benefits in the mice, especially when compared to directly feeding the mice supplements of coenzyme Q10. The drug prevented the mice from developing kidney disease, and reversed kidney disease in mice that had already developed it. It also raised the levels of coenzyme Q10 within the animals' tissues and corrected signaling abnormalities. These results were published in *EMBO Molecular Medicine*.



"If using probucol or a similar drug can benefit patients with defects in the respiratory chain, this could be a significant advance in treating mitochondrial diseases," says Dr. Falk, who received support for this study from the National Institutes of Health. "If this approach can be safely translated to humans, we may have a more effective treatment for mitochondrial disease than anything currently being used." Dr. Falk's collaborators were from The Children's Hospital of Philadelphia, the University of Pennsylvania School of Medicine, and the University of California Los Angeles.

# GENE VARIANTS PLAY ROLE IN CHILDHOOD OBESITY

The number of children and adults with obesity has increased dramatically over the past decade. Public health experts have connected obesity and environmental contributors such as sedentary lifestyles and the wide availability of high-calorie convenience foods.

Research has suggested that there is a strong genetic component; however, this association has been analyzed more frequently in adults than in children. A new study by pediatric researchers, led by Struan F.A. Grant, PhD, associate director of the Center for Applied Genomics (CAG), has added to the evidence that genes have a strong influence on childhood obesity.

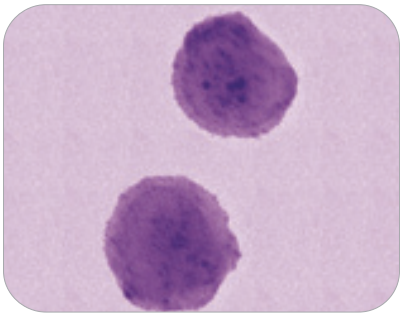


The study team searched across the whole genomes of thousands of obese children and lean children for copy number variations (CNVs) – deletions or duplications of DNA sequences. They found 17 CNVs in obese European Americans, eight of which also occurred in obese African-Americans. "Because many gene variants have different frequencies in different ethnic groups, detecting these same CNVs in both groups, exclusively in obsese subjects, strengthens the probability that these CNVs play a genuine role in the development of obesity," says Hakon Hakonarson, MD, PhD, study co-leader and director of CAG.

Although the CNVs found in this study are rare within the population, the data suggest that individuals harboring such variants are at a very high risk of becoming obese. The majority of the genes located at the CNV sites were not previously reported to be associated with obesity. However, at one location, near the gene *ARL15*, researchers previously linked a gene variant with a higher risk of coronary heart disease and type 2 diabetes via levels of adiponectin, a hormone involved in glucose regulation.

The current study, published in the *American Journal of Human Genetics* and supported by Children's Hospital, the National Institutes of Health, and the Cotswold Foundation, does not have immediate applications to diagnosis and treatment. But it does add another piece to the puzzle of understanding the increasingly common condition. Future studies will uncover additional genetic influences and biological details of how genes contribute to childhood obesity.

# III. TECHNOLOGY



## BRINGING HOPE TO THE MARKETPLACE: HOSPITAL'S FIRST SPIN-OUT COMPANY TO ESTABLISH NEW TREATMENT, OPEN DOOR FOR FUTURE VENTURES

CHOP Research investigators are working every day to translate basic research discoveries into innovative medical treatments. But the journey from a basic discovery through the development pipeline is long, and the expense and risk of development are both high. Only a fraction of promising therapies makes it to the marketplace. New approaches and a tenacious spirit are the keys to overcoming the fundamental challenges involved in transitioning academic discoveries to commercial products available to the patients who need them.

Children's Hospital added another "first" to its rich history of research innovation this fiscal year when spinning out its first startup company, Vascular Magnetics Inc. (VMI). By licensing its technology to VMI, Children's Hospital aims to create a commercially viable therapy that builds upon the Hospital's extensive laboratory research using magnetic nanoparticles to deliver drugs to diseased blood vessels.



Investigators with promising research discoveries that have the potential to help patients often face an unusual problem: they are too innovative for the marketplace. The traditional pathway for bringing innovations developed at academic institutes to market involves licensing the technology to a large commercial company such as a pharmaceutical, device, or biotech firm. When a newly developed technology is outside the range of therapies companies are focusing on, new ways to commercialize the technology are needed.

Children's Hospital recognized the need for an innovative approach to commercialization for a technology invented by Robert J. Levy, MD, the William J. Rashkind Endowed Chair in Pediatric Cardiology at Children's Hospital. In a series of animal studies over the past decade, Dr. Levy and his team at Children's Hospital investigated a new approach to stent-based therapy, which is the conventional technology used to treat several cardiovascular conditions.

The team, which included CHOP Research co-inventors Michael Chorny, PhD, Boris Polyak, PhD, Ilia Fishbein, MD, PhD, Ivan Alferiev, PhD, and Darryl Williams, developed nanoparticles, extremely tiny spheres made of a biodegradable polymer impregnated with iron oxide. Under a low-power, uniform magnetic field, much lower than that produced by existing MRI machines, magnetic forces drive the nanoparticles into metal stents and the surrounding artery.

The nanoparticles carry a therapeutic payload of the drug paclitaxel, which is released into the surrounding blood vessel tissue in order to slow arterial re-blockage. In 2008, *Forbes* magazine named Dr. Levy's work a promising "disruptive technology," one that might eventually supplant drug-eluting stents.

Developing this innovation through a spin-out company, which is independent of the Hospital but tied to it through a licensing agreement, creates two types of advantages. First, it is an avenue to bring the Hospital's early stage discovery to the marketplace, where it could ultimately benefit patients. VMI plans to advance the technique to clinical development and show safety through Phase I clinical trials, findings that would reduce the risk profile of the innovation enormously and could attract the attention of a large commercial partner. The resources and expertise of a large commercial partner would help to usher the technology through continued development and production, and make it available to patients.

Second, the success of VMI would provide revenue to CHOP Research through the Hospital's part ownership of the company and technology transfer agreements, money that the Institute would use to fund further research, support new research projects, and build new facilities. Also, by creating an independent source of revenue, CHOP Research would have a reduced need to secure external grants, a significant concern in the current economic climate.



Dr. Levy co-founded VMI with Richard S. Woodward, PhD, the company's chief executive officer. Drs. Levy and Woodward first joined forces through the QED Proof-of-Concept Program sponsored by the University City Science Center in West Philadelphia, the nation's first multi-institutional proof-of-concept program for life sciences technologies targeted at accelerating research from academic laboratories into the marketplace. The program matches academic scientists with experienced business advisors like Dr. Woodward, who has a background that includes developing nanoparticles and polymeric coatings.

VMI will advance the technology to human trials for peripheral artery disease (PAD), which is characterized by blocked arteries, primarily in the legs. PAD affects more than 27 million older adults in North America and Europe, with diabetes patients and smokers at particularly high risk. Current treatments for PAD, including drug-eluting stents, are ineffective, with re-blockage of the arteries occurring at a high rate.

In addition to being the Hospital's first startup company, the program targets patients outside the Hospital's usual pediatric age group. "While our first target group is adult patients, the technique represents a new platform technology, potentially adaptable to delivering a variety of therapies to children as well as adults," says Dr. Levy.

Drs. Levy and Woodward envision developing the technology into a future therapy called Vascular Magnetic Intervention™, which would serve as an adjunct to artery stenting. Instead of paclitaxel, the technology could deliver other therapeutic compounds, DNA for site-specific gene therapy, therapeutic cells, or other treatments. In addition to treating PAD, the technique might carry paclitaxel to narrowed coronary arteries, chemotherapy drugs to a tumor, or other medications to a bile duct or a urinary tract. Eventually, says Dr. Levy, the technology could be applied to types of pediatric heart disease, such as primary pulmonary hypertension or heart defects.

"Creating a spin-out company is another avenue for developing discoveries into products that will fulfill our mission and have a return to the Hospital that will fuel further innovations," explains Ellen Purpus, PhD, director of the Office of Technology Transfer. "Besides the great potential benefit in PAD, commercial success for this technology could enhance our mission of improving children's health – by setting the stage for developing and investing in innovative therapies for children," adds Dr. Purpus.

Children's Hospital continues to invest in Dr. Levy's research that builds upon the technology licensed to VMI. The Hospital's support includes providing funding for the development of a prototype of the technology for use in large animal studies. VMI has the option to license technologies that emerge from the continued investigations, all of which continue to be conducted under Dr. Levy's guidance at CHOP Research.



As lab research continues, VMI is moving ahead to attract venture capital for Phase I trials. "Our plan is to prove the efficacy of this therapy in humans by late 2015," says Dr. Woodward. "The revenue projections for the company suggest sales of over a billion dollars per year within about four years after commercial launch." All co-inventors, including several investigators at Drexel University and the University of Pennsylvania, will receive a share of royalties should products result from the attempt to commercialize the technology licensed to VMI.

Establishing VMI was possible because of CHOP Research's dedication to maximizing the potential of new discoveries. With the support of a visionary board and the oversight of general counsel and compliance experts, CHOP Research leadership continues to find avenues of getting early stage research discoveries to the marketplace.

"Spinning out VMI was very exciting. It's always a hard road when you are first for anything, but the policies and procedures for establishing a spin-out company are being set in place," says Dr. Purpus. "Now the path is formed for other discoveries in our pipeline."

**61**
Active Licenses

**38**
New U.S. Patents Filed

**2**
U.S. Patents Issued

**56**
Invention Disclosures Received



## US PATENT NUMBER 7,939,063 B2

In collaboration with University of Pennsylvania researcher Douglas Cines, MD, Mortimer Poncz, MD, has developed methods to promote either formation or dissolution of blood clots by genetically engineering blood progenitor cells or their more fully differentiated progeny, such as platelets. Previous studies have shown that when thrombi (clots) are rich in platelets they are more resistant to antithrombotic therapy due to decreases in the expression of urokinase-type plasminogen activator (u-PA). By placing u-PA under control of the appropriate regulatory mechanisms, its expression is modulated, thus regulating its ability to promote or inhibit clotting. This method could be useful in treating bleeding disorders — or, conversely — disorders such as stroke where it is important to reduce clot formation.

## US PATENT NUMBER 7,846,201

This patent, issued to Robert Levy, MD, Ivan Alferiev, PhD, Michael Chorny, PhD, and Boris Polyak, PhD, is central to the investigators' research into the delivery of biomaterial or small molecule-associated nanoparticles to cells or tissues. It is one in the portfolio of patents and patent applications seminal to the technology that Vascular Magnetics Inc., the Hospital's first startup company, will be further developing and commercializing. The patent involves the synthesis and use of nanoparticles coated or loaded with biomaterials such as DNA, peptides, antibodies, and the like, or with small molecule therapeutics intended to treat specific conditions. The nanoparticles are magnetic and when a weak magnetic field is applied to the site to be treated, the nanoparticles can be guided to the site. Different sized particles can be synthesized to facilitate rapid uptake in multiple tissue and cell types. The carrier particle is made of a biodegradable polymer that will not remain in the tissues for long periods of time, thus rendering the particles non-toxic.

# IV. INVESTMENT

## NAVIGATING THE PATH FROM BENCH TO BEDSIDE: THE OFFICE OF IND-IDE SUPPORT KEEPS INVESTIGATORS FOCUSED ON RESEARCH, REDUCES ADMINISTRATIVE BURDEN

When new drugs or devices become available to patients, much of the credit goes to the pharmaceutical and device companies whose names are associated with the innovations. Yet CHOP Research and other academic health centers play a large role in the discovery of drugs, vaccines, and devices that make a difference in the lives of children around the world.

CHOP Research investigators are committed to true translational research, in which ideas conceived in the lab are moved from the bench to the first studies in humans. Before clinical trials of cutting-edge therapies can begin, the Food and Drug Administration (FDA) requires an application to justify that a new therapy is reasonably safe to test for the first time in humans or in a new population, such as children.



An Investigational New Drug (IND) application or an Investigational Device Exemption (IDE) enables an investigator to take the first steps essential to translating basic science to clinical applications. It also requires a large number of regulatory responsibilities that keep the FDA informed about the progress of the studies.

An IND or an IDE sponsor – typically a pharmaceutical, biologic, or device company – takes ultimate responsibility for a clinical investigation. But when an investigator also acts as the sponsor, he or she is required to take on the responsibilities of both roles. Adding FDA's requirements for a study sponsor to an investigator's already long list of tasks can create a burden on the investigator and open the institution to unnecessary risks.

To lessen the administrative burden on principal investigators (PIs), CHOP Research established the Office of IND-IDE Support. The office provides regulatory guidance, operational support, and institutional oversight for research conducted by CHOP investigators holding an IND or IDE.

"We want to take the administrative burden away from PIs so they can focus on what they do best – treating the children," says Lisa Speicher, PhD, director of the Office of IND-IDE Support. "We work with PIs from the point of inception when they look at their promising bench research and think 'can I get this into the clinic?'"

Because of the Hospital's commitment to innovation, there is often a fine line between research and cutting-edge clinical care. The Office of IND-IDE Support acts as a resource to investigators to help ensure these lines are not inadvertently blurred. The office's monitoring plans also provide an opportunity to help investigators ensure they are meeting institutional and FDA requirements. Study monitoring, conducted by Christina McGee, mitigates risk to investigators and the institution by finding issues and preventing future problems, as well as identifying opportunities for investigator education.

Many investigators – while experts in the clinical and technical aspects of the research protocol – are not familiar with the depth of FDA regulations. "An IND or an NDA isn't a simple 'form,' there is a depth to the requirements that presents a huge learning curve," explains administrative director Alice Laneader. "We liaison directly with the FDA to gain an understanding of their expectations, address questions, and submit required reports, and work with investigators and their clinical teams to get them through the process."



In addition to regulatory hurdles, the path that must be followed to coordinate the vendors, funding, and programs required to move basic science to new treatments is so precarious it is often called the "Valley of Death." The Office of IND-IDE Support Office is available to assist CHOP Research investigators with strategies to navigate that road.

The office currently supports more than 15 clinical studies conducted under an IND or IDE, allowing the sponsor-investigators to remain razor-focused on research that will bring new treatments to patients. The studies the office supports involve innovations for conditions as diverse as the childhood cancer neuroblastoma, a genetic bone disorder called osteogenesis imperfecta, the rare immune disorder Wiskott-Aldrich syndrome, congenital diaphragmatic hernia requiring fetal surgery, and a genetic disorder of pancreatic function known as congenital hyperinsulinism (CHI).

The extent of the office's support is shown in its involvement in an IND held by sponsor-investigator Diva DeLeon, MD, for an investigational drug called exendin-(9-39) that has shown promising effects in preclinical studies and in patients with CHI. If inadequately treated, CHI can lead to brain damage or death, and currently available treatments are not always effective. To support the translation of this research into a needed pediatric treatment, the Office of IND-IDE Support provides a host of services for three studies being conducted under Dr. DeLeon's IND.

"The office has been very helpful in providing support for my IND studies," says Dr. DeLeon. "They have provided on site monitoring for my studies, training for myself and my staff, support with progress report submissions, protocol submission, communication with FDA staff, etc. It has been wonderful to have this support that has facilitated my research."

Additionally, the office assisted Dr. Leon's team with a request to the FDA for an Orphan Designation, a special status that supports the clinical development of products for use in rare diseases or conditions and can make a product more attractive for development by an outside company through a technology transfer arrangement.

The impact of the Office of IND-IDE Support has a direct relationship to the success of bringing new treatment approaches to the kids who need it most. "The office has consistently simplified an overwhelming set of regulatory requirements to enable those that are not full time clinical trialists to participate in clinical research of the highest quality and caliber," says Jordan Orange, MD, PhD, who holds an IND for an investigational drug for Wiskott-Aldrich syndrome, a fatal genetic disease of the immune system. "Without their support I am not sure if our clinical study would have been possible."



"Fulfilling the requirements is not simple, but it does not have to be hard," says Alice. "We help investigators do things right on the front end, which saves time on the back end so investigators can get their new treatments to kids."


# A 'GOLD SEAL' OF APPROVAL: CHOP RESEARCH'S HUMAN SUBJECTS PROGRAM RECEIVES FULL AAHRPP ACCREDITATION

Patients and volunteers who take part in clinical research studies are essential to the Hospital's success in improving the health of children. Major research findings at CHOP Research Institute have led to significant advances in a variety of areas including cardiology, genetics, and oncology treatments, as well as fetal surgery, neonatology, and automobile safety. While much of the credit for these advances goes to the investigators who led the groundbreaking research, none of it would be possible without the patients and families who volunteer to take part in clinical studies.



Bringing discoveries out of the laboratory to a patient's bedside requires rigorous testing and an acute awareness of the risks of new drugs, devices, therapeutics, and procedures. Research involving human subjects is an essential part of testing, evaluating, and validating new approaches to care. The Hospital's commitment to improving the health of patients includes continuously assessing and reducing risks to the patients who take part in studies that may provide access to a cutting-edge approach to care or help secure a healthy future for other families.

CHOP Research demonstrated its dedication to protecting those taking part in clinical studies by voluntarily participating in an extensive and lengthy accreditation process for its human subjects research program by the Association for the Accreditation of Human Research Protection Programs (AAHRPP), an independent, non-profit accrediting body.

AAHRPP, pronounced "a-harp," promotes high-quality research by helping organizations throughout the world strengthen their human research protection programs. AAHRPP's standards meet, and often exceed, requirements from federal regulatory agencies such as the U.S. Food and Drug Administration.

The Office of Research Compliance and Regulatory Affairs led an institution-wide effort to demonstrate the quality of the Hospital's human research protection program and prepare for AAHRPP review. The office conducted a self-assessment, managed application submissions and responses, and facilitated a site visit, during which AAHRPP representatives evaluated the CHOP Research Institutional Review Board (IRB) procedures and records and interviewed researchers, coordinators, IRB chairs and members, IRB staff, and other members of Research Administration and CHOP leadership.

Based on these efforts, Children's Hospital achieved full AAHRPP accreditation this fiscal year. Considered the "gold seal" in human subjects protection, full accreditation by AAHRPP establishes a high threshold for knowledge and training and represents an assurance of the quality of the program at CHOP Research. AAHRPP determined that CHOP Research demonstrates – through policies, procedures, and practices – a commitment to scientifically and ethically sound research and to continuous improvement.

"This notable achievement underscores our commitment to protecting the rights and welfare of those who participate in research," says Deb Barnard, Director of the Office of Research Compliance and Regulatory Affairs.



CHOP Research is one of only a handful of other independent U.S. children's hospitals to achieve full accreditation of their human subjects research programs. A standard of excellence recognized throughout the world, AAHRPP accreditation marks a strong program of human subjects protections and serves as public documentation of the Institute's commitment to regulatory compliance and best practices.

"Accreditation by AAHRPP ensures CHOP's position not only at the cutting-edge of science, but also as a leader in protecting our most valuable resource in research – volunteers who take part in clinical studies," says Philip R. Johnson, MD, chief scientific officer at Children's Hospital.

# CHOP COORDINATING NEW NEURODEVELOPMENTAL DISABILITIES NETWORK

Difficulties with learning, attention, sleep, inappropriate behaviors, and social skills are often hallmark signs of neurodevelopmental disabilities. Untreated developmental disabilities like autism spectrum disorders, attention-deficit hyperactivity disorder (ADHD), and intellectual disability (formerly referred to as mental retardation) are highly challenging to families, educational systems, and caregivers.

Although the problems may be relatively common, a significant number of patients do not respond well to existing treatments, and therapies for many other developmental disorders have either not been developed or have yet to be adequately evaluated.



Children's Hospital has coordinated a new collaborative organization, called the Developmental-Behavioral Pediatrics Research Network, uniting experts in neurodevelopmental disabilities to provide greater opportunities to investigate the effectiveness of new therapies, and more rapidly translate basic science findings into eventual clinical treatments.

"Two of our largest challenges are how to best individualize treatments to our patients, and how to develop more effective interventions for these conditions," says Nathan Blum, MD, chair of the network's executive committee and the director of the Leadership Education in Neurodevelopmental Disabilities program at Children's Hospital.

The initial three-year, $200,000 per year grant from the Maternal and Child Health Bureau connects 12 leading pediatric programs to facilitate studies that include enough participants to properly evaluate new treatments as they are developed. The network will also provide opportunities to apply recent advances in genetics and neuroimaging to neurodevelopmental disorders. In particular, genetic studies such as those conducted at Children's Hospital's Center for Applied Genomics and other facilities are identifying biochemical pathways that are altered in neurodevelopmental conditions. Applying the findings of these discoveries to clinical trials may lead to better diagnostic tools for early diagnosis and possibly earlier interventions.

CHOP Research investigators manage the Network Coordinating Center and work with other network members at Albert Einstein College of Medicine; Boston University Medical Center; Children's Hospital, Boston; Cincinnati Children's Hospital Medical Center; Hasbro Children's Hospital; Lucile Packard Children's Hospital; Rainbow Babies and Children's Hospital; the University of Arkansas Medical Center; the University of California at Davis MIND Institute; the University of Oklahoma Health Sciences Center; and the Yale-New Haven Children's Hospital.

# v. LEADING THE WAY

## ORTHOPEDIC RESEARCHER LAUNCHES TRANSLATIONAL PROGRAM

Running, jumping, and playing – the little joys of childhood – are supported by healthy bones that provide a framework for a child's muscles, tissues, and organs. Children born with skeletal disorders often miss out on these joys, and can encounter problems with growth, deformations, chronic pain, and in some cases, an increased risk for developing cancer. While surgical interventions are available for some skeletal disorders, these interventions are not a cure, and patients may require multiple surgeries and treatments throughout life.



Leading orthopedic researcher, Maurizio Pacifici, PhD, joined CHOP Research this fiscal year to continue his research on skeletal development and growth during fetal and postnatal life. An understanding of these fundamental processes can be used to uncover the chain of events leading to skeletal diseases. His investigations are designed to identify the mechanisms that control how a bone – such as a rib, femur, or kneecap – develops its unique three-dimensional structure and shape. They also look at how skeletal tissues acquire and establish their unique biological properties and maintain them through life.

Dr. Pacifici, who holds the Dr. Bong S. Lee Endowed Chair in Pediatric Orthopaedics and is director of Orthopaedic Research, established the Translational Medicine Program in Pediatric Orthopaedics at CHOP Research, a team of multidisciplinary experts who combine basic and clinical research to develop new therapies for skeletal disorders. By establishing an in-depth understanding of the normal process of skeletal development and growth, Dr. Pacifici and his team predict possible disease mechanisms, test the predictions, and envision and develop potential treatments.

The success of this process is seen in Dr. Pacifici's recent work on heterotopic ossification (HO), a painful and often debilitating abnormal buildup of bone tissue. Conducted with Masahiro Iwamoto, DDS, PhD, who also joined Children's Hospital this year as a member of the Translational Medicine Program in Pediatric Orthopaedics, the investigators found an agent that prevented HO from occurring in an animal study. Dr. Pacifici plans to test the agent further in future clinical trials as part of his strategy to apply fundamental knowledge to treat disease.

# BLOOD DISORDERS EXPERT JOINS CHOP, ESTABLISHES NEW CENTER

Found inside the bones, bone marrow plays a vital role in the production of blood cells, which are needed for a variety of biological functions. But sometimes, bone marrow can fail, and the causes of that failure are often unclear.

One of the world's leading experts in bone marrow failure and related blood disorders has joined Children's Hospital to lead the effort to understand the origins of bone marrow disease. Monica Bessler, MD, who is the first person to hold the Buck Family Endowed Chair in Pediatric Hematology, established the Hospital's Pediatric and Adult Comprehensive Bone Marrow Failure Center.

In addition to heading the new center, Dr. Bessler maintains an active research program on the molecular and genetic events that give rise to bone marrow failure in children and adults. Her research involves refining diagnostic tools and developing more effective and comprehensive treatments by targeting the reduced or abnormal production of blood cells in bone marrow failure. Because blood cells play key roles in a number of important biological processes, a better understanding of their production and functions may have medical implications beyond blood disorders.

# GENE THERAPY EXPERT JOINS PRESTIGIOUS AMERICAN ACADEMY OF ARTS AND SCIENCES

Mentioning the American Academy of Arts and Sciences may conjure images of actors standing on a stage before their peers receiving awards for their performances in movies. But the academy recognizes far more than the achievements of movie stars; it also celebrates the nation's premier scholars, scientists, writers, artists, and civic, corporate, and philanthropic leaders.

In fact, the academy is one of the nation's most prestigious honorary societies and is a leading center for independent policy research. Its members include Nobel laureates, Pulitzer Prize awardees, and winners of MacArthur Fellowships, Oscar awards, and Kennedy Center honors.



A renown gene therapy expert at Children's Hospital joined the ranks of the nation's most celebrated when she was elected to the 2011 class of the American Academy of Arts and Sciences.

Hematologist Katherine A. High, MD, HHMI, is internationally recognized for her groundbreaking research on gene therapy, particularly in developing and conducting landmark clinical studies. She continues to lead efforts to develop gene therapy for the inherited bleeding disorder hemophilia. In addition, as director of the Hospital's Center for Cellular and Molecular Therapeutics, Dr. High and her colleagues conducted a clinical trial that produced dramatic improvements in children and young adults with Leber's congenital amaurosis, a congenital form of blindness.

Dr. High is a Howard Hughes Medical Institute Investigator and the William H. Bennett Professor of Pediatrics at the University of Pennsylvania School of Medicine. She also is a past president of the American Society of Gene Therapy.

Founded in 1780 by John Adams, John Hancock, and other scholar-patriots, the Academy elects leading "thinkers and doers" from each generation. Past members have included George Washington, Benjamin Franklin, Daniel Webster, and Albert Einstein.

Among the other members of the 2011 Academy class are astronomer Paul Butler, stem cell scientist George Q. Daley, singer-songwriters Bob Dylan and Paul Simon, filmmaker Ken Burns, jazz musician Dave Brubeck, novelist Oscar Hijuelos, and actors Daniel Day-Lewis and Sam Waterston.

# PRESTIGIOUS SCIENTIFIC PRIZE AWARDED TO EPILEPSY RESEARCHER

An estimated 50 million people worldwide suffer from epilepsy, which is the third most common neurological disorder after Alzheimer's disease and stroke.

Epilepsy is at the heart of the research program of neuroscientist Douglas Coulter, PhD, who was the recipient of the 2010 Epilepsy Research Recognition Award for Basic Science from the American Epilepsy Society.

Considered the most prestigious prizes for research in the field, the Epilepsy Research Recognition Awards annually honor active scientists for professional excellence and distinguished research. One award recognizes a basic science investigator, the other a clinical investigator.

The Basic Science Award to Dr. Coulter acknowledged his "highly original and pioneering contributions to the understanding of altered brain cell and circuit function in the development of epilepsy."

Part of his research has centered on a fundamental question of how an injury to neurons ultimately results in the recurrent seizures that characterize epilepsy. Other aspects of Dr. Coulter's research have focused on how abnormal changes in brain cells called astrocytes reduce inhibition signals in the brain, allowing uncontrolled firing among neurons to give rise to epileptic seizures. He also investigates cellular activities of several anti-epileptic drugs.

The ultimate goal Dr. Coulter's research is to help translate detailed knowledge of how epilepsy develops to establish better therapies for treating children and adults with epilepsy.

# TREATMENT AGGRESSIVENESS RESEARCH NAMED ARTICLE OF THE YEAR BY ACADEMYHEALTH

In today's news, few topics are as talked about – or as heavily debated – as healthcare reform. The issue of decreasing the cost and social burden of healthcare while improving the quality of care impacts every American, and strategies for addressing the issue are hotly debated in the Congress and media.

Many in the government, research community, and lay press have suggested that an aggressive treatment style is both dangerous and wasteful. The implication of this argument is that cutting healthcare expenditures can be achieved without reducing quality.

Yet just as comparative effectiveness research is needed to establish evidence-based standards of care, outcomes research is essential to understanding the true impact of medical care spending on health. Through research that evaluates cost effectiveness in clinical care, researchers will peel back the issues covering the core sources of spending inefficiencies.



Jeffrey H. Silber, MD, PhD, director of the Center for Outcomes Research at CHOP Research, and Robert Kaestner, PhD, from the University of Illinois, received the Article-of-the-Year Award for two papers that evaluate how medical outcomes and financial costs are associated with the intensity, or aggressiveness, of treatment.

Given by AcademyHealth, the nation's largest health services research professional organization, the award recognizes the best scientific work that the fields of health services research and health policy have produced and published during the previous calendar year. It is awarded for an article that provides new insights into the delivery of healthcare and advances the knowledge of the field.

In the award winning companion papers, Drs. Silber and Kaestner evaluated the influence of an aggressive treatment style on surgical outcomes using data collected from more than 4.5 million Medicare patients admitted to one of more than 3,000 hospitals for surgery.

The authors examined treatment aggressiveness as defined by the Dartmouth Atlas of hospital spending intensity, which has been used in studies that assert aggressiveness increases complications and worsens mortality rates.

However, using the same definition of aggressiveness, the current articles indicate that a more aggressive treatment style increases survival, contradicting previous studies and cost-cutting arguments that argue patients would not be harmed by reductions in Medicare spending.

"Previous studies have looked at the end of life care for patients who have died, under the assumption that they are equally sick," says Dr. Silber, who is also a professor of pediatrics and anesthesiology and critical care medicine at the University of Pennsylvania, a professor of healthcare management at the Wharton School, and a senior fellow at the Leonard Davis Institute of Health. "But these studies are not looking at everyone. We wanted to know what to do with patients moving forward, when we don't know what their outcome will be yet. What is the impact of aggressive treatment when a patient is admitted, looking forward?"

In the first paper, published in *Health Services Research*, Drs. Silber and Kaestner asked whether hospitals with more aggressive treatment had better surgical quality compared to less aggressive hospitals. They found that surgery at more aggressive hospitals had significantly lower mortality and failure-to-rescue rates. They also found that the aggressive treatment style did not lead to increased complications, which can contribute to much of the high cost associated with surgery.



To further explore the issue, Drs. Silber and Kaestner estimated the cost effectiveness of aggressive care by looking at the association between inpatient spending and mortality of Medicare patients admitted to hospitals for surgery. Published in *Milbank Quarterly*, the research showed that in many types of surgery, a 10 percent increase in expenditure was associated with 4 to 11 percent increase in the number of patients who survived 30 days following surgery. This benefit was stable after the 30-day mark, showing that patients who survive at aggressive hospitals are no more fragile than survivors at less aggressive hospitals.

By identifying improved outcomes at hospitals with a more aggressive treatment style, Drs. Silber and Kaestner found that aggressive treatment does not push beyond the commonly cited "flat of the curve," the point at which additional healthcare spending cannot provide better quality of care. The conclusion from this research indicates that inefficiencies in health spending are less than conventionally believed, at least for inpatient care.

The award-winning findings should be taken into account when attempting to find cost efficiencies by reducing aggressive care. "In our study the more aggressive hospitals did better, which shows aggressive treatment is not waste or abuse, it is a style of practice," says Dr. Silber. "While there are opportunities for tremendous savings in health spending, a blunt approach to cutting costs can hurt patients. If you think that aggressiveness is bad, you'll want to cut it. But if it were your life, you'd be interested in that extra benefit in survival. We need to be careful."

# GENETICIST HONORED FOR OUTSTANDING RESEARCH

In gene expression, information in DNA sequences is interpreted as proteins that play myriad biological roles in the body. The levels of expression may vary significantly from one person to the next.

The genetics of human gene expression has long been a research focus of Vivian G. Cheung, MD, HHMI, the William Wikoff Smith Chair of Pediatric Genomics at Children's Hospital, who received the Curt Stern Award of the American Society of Human Genetics for her pioneering work. The annual award recognizes scientists for major scientific achievements in human genetics.

Dr. Cheung and her collaborator and husband, the late Richard S. Spielman, PhD, were the first to show that human gene expression is extensively inherited. They measured that variation, identified DNA variants that influence gene expression, and analyzed levels of expression as measurable traits. By uncovering many genes that regulate the expression of other genes, they made groundbreaking advances in understanding how gene regulation works.



This work continues to have an important impact on human genetics research. Dr. Cheung's novel approach of measuring levels of gene expression enabled investigators around the world to analyze thousands of gene expression levels simultaneously, transforming the scale of human genetic studies. Other scientists have adopted Dr. Cheung's and Dr. Spielman's methods in ongoing investigations of genetic susceptibility to complex human diseases.

# INNOVATOR IN FETAL MEDICINE HONORED WITH PRESTIGIOUS LECTURESHIP

Not so long ago, the idea of operating on babies still in the womb was almost unthinkable. N. Scott Adzick, MD, surgeon-in-chief, is one of the true innovators in the field of fetal medicine who helped to change our perception of what is possible. Dr. Adzick has dedicated his career to developing prenatal surgical treatments for debilitating birth defects. His unwavering focus has included spina bifida, a disabling neurological condition that affects about 1,500 babies born each year in the United States.

Dr. Adzick, who is also the C. Everett Koop Professor of Pediatric Surgery and the founder and director of the Center for Fetal Diagnosis and Treatment, was honored as The Isabella Forshall Lecturer at the British Association of Pediatric Surgeons' annual meeting in Belfast, Ireland. Given by the oldest and most prestigious international pediatric surgical society, the lectureship is named after Isabella Forshall, CHM, FRCS, FRCSED, a former president of the association whose work resulted in considerable advances in the surgical treatment of children.

As the honored overseas guest, Dr. Adzick presented "Fetal Surgery for Spina Bifida — Tribulations and Trials" to an audience of international surgeons dedicated to the advancement of study, practice, and research in surgery for children. Based on research initiated more than 20 years ago by Dr. Adzick, the Management of Myelomeningocele Study (MOMS) — conducted at CHOP, Vanderbilt University, and the University of California San Francisco – found that performing delicate surgery in the womb, months before birth, can substantially improve outcomes for children with myelomeningocele, the most severe form of spina bifida.

The study, which appeared in the *New England Journal of Medicine*, showed that two and a half years after fetal surgery, children with spina bifida were better able to walk when compared to children who received surgery shortly after birth. Patients who received fetal surgery also scored better on tests of motor function. Within a year after fetal surgery, they were less likely to need a shunt, a surgically implanted tube that drains fluid from the brain. The National Institutes of Health ended the trial early based on clear evidence of efficacy for the prenatal procedure. This trial demonstrates scientifically that fetal surgery can be offered as a standard of care for prenatally diagnosed spina bifida.

# HUMANISM AWARD GIVEN TO MEDICAL ETHICIST FOR OUTSTANDING COMPASSION

Respectful and compassionate relationships between physicians and patients are the foundation of humanism in medicine, and are at the heart of the philosophy of care at Children's Hospital. Because Children's Hospital is at the forefront of treatments and research, it is also at the forefront of conversations about ethical issues that are suddenly no longer abstract concepts, but are entering into the real world of patients, families, and care providers making difficult decisions. Chris Feudtner, MD, PhD, MPH, the Steven D. Handler Endowed Chair of Medical Ethics and director of the Department of Medical Ethics, works closely with many groups to prepare for and address ethical issues as they emerge, and enable effective partnerships with patients, parents, and family members that are essential to family-centered care.

In honor of his outstanding compassion and respect for patients, Dr. Feudtner received the 2011 Leonard Tow Humanism Award from the Arnold P. Gold Foundation through the University of Pennsylvania School of Medicine. This award is given annually to a faculty member who illustrates professional behavior by example, who displays cultural sensitivity in working with patients and family members of diverse ethnic or religious backgrounds, and who demonstrates the highest standards of compassion and empathy in the delivery of care to patients.

Dr. Feudtner is director of research for the Pediatric Advance Care Team and the Integrated Care Service and provides direct patient care to patients on both of these clinical services. His research focuses on how hospitals can better support families facing difficult decisions about a child's care, and how regional systems of care could be better organized to provide palliative support care services to children and their families. The goal of these investigations are to determine what forms of medical interventions or modes of assistance are most helpful for children with life-threatening diseases and their families, and what types of policies best serve their needs. Dr. Feudtner's recent publications have highlighted differences between adults and children needing end-of-life care and the patterns of drug and therapeutic agent exposure in hospitalized children.

# SUPPORTING RESEARCH THROUGH PHILANTHROPY

Among the highest honors a scientist can hold – and the most influential form of philanthropy at Children's Hospital – endowed chairs recognize established leaders in a particular field of learning or science.

Since it's inception in 1988, the Endowed Chair Program at Children's Hospital has supported highly-skilled investigators and physician-scientists seeking to break new ground and forge novel paths critical to understanding and treating disease and improving children's health.

The endowed chairs provide crucial, assured funding to support innovative research. This is particularly critical at times of global economic concerns and decreased budgets among organizations that provide critical funding to our investigators.



Over the past 23 years, the Endowed Chair program at Children's Hospital has flourished and now includes nearly 80 endowed chairs. In FY11 the Hospital announced the establishment of several new endowed chairs.

The Jeffrey Modell Endowed Chair in Pediatric Immunology Research was awarded to pediatric immunologist Jordan S. Orange, MD, PhD, who will continue his groundbreaking research aimed at understanding and developing new treatment strategies for primary immunodeficiency disorders in children.

Primary immunodeficiencies include more than 150 genetic disorders in which the immune system's ability to produce specific antibodies to fight off infection is greatly impaired or absent. Early diagnosis and treatment are essential to preventing recurrent infections from doing permanent damage.

Dr. Orange is already the director of the Jeffrey Modell Diagnostic Center at Children's Hospital, a premier program among dozens of centers worldwide that have been established by the Jeffrey Modell Foundation to provide expert diagnosis and treatment to patients with primary immunodeficiency diseases. Co-founded by Fred and Vicki Modell in 1986, the Foundation honors the memory of their son Jeffrey, who died at age 15 from complications of primary immunodeficiency.

Dr. Orange's research focuses on the biology of natural killer cells and the innate immune system, with a clinical focus on primary immunodeficiency disease. Over the past decade, he has redefined the field of human natural killer cell deficiencies in various genetic disorders. He recently collaborated with European researchers who achieved marked clinical improvements in using gene therapy to treat young children with Wiskott-Aldrich syndrome, a rare but often severe immunodeficiency disorder. At Children's Hospital, he is currently conducting clinical trials testing the use of immunotherapy to boost immune function in children with Wiskott-Aldrich syndrome.

In addition to the endowed chair awarded to Dr. Orange, Children's Hospital established two endowed chairs under the new "President's Scholars Program," a new initiative dedicated to attracting and retaining the best and brightest scientific talent in pediatric medicine.

The chairs were named in honor of two of the founding physicians at Children's Hospital -- R.A.F. Penrose and T. Hewson Bache – and were made possibly through an anonymous $7 million donation to the Hospital.



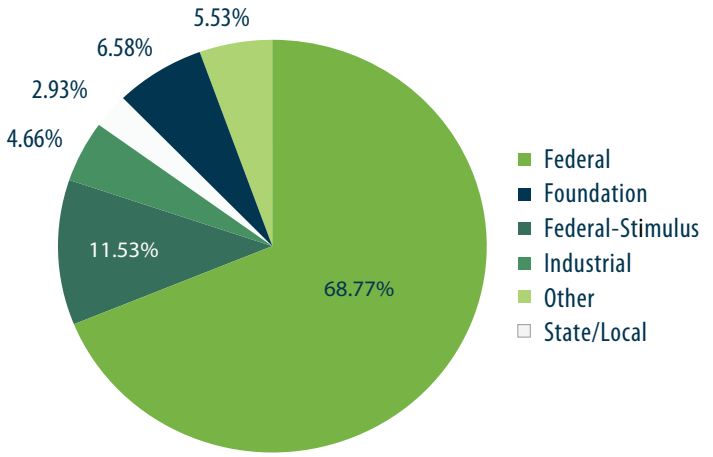
Under the program, individual scholars will hold endowed chairs and will be identified and selected by a special council including the Hospital's chief scientific officer, research faculty, and trustees.

Other endowed chairs established during FY11, which are still pending appointment, are the Irma and Norman Braman Endowed Chair for Research in GI Motility Disorders; Suzi and Scott Lustgarten Endowed Chair for Clinical Care of GI Motility Disorders; and the Howard M. Snyder III Endowed Chair in Pediatric Urology.

# FACTS AND FIGURES

## BY THE NUMBERS

SOURCES OF
### GRANTS & CONTRACTS

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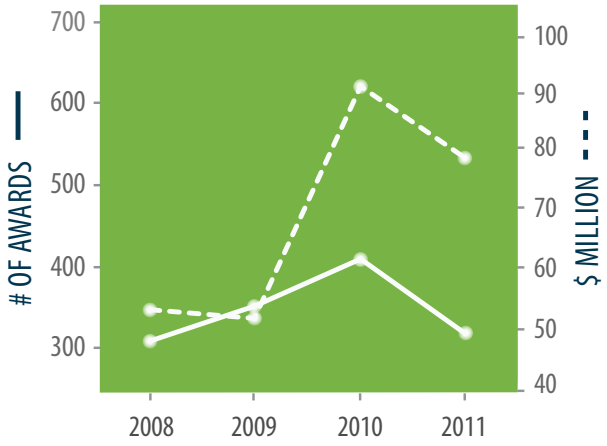

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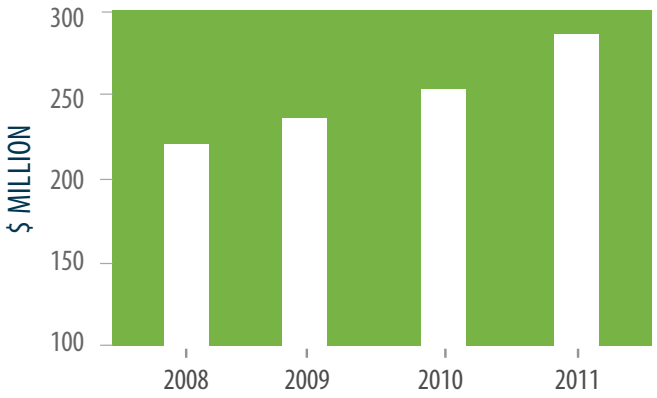
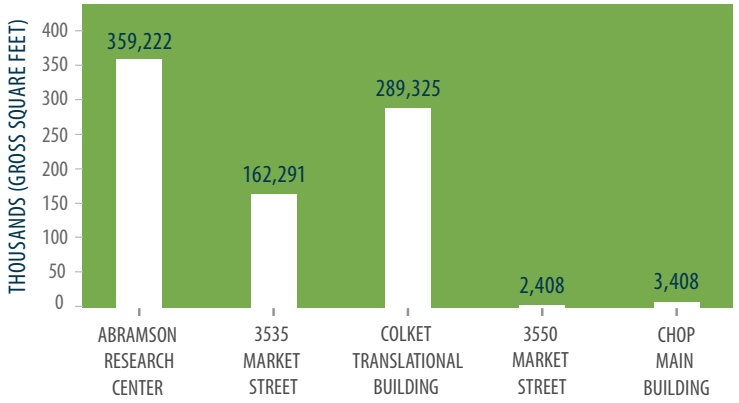



## PUBLICATIONS

## TOTAL RESEARCH SPACE

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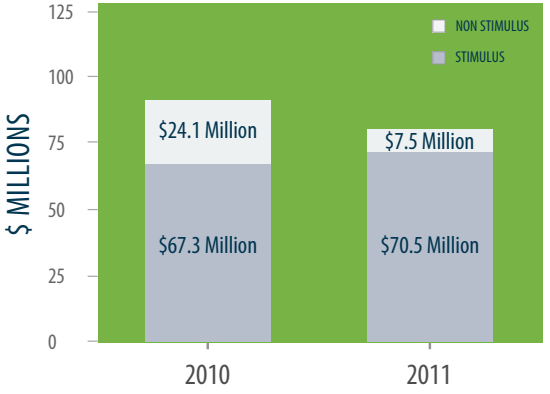
STIMULUS/NON STIMULUS



# WHO'S WHO

## *CHOP Research Institute Leadership*

Philip R. Johnson, MD
Chief Scientific Officer
Executive Vice President, Translational Medicine and Science Director, The Children's Hospital of Philadelphia Research Institute

Tom Curran, PhD, FRS
Deputy Scientific Director

Mary Leonard, MD
Director, Office of Clinical and Translational Research

Mary Tomlinson
Deputy Administrative Director
Vice President, Research Administration

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Mark Fishman
Asuka Nakahara
R. Anderson Pew

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Alan Flake, MD
Lisa MacDowell
Eric Rappaport, PhD
Nancy Spinner, PhD
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Lyngine Calizo, PhD
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Yvonne Paterson, PhD
Berenice Saxon
Gail Slap, MD
Prema Sundaram, PhD
David Taylor, PhD
Mary Anne Timmins
Rita Valentino, PhD
Mitch Weiss, MD, PhD
Susan Weiss, PhD



## *Centers of Emphasis*

***Center for Applied Genomics***
Director: Hakon Hakonarson, MD, PhD

***Center for Autism Research***
Director: Robert Schultz, PhD

***Center for Biomedical Informatics***
Director: Peter White, PhD

***Center for Cellular and Molecular Therapeutics***
Director: Katherine High, MD, HHMI

***Center for Childhood Cancer Research***
Director: John Maris, MD

***Center for Developmental Biology***
Director: Jeffrey Golden, MD

***Center for Injury Research and Prevention***
Directors: Flaura Winston, MD, PhD and
Dennis Durbin, MD, MSCE

Center for Mitochondrial and Epigenomic Medicine
Director: Douglas Wallace, PhD

***Center for Pediatric Clinical Effectiveness***
Director: Ron Keren, MD, MPH

***PolicyLab***
Director: David Rubin, MD, MSCE

## *Research Affinity Groups*

***Fetal Biology and Therapy***
Group Leader: Alan Flake, MD

***Genes, Genomes, and Pediatric Disease***
Group Leaders: John Maris, MD, and Nancy Spinner, PhD

***Health and Behavior***
Group Leaders: Anne Kazak, PhD, and Joel Fein, MD, MPH

***Metabolism, Nutrition, and Physical Development***
Group Leader: Babette Zemel, PhD

***Mitochondria***
Group Leaders: Marni Falk, MD, and Neal Sondheimer, MD, PhD

***Neuroscience***
Group Leader: Michael Robinson, PhD

***Normal and Malignant Hematopoiesis***
Group Leader: Carolyn Felix, MD

***Proteins***
Group Leader: Yair Argon, PhD

***Vaccine and Immunotherapies***
Group Leaders: Terri Finkel, MD, PhD, and Steven Douglas, MD

***Endowed Chairs***

**Anesthesiology and Critical Care Medicine**

James Battaglia Endowed Chair in Pediatric Pain Management
Gordon Barr, PhD

Children's Hospital of Philadelphia Endowed Chair in Critical Care Medicine
Vinay Nadkarni, MD

John J. Downes, MD, Endowed Chair in Pediatric Anesthesiology and Critical Care Medicine
William J. Greeley, MD

Russell C. Raphaely Endowed Chair in Critical Care Medicine
Robert A. Berg, MD

Josephine J. Templeton Endowed Chair in Pediatric Anesthesiology Clinical Education
Susan C. Nicolson, MD

## Child and Adolescent Psychiatry

Frederick H. Allen Chair in Child Psychiatry
Pending Appointment

## Information

William Wikoff Smith Endowed Chair in Pediatric Genomic Research
Bryan Wolf, MD, PhD

## Nursing

Ruth M. Colket Endowed Chair in Pediatric Nursing
Barbara Medoff-Cooper, RN, PhD

## Pathology

Michael and Charles Barnett Endowed Chair in Pediatric Mitochondrial Medicine and Metabolic Diseases
Douglas Wallace, PhD

Evelyn Willing Bromley Endowed Chair in Clinical Laboratories and Pathology
Michael Bennett, PhD

Evelyn Willing Bromley Endowed Chair in Pathology and Clinical Laboratories
Nancy B. Spinner, PhD

Mildred L. Roeckle Endowed Chair in Pathology
Andrei Thomas-Tikhonenko, PhD

Lucy Balian Rorke-Adams Endowed Chair in Neuropathology
Jeffrey A. Golden, MD

Evelyn and George Willing Endowed Chair in Pathology Research
Janis Burkhardt, PhD

## Pediatrics

Leonard and Madlyn Abramson Endowed Chair in Pediatrics
Alan R. Cohen, MD

Gisela and Dennis Alter Endowed Chair in Pediatric Neonatology
Haralambos Ischiropoulos, PhD

David Lawrence Altschuler Endowed Chair in Genomics and Computational Biology
Peter S. White, PhD



Mary D. Ames Endowed Chair in Child Advocacy
Pending Appointment

Lester Baker Endowed Chair in Pediatric Diabetes
Michael A. Levine, MD

William H. Bennett Professor of Pediatrics at the University of Pennsylvania Perelman School of Medicine
Katherine High, MD

Fred and Suzanne Biesecker Endowed Chair in Pediatric Liver Disease
David A. Piccoli, MD

Irma and Norman Braman Endowed Chair for Research in GI Motility Disorders - *NEW*
Pending Appointment

Catherine D. Brown Endowed Chair in Pediatric Epilepsy
Dennis Dlugos, MD

Buck Family Endowed Chair in Hematology Research
Monica Bessler, MD, PhD

Daniel B. Burke Endowed Chair for Diabetes Research
Pending Appointment

Louis and Amelia Canuso Family Endowed Chair for Clinical Research in Oncology
Frank M. Balis, MD

Henry S. Cecil, MD, Endowed Chair in Rehabilitative Medicine at Children's Seashore House
Susan E. Levy, MD

Children's Hospital of Philadelphia Endowed Chair in Pediatric Hematology
Mortimer Poncz, MD

Children's Hospital of Philadelphia Endowed Chair in Pediatric Neurology
Robert R. Clancy, MD



Children's Hospital of Philadelphia Endowed Chair in the Prevention of Child Abuse and Neglect
Cindy Christian, MD

Colman Family Endowed Chair in Pediatric Inflammatory Bowel Disease
Robert N. Baldassano, MD

David Cornfeld Endowed Chair in Pediatrics
Richard Rutstein, MD

Jean Cortner Endowed Chair in Pediatric Gastroenterology
Virginia A. Stallings, MD

Nicholas Crognale Endowed Chair in Pediatric Emergency Medicine
Kathy M. Shaw, MD

Giulio D'Angio Endowed Chair in Neuroblastoma Research
John Maris, MD

Audrey E. Evans Endowed Chair in Pediatric Oncology
Garrett M. Brodeur, MD

William T. Grant Endowed Chair in Child Development and Rehabilitation, University/CHOP Chair
Marc Yudkoff, MD

Jane Fishman Grinberg Endowed Chair in Stem Cell Research
Mitch Weiss, MD, PhD

Steven D. Handler Endowed Chair in Medical Ethics
Christopher Feudtner, MD, PhD

Robert and Dolores Harrington Endowed Chair in Pediatric Cardiology
Jack Rychik, MD

Werner and Gertrude Henle Endowed Chair
Phyllis Dennery, MD

Maurice R. Hilleman Endowed Chair in Vaccinology
Paul Offit, MD

Joseph Lee Hollander Endowed Chair in Pediatric Rheumatology, University/CHOP Chair
Terri Finkel, MD, PhD

Orton P. Jackson Endowed Chair in Adolescent Medicine
Carol Ford, MD

John H. and Hortense Cassell Jensen Endowed Chair in Pediatric Development and Teaching
Stephen Ludwig, MD

Joshua Kahan Endowed Chair in Pediatric Leukemia
Pending Appointment

Laffey-Connolly Endowed Chair in Pediatric Nephrology
Susan Furth, MD

Grace R. Loeb Endowed Chair in Neurosciences
Gihan I. Tennekoon, MD

Stephen Ludwig Endowed Chair in Medical Education
Patricia J. Hicks, MD

Suzi and Scott Lustgarten Endowed Chair for Clinical Care of GI Motility Disorders - *NEW*
Pending Appointment

Jeffrey Modell Endowed Chair in Pediatric Immunology Research
Jordan Orange, MD, PhD

Robert Gerard Morse Endowed Chair in Pediatric Pulmonary Medicine
Julian Allen, MD

Thomas Moshang Endowed Chair in Endocrinology
Pending Appointment

Yetta Deitch Novotny Endowed Chair in Pediatric Oncology
Beverly J. Lange, MD

Patrick S. Pasquariello Jr. Endowed Chair in General Pediatrics
Louis M. Bell, MD

Stanley Plotkin Endowed Chair in Pediatric Infectious Diseases
Jeffrey M. Bergelson, MD

William J. Rashkind Endowed Chair in Pediatric Cardiology
Robert J. Levy, MD

Regional Autism Center Endowed Chair
Robert T. Schultz, PhD

Richard and Sheila Sanford Endowed Chair in Pediatric Oncology
Pending Appointment

Hubert J.P. and Anne Faulkner Schoemaker Endowed Chair in Pediatric Neuro-oncology
Peter C. Phillips, MD

Elias Schwartz, MD, Endowed Chair in Hematology
Kim Smith-Whitley, MD

Letitia B. and Alice Scott Endowed Chair in Human Genetics and Molecular Biology
Elaine H. Zackai, MD

Evelyn Rome Tabas Endowed Chair in Pediatric Cardiology
Victoria L. Vetter, MD

Jennifer Terker Endowed Chair in Pediatric Cardiology
Robert E. Shaddy, MD

Charles E.H. Upham Endowed Chair in Pediatric Medicine
Beverly S. Emanuel, PhD

Frank R. Wallace Endowed Chair in Infectious Diseases
Kathleen Sullivan, MD, PhD

Wawa Endowed Chair in International Adoption
Susan Friedman, MD

Frank E. Weise III Endowed Chair in Pediatric Hematology
Gerd Blobel, MD, PhD

Richard D. Wood Jr. and Jeanette A. Wood Endowed Chair in Pediatric Diagnostic Medicine
Pending Appointment



## President's Scholars - *NEW*

T. Hewson Bache Endowed Chair in Pediatrics - *NEW*
Pending Appointment

R.A.F. Penrose Endowed Chair in Pediatrics - *NEW*
Pending Appointment

## Radiology

Children's Hospital of Philadelphia Endowed Chair in Pediatric Neuroradiology
Robert Zimmerman, MD

Children's Hospital of Philadelphia Endowed Chair in Pediatric Radiology
James S. Meyer, MD

Oberkircher Family Endowed Chair in Pediatric Radiology
Timothy Roberts, PhD

William L. Van Alen Endowed Chair in Pediatric Radiology
Diego Jaramillo, MD

## Research Institute

Edmond F. Notebaert Endowed Chair in Pediatric Research
Phillip R. Johnson Jr. MD

Mai and Harry F. West Endowed Chair in Pediatric Research
Thomas Curran, PhD

## Surgery

Leonard and Madlyn Abramson Endowed Chair in Pediatric Urology
Douglas A. Canning, MD

Richard M. Armstrong Jr. Endowed Chair in Pediatric Orthopaedic Surgery
John P. Dormans, MD

Children's Hospital of Philadelphia Endowed Chair in Pediatric Otolaryngology
Steven D. Handler, MD

Mary Downs Endowed Chair in Pediatric Craniofacial Treatment and Research
Pending Appointment

John W. Duckett Jr. Endowed Chair in Pediatric Urology
Stephen A. Zderic, MD

George Leib Harrison Endowed Chair in Fetal Therapy
Mark Paul Johnson, MD

C. Everett Koop Endowed Chair in Pediatric Surgery
N. Scott Adzick, MD

Dr. Bong S. Lee Endowed Chair in Pediatric Orthopaedics
Maurizio Pacifici, PhD

Mabel E. Leslie Endowed Chair in Pediatric Ophthalmology
Monte Mills, MD

E. Mortimer Newlin Endowed Chair in Pediatric Otolaryngology and Human Communication
Ralph Wetmore, MD

William Potsic Endowed Chair in Pediatric Otolaryngology and Childhood Communication
Pending Appointment

Peter Randall Endowed Chair in Plastic and Reconstructive Surgery
Scott P. Bartlett, MD

Howard M. Snyder III Endowed Chair in Pediatric Urology - *NEW*
Pending Appointment

Daniel M. Tabas Endowed Chair in Pediatric Cardiothoracic Surgery
J. William Gaynor, MD

Josephine J. and John M. Templeton Jr. Endowed Chair in Pediatric Trauma
Michael L. Nance, MD

Alice Langdon Warner Endowed Chair in Pediatric Cardiothoracic Surgery
Thomas L. Spray, MD

Ruth M. and Tristram C. Colket Jr. Endowed Chair in Pediatric Surgery
Alan W. Flake, MD

Friends of Brian Endowed Chair in Pediatric Plastic and Reconstructive Surgery
Pending Appointment

## Administrative Units

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Lisa Speicher, PhD, Director
Nirmala Thevathasan, Associate Director

Clinical and Translational Research
Mary Leonard, MD, Director

Clinical Trials Financial Management
Mitch Appleson, Director

Core Facilities Administration
Lisa MacDowell, Administrative Director

Faculty Development
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Mary Blitzer Field, Assistant Director

Postdoctoral Affairs
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Jodi Leckrone, Assistant Director

Research Communications
Jennifer Long, Director

Research Compliance and Regulatory Affairs
Deborah Barnard, Director

Research Finance
Steve Wiley, Director
Luz Arrison, Assistant Director
Bethann Kurek, Assistant Director

Research Human Resources
Alexandra Jorgensen, Director

Research Information Systems
Peter Witzleb, Director
Robert Del Campo, Assistant Director

Research Resources
Howard Eck, Director

Research Safety
Raymond Colliton, Director

Responsible Research Training
Wendy Williams, PhD, Director
Jodi Leckrone, Assistant Director

Sponsored Projects and Research Business Management
Sara Dubberly, Director
Brigid Czyszczin, Assistant Director
Robert Denight, Assistant Director

Supply Chain
Kim Gossin, Manager

Technology Transfer
Ellen Purpus, PhD, Director
Greg Baker, PhD, Associate Director
Debbie Schmidt, Associate Director

# CREDITS

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## LINKS OF INTEREST

The Children's Hospital of Philadelphia Research Institute Website

The Children's Hospital of Philadelphia Website

The CHOP Research Institute Press Releases

*Bench to Bedside*, CHOP Research's Monthly News Publication

*Discovery to Innovation*, CHOP Research's Quarterly News Source


CHOP Research's Facebook Page


CHOP Research's Twitter Feed

The Children's Hospital of Philadelphia YouTube Channel

The Children's Hospital of Philadelphia Foundation Web Site