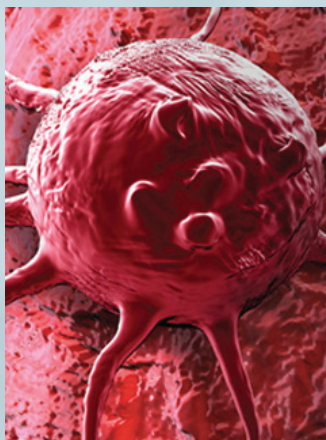
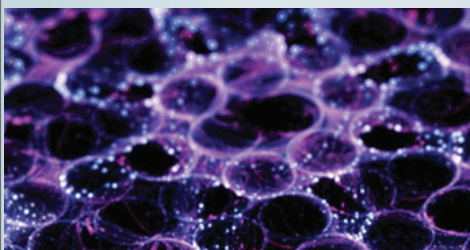


2014 Research Annual Report

*"It really moves the field along
toward a potentially major,
new cancer immunotherapy."*



Distinction.



*The New England
Journal of Medicine*



*Center for Pediatric
Clinical Effectiveness*

Distinction.

3. Bridging the Gap Between Womb and World
5. New Antitumor Immunotherapy Approach Advances
7. Nanocarrier Formulation Developed for Neuroblastoma
9. Preventive Antibiotics Cut Risk of UTI in Half
11. PCORI Awards Support Data Network, Antibiotic Study
13. Pennsylvania Bio Extends Two Honors to CHOP Research

Discovery. >



Bridging the Gap Between Womb and World

In 2012 more than 10 percent of births in the United States were preterm, and nearly 1 percent of births were critically preterm (younger than 26 weeks). These numbers point to a sobering truth: every year, hundreds of thousands of babies are born before they're ready, requiring urgent medical care immediately after (and likely during) birth.

Coming into the world too early can lead to myriad health issues. Preterm babies, particularly those born before 28 weeks, face a host of challenges, including the fight just to survive. And preterm babies don't just face health challenges in the hours and days following their births — many are confronted with obstacles throughout their lives. Those infants who do survive may experience temperature fluctuations, respiratory issues, gastrointestinal and cardiovascular problems, and neurological problems like abnormal blood vessel development, or damage and scarring of blood vessels in the retina.

But investigators at The Children's Hospital of Philadelphia are on the cusp of an innovative approach to caring for these most delicate infants, one that could radically transform the way they are treated and significantly improve their outcomes.

Alan W. Flake, MD, an attending surgeon and director of the Hospital's Center for Fetal Diagnosis and Treatment, has been leading a groundbreaking project on the development of an extracorporeal support of the premature infant (ESPI) system. Far more than a standard incubator or isolette, the device Dr. Flake's team has been developing is exactly what it sounds like: an external uterus designed to help preterm infants bridge the gap between their mother's womb and the world.

A key member of Dr. Flake's team is one of the project's biggest champions, Emily Partridge, MD, PhD, a research fellow in the Center.

Dr. Partridge's experience during her OB/GYN rotation inspired her to work to improve outcomes for preterm infants. She witnessed the birth of a 21-week-old infant who was born early because of the mother's health issues, despite the fact that the baby was otherwise healthy. Because the baby was so young, "There was really nothing that could be done," Dr. Partridge said. "It's just the most frustrating thing . . . it's quite awful."

And those preterm infants who are old enough to be born at 24 weeks have numerous problems. "Even the babies who do survive sometimes have quite catastrophic injuries because of the relative immaturity of their organs and the fact that, at a very simplistic level, they're just not ready to be out here yet," Dr. Partridge added.

The concept for a device that could improve outcomes for preterm babies is not new, as the idea for an external uterus has been around since the 1960s. Indeed, the work of Children’s Hospital’s own William J. Rashkind, MD, indirectly contributed to the ESPI project. The former chief of the Division of Cardiology, Dr. Rashkind was a balloon catheter and artificial lung pioneer who led a study in 1965 that showed the viability of a pumpless oxygenator in children with respiratory failure. His study was one of several integral to the development of extracorporeal membrane oxygenation (ECMO), which is designed to give respiratory and cardiac support to critically ill patients. However, ECMO is generally contraindicated in infants with gestational ages less than 34 weeks and weighing fewer than 2,000 grams.

Building on elements of other designs and previous work, Drs. Flake and Partridge — as well as team members Holly L. Hendrik, MD; Marcus Davey, PhD; and Kevin Dysart, MD — have been working on a device that is designed to mimic the intrauterine environment by allowing neonates to breathe fluid (as opposed to a traditional incubator’s gas) while promoting growth and organ development.

“We’ve tried to mirror what would be happening in utero,” Dr. Partridge noted.

The ESPI device started as a glass incubator tank combined with monitoring devices, but has since evolved into a plastic bag with an incorporated oxygenator and a continuous amniotic fluid exchange system. The fetus — or in this case, the preterm lambs with which the researchers have been working — rest in the device. Lambs have long been the model animal for fetal surgery research, Dr. Partridge noted, because they are roughly the same size as human fetuses and exhibit similar fetal movements.

Within their bags, the lambs are supported by a water pillow in a temperature-controlled environment, with cannulas running into and out of the bag to the pumpless oxygenator, amniotic fluid exchange system, waste removal system, and other ports for a variety of monitors. Vital signs, blood flow, fetal blood gases, and other parameters are continuously monitored in the ESPI system. And by using a pumpless system, the fetus’ heart acts as the pump, as it does in the mother’s uterus.

Despite the challenges of supporting a fetus in a sterile environment outside the womb and the huge engineering and circulatory challenges posed by ESPI, the project has been enormously informative — and successful. In addition to making great strides toward designing “a perfectly closed system,” the research team has learned a number of things about how the placenta functions and are turning their attention to questions about how fetuses and their mothers interact, Dr. Partridge noted.

Going forward, Dr. Flake and his team will study the viability of their system in increasingly preterm lambs, and will work to improve the system’s design. They also plan to further study fetal metabolism and growth, and they hope to expand their work to include models of diseases like congenital diaphragmatic hernia, a condition in which a hole in the diaphragm fails to close during development.

“I truly believe that this is the future of how preterm infants will be cared for, that one day you’ll see rows of bags in the NICU,” Dr. Partridge said. Added Dr. Flake, “This is an enormously promising study. Our system is designed, as much as possible, to avoid the deleterious effects of preterm birth.”



Perhaps one of the most promising approaches to cancer treatment lies in immunotherapy, which involves harnessing the body's immune system to attack tumors.

By carefully adjusting the function of these crucial immune cells, Children's Hospital investigators may have developed a completely new type of cancer immunotherapy. To accomplish this, they had to thread a needle in immune function, shrinking tumors without triggering unwanted autoimmune responses.

The new research, performed in animals, is not yet ready for clinical use in humans. However, the approach, which makes use of a key protein to control immune function, lends itself to further study using candidate drugs that employ the same mechanisms.

"There's a basic paradox in immunology: Why doesn't the immune system prevent cancer in the first place?" said the study's leader Wayne W. Hancock, MBBS, PhD, chief of the Division of Transplant Immunology.

The answer is complicated, but much of it involves a delicate balancing act among elements of the immune system. While immunity protects us against disease, an overly aggressive immune response may trigger dangerous, even life-threatening, autoimmune reactions in which the body attacks itself.

In the study, published in *Nature Medicine*, Dr. Hancock and his colleagues focused on a subtype of immune cells called Foxp3+ T regulatory cells, or Tregs. Tregs were already known to limit autoimmunity, but often at the cost of curtailing immune responses against tumors.

"We needed to find a way to reduce Treg function in a way that permits antitumor activity without allowing autoimmune reactions," Dr. Hancock said.

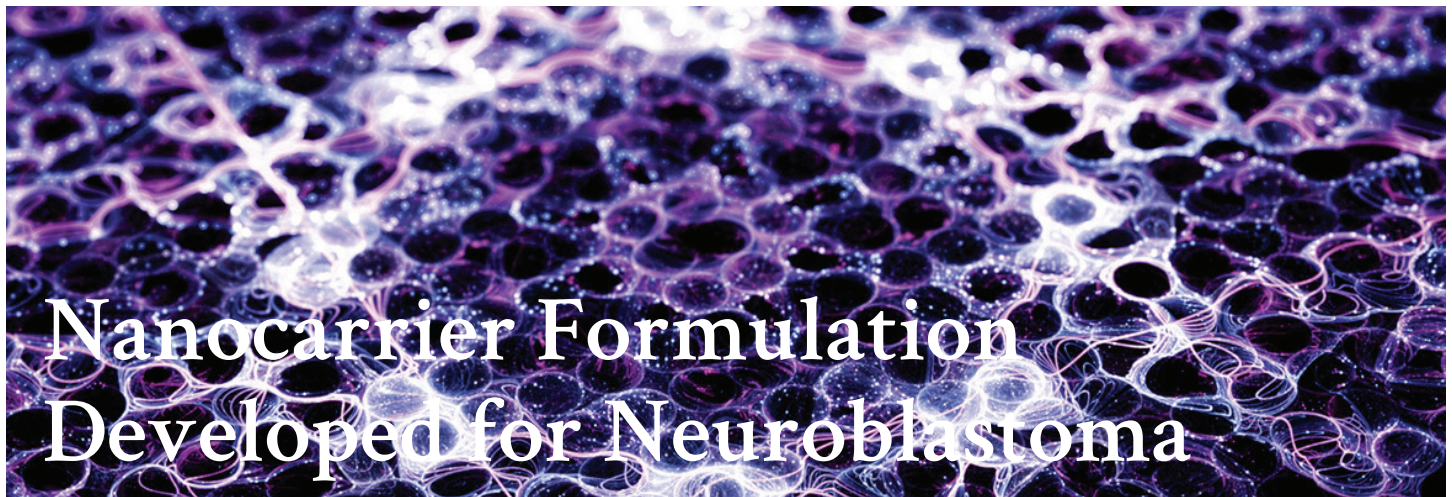
The investigators showed that inhibiting the enzyme p300 can affect the functions of another protein, Foxp3, which plays a key role in controlling the biology of Tregs. By deleting the gene that expresses p300, the researchers safely reduced Treg function and limited tumor growth in mice. Notably, they also achieved the same effects on p300 and Tregs by using a drug that inhibits p300 in normal mice.

"The study demonstrated proof of principle that using a drug to regulate the function of a special, immunosuppressive subset of Treg cells safely controls tumor growth," Dr. Hancock said. "It really moves the field along toward a potentially major, new cancer immunotherapy."

Dr. Hancock plans to pursue further investigations into targeting p300 in immunotherapy. The preclinical findings offer encouraging potential for being translated into the clinic, Dr. Hancock said, who added that pharmaceutical companies have expressed interest in researching this approach as a possible cancer therapy.

The antitumor study, down-regulating Treg function, is the flip side of another part of Dr. Hancock's Treg research. In a 2007 animal study, also in *Nature Medicine*, he increased Treg function with the goal of suppressing the immune response to allow the body to better tolerate organ transplants. In the current study, decreasing Treg activity permitted the immune system to attack an unwelcome visitor — a tumor. In both cases, he relied on epigenetic processes — using groups of chemicals called acetyl groups to modify key proteins — but in opposite directions.

“This is the yin and yang of immune function,” Dr. Hancock noted.



Nanocarrier Formulation Developed for Neuroblastoma

A compelling approach to targeted delivery of drugs in pediatric oncology aims chemotherapeutic agents more selectively in order to give less total drug and get much more effect. Researchers at [The Children's Hospital of Philadelphia](#) are formulating ways to pack this punch into biodegradable nanoparticles — 100 times smaller than red blood cells — to help treat patients with [neuroblastoma](#).

A tumor of the sympathetic nervous system, neuroblastoma has lagged behind cure rates for other solid tumors of childhood. It accounts for 8 to 10 percent of all childhood cancers and 15 percent of deaths from cancer in children, as the majority of patients have advanced metastatic disease. Few new treatment agents are in the pipeline, so researchers are concentrating on how to improve the performance of more conventional anticancer chemotherapeutics in new ways.

[Garrett M. Brodeur, MD](#), acting director of CHOP's [Center for Childhood Cancer Research](#), and a member of the Division of [Oncology at CHOP](#), together with a team of cardiology researchers, [Michael Chorny, PhD](#); [Ivan Alferiev, PhD](#); and [Robert Levy, MD](#); have studies under way that use nanoparticles as delivery vehicles for SN38-TS, a precursor of SN38. SN-38 is a cytotoxic agent which cannot be administered as is, and is currently delivered in the form of another precursor (also called a “prodrug”) irinotecan, used as a treatment for recurrent or resistant neuroblastomas.

A prodrug is a compound that becomes an active drug in the body. Unlike irinotecan, the prodrug design of SN38-TS was adjusted for incorporation into biodegradable nanoparticles finely tuned by the researchers as tumor-targeted delivery vehicles.

“We are taking a uniquely integrated prodrug/nanocarrier-based approach where all formulation components work together to effectively deliver the therapy,” Dr. Chorny said. “SN38-TS is designed to travel with the nanoparticle, get released at a slow rate directly in the tumor, and become converted into the pharmacologically active drug rapidly. This way, we can take advantage of the tumor-targeted delivery to the highest possible extent.”

Using mouse models, the research team has demonstrated that lower total doses of the nanoparticle-delivered drug, SN38-TS, can kill tumors more effectively and with less toxicity than conventional delivery of irinotecan.

“This is huge because irinotecan has a narrow therapeutic window, which is the difference between the lowest dose you can give to kill the tumor and the highest dose before it exerts serious short- and long-term adverse effects,” Dr. Brodeur said.

“Now we can take that window and open it to the ceiling because we can get 10 to 100 times more drug into the tumor by using these nanoparticles as drug delivery vehicles while exposing the patient’s systemic circulation to much less of the drug.”

This nanocarrier formulation protects the active agent, SN38, from inactivation, and its controlled release once inside the tumor tissue enables its accumulation and protracted presence at therapeutically effective levels. The drug is exposed to healthy tissue less because it is entrapped in the nanoparticles while it is circulating. Also, as opposed to irinotecan, it does not need to be metabolized by the liver to be activated.

The administration of SN38-TS in its nanoencapsulated form allows it to take advantage of a principle called the EPR effect, which stands for “enhanced permeability and retention.” Dr. Brodeur explained how it works:

Normal blood vessels have tight junctions between the cells, so very little can get between the cells and into normal tissues. On the other hand, tumor blood vessels are leaky. Nanoparticles in a specific ultrasmall-size range (less than 100 nanometers) will pass by the normal cells and tissues and accumulate in the tumor. Tumors also do not have an efficient circulatory system, so the nanoparticles are retained in the tumor longer.

“That plays to our advantage in terms of the nanoparticles because we can get drug in, have it slowly break down in the tumor, and then we can expose the tumor to more drug,” Dr. Brodeur said.

Drs. Chorny, Alferiev, and Levy are experts at designing the nanoparticles so that they are the ideal size and composition. If they are too big, macrophages from the patient’s liver and spleen will identify them as foreign, like a virus, and eliminate them, so exposure to the tumor is limited. If they are too small, they could enter normal tissues, just like the free drug. As in the fairytale Goldilocks, the nanoparticles cannot be too big or too small; they must be just right.

The researchers use polymeric nanoparticles, which are chains of polymerized lactic acid. Polyethylene glycol is added to make them stealthy so that the patient’s immune system does not recognize them easily. These components also are completely biocompatible and bioeliminable.

“They are simple molecules that are fairly easy and inexpensive to make,” Dr. Brodeur said. “They are very effective at doing their job, and then they just break down.”

Dr. Brodeur anticipates that the SN38-TS nanoparticle formulation may be ready to be tested in clinical trials as early as the end of 2015.

“We think the potential application is great, not just for neuroblastoma patients, but to any patient who you might treat with irinotecan, so that includes a number of other solid tumors in children and adults,” Dr. Brodeur said.

In the future, nanoparticle formulations could be created for other drugs, and this has important implications for tumors that currently are considered to be natively resistant. The research team also will explore the nanoparticle delivery of co-drugs that may be synergistic when given together, and they will try pairing nanomedicines with conventional drugs to see if they have a combined effect.



Preventive Antibiotics Cut Risk of UTI in Half

Prophylactic antibiotics are prescribed to prevent — rather than treat — the spread of bacteria that can lead to serious and, at times, life-threatening, infections.

Many patients with vesicoureteral reflux (VUR) who suffer from a urinary tract infection often receive the antibiotics daily, and they must take them for years to prevent infection. About 5 percent of children will have a UTI by age 6, and approximately one-third of these patients have VUR. When a child with VUR urinates, some urine backs up in the ureters toward the kidneys and therefore the bladder does not empty completely. This increases the chance of a UTI and, if the urine reaches the kidneys, it is often accompanied by a fever and is called pyelonephritis.

“The problem with pyelonephritis is that it sometimes results in kidney scarring, and there is a concern that this could lead to high blood pressure and renal failure when you get older,” said [Ron Keren, MD, MPH](#), who was a co-investigator on a multisite clinical trial on the use of prophylactic antibiotics to prevent UTIs in children with VUR.

Clinicians currently use either a long-term course of daily antibiotics or antireflux surgery to treat children with VUR. However, an international clinical study conducted in the 1980s showed no difference in the rates of recurrent UTIs or renal scarring between the two approaches. More recent trials that looked at antibiotics’ effectiveness had conflicting results and methodological weaknesses, so researchers launched the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial to obtain more evidence to guide clinical practice.

Dr. Keren and his fellow investigators on the RIVUR trial studied 607 children from 19 clinical sites across the U.S. and followed them for two years. They poured through data to determine if children who received daily doses of the antibiotic trimethoprim-sulfamethoxazole had fewer recurrences of UTIs than those who received the placebo. They also looked to see if there were any differences in the occurrence of renal scarring.

The results of the study were “pretty dramatic,” Dr. Keren said.

The research team found that those who received prophylactic antibiotics had their chance of developing a UTI cut in half. The percentage of children getting UTIs increased over time in the placebo group but not in the treatment group, Dr. Keren pointed out, which demonstrated the sustained effectiveness of the antibiotic.

The investigators, who published their study in the *New England Journal of Medicine*, also found little difference between the treatment and placebo groups when it came to renal scarring.

Dr. Keren said he was surprised that the prophylactic antibiotics worked as well as they did, although he cautioned that the team's finding about renal scarring will likely add fuel to the ongoing debate about the use of prophylactic antibiotics.

"Some physicians will say it is not worth using daily antibiotics in children with VUR if they don't prevent kidney damage," he said. "Others will say it is important to continue to treat these children with antibiotics because a UTI recurrence could land them in the emergency room or hospital."

The findings in the RIVUR study will likely affect the use of urinary tract imaging — called voiding cystourethrogram (VCUG) — to screen patients for VUR. While the imaging can be a helpful diagnostic tool, it involves radiation exposure and is invasive, uncomfortable, and often traumatic for children. The current guidelines recommend that physicians take a watchful waiting approach before suggesting the procedure. Part of the rationale for this approach was the lack of strong evidence for the effectiveness of prophylaxis in children with VUR.

Now that we know that prophylaxis works, this may change the calculus for some providers about the risks and benefits of getting a VCUG on every child who has a first UTI, though the American Academy of Pediatrics still recommends waiting for a second UTI, as the majority of children will never have another one, Dr. Keren said.

With so many ongoing discussions about the best ways to approach UTIs, the issue is ripe for further research. Dr. Keren is involved with another NIH-supported study that follows a design similar to RIVUR, known as the Careful Urinary Tract Infection Evaluation (CUTIE) trial, but it is focusing on the rate of recurrent UTIs and kidney scarring in children who do not have VUR.



Children's Hospital investigators continue to be on the forefront of pediatric medicine, as evidenced by two new awards from the [Patient-Centered Outcomes Research Institute](#) (PCORI). The awards, which aim to support the development of a data network and a landmark study of antibiotics, draw on the Hospital's large repository of health data and on its sprawling regional network of healthcare providers.

PCORI was established by the [Affordable Care Act](#) to fund and carry out [comparative effectiveness research](#), which compares healthcare approaches currently in practice to determine which approaches are the most effective and beneficial. Since PCORI began funding research projects in 2012, the organization has been awarded a staggering \$464 million to support 279 projects.

In September 2013, [Jeffrey S. Gerber, MD, PhD](#), received an [approximately \\$1.8 million contract](#) from PCORI to compare the effectiveness of broad- and narrow-spectrum antibiotics in treating acute respiratory infections. An infectious diseases specialist and a faculty member in the [Center for Pediatric Clinical Effectiveness](#), Dr. Gerber investigates the epidemiology and outcomes of antibiotic use in children.

Dr. Gerber's three-year investigation focuses on the use of antibiotics to treat acute respiratory tract infections (ARTI), such as ear and sinus infections. Despite the fact that guidelines frequently recommend clinicians use narrow-spectrum antibiotics to treat ARTI, many doctors often prescribe broad-spectrum antibiotics.

"Using parent- and patient-centered outcomes, this study is designed to identify which antibiotic choices best optimize clinical outcomes while minimizing side effects," Dr. Gerber said. In addition to assessing traditional medical outcomes, the investigators are seeking to gauge "outcomes that aren't typically on a medical chart" — like diarrhea or absence from school, which may not require a visit to the hospital but can be disruptive for patients and families, Dr. Gerber said.

Between 2006 and 2008, there were [approximately 65.6 million doctor visits](#) for respiratory conditions, according to a [2011 *Pediatrics* study](#). During those 65.6 million visits, there were 31.7 million antibiotic prescriptions made.

While prescribing antibiotics can be challenging for general practitioners, the guidelines are relatively straightforward for antibiotic prescribing for the most common conditions that affect kids: ear infections, strep throat, sinus infections, and pneumonia, Dr. Gerber said.

The possible implications of the project are extensive, as antibiotic prescribing and ARTI are so widespread. “Given that these four conditions account for 80 percent of antibiotic prescribing, and given that outpatient antibiotic prescribing accounts for 80 percent of all antibiotic prescribing, even a small difference in efficacy can have huge implications,” Dr. Gerber said.

The second PCORI award received during fiscal 2013 supports the CHOP-led data network PEDSnet, which is comprised of children’s hospitals, data partners, and specialty networks. The PCORI contract, announced in December 2013, funds work to develop and expand PEDSnet as part of PCORnet: The National Patient-Centered Clinical Research Network.

PEDSnet combines a clinical data research network — including eight of the nation’s largest children’s hospital systems — with three condition-specific networks and two national data partners. CHOP’s Christopher Forrest, MD, PhD, serves as the principal investigator of PEDSnet.

PCORnet will be a secure, national data network that, according to PCORI, will improve the speed, efficiency, and use of patient-centered comparative effectiveness research. By integrating data available in the individual networks, PCORnet aims to provide access to a large amount of health information that can support a range of study designs.

Moreover, by enabling researchers and patients to interact directly and jointly determine research priorities, PCORnet aims to advance the shift in clinical research from investigator-driven to patient-centered studies.

“The Children’s Hospital of Philadelphia is thrilled to lend its efforts to PCORnet,” said Philip R. Johnson, MD, chief scientific officer and director of the Research Institute. “Multidisciplinary collaborations like this, that help researchers share findings and speed investigations, will help move innovative research from the bench to bedside and improve the care of children and families worldwide.”



Pennsylvania Bio Extends Two Honors to CHOP Research

Working in research reaps many rewards, including the understanding that the fruits of that work contribute to the collective scientific knowledge and inspire more research questions and discoveries. But perhaps the greatest reward for Children’s Hospital investigators comes in knowing that their research — whether in a clinic or laboratory — may improve the health of children across the globe.

The journey to that goal may be marked by honors and awards to CHOP investigators or for ground-breaking research programs. This year, [Pennsylvania Bio](#), a biosciences global leader representing the “entire life sciences industry” in the Commonwealth, bestowed two prestigious awards on Children’s Hospital in recognition of its business and research innovations.

First, Children’s Hospital received the “Deal of the Year” award for its successful spinoff of gene company [Spark Therapeutics](#). The award is intended for “a company that has promoted the growth of Pennsylvania’s bioscience industry by way of a substantial deal or strategic partnership,” according to PA Bio.

Based in part on the innovative work on adeno-associated virus vectors by [Katherine A. High, MD, HHMI](#), and CHOP Research Institute’s Center for Cellular and Molecular Therapeutics, Spark Therapeutics was launched in October 2013 with a \$50 million capital commitment from CHOP. A fully integrated gene therapy company, Spark is currently pursuing a Phase 3 program in blindness caused by mutations of the RPE65 gene, as well as a Phase 1/2 program in hemophilia B. The company is also involved in preclinical programs in neurodegenerative diseases and other hematologic disorders and forms of inherited blindness, according to its website.

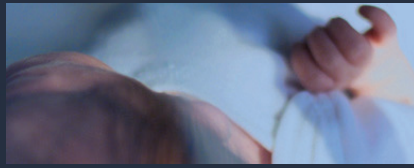
The “Patient Impact Award,” given for contributions to the quality of healthcare or length of patients’ lives, was the second honor to Children’s Hospital from PA Bio this year. CHOP shared the award with the [University of Pennsylvania](#) for their joint immune therapy research program.

Led at CHOP by [Stephan A. Grupp, MD, PhD](#), and at Penn by [Carl H. June, MD](#), the immune therapy research team has been investigating using modified versions of patients’ own immune cells to attack — and destroy — tumors.

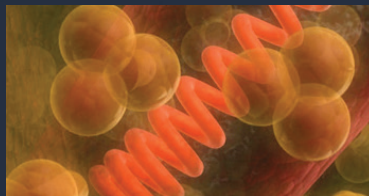
Last year the partnership led to dramatic, extraordinary results: Two children with acute lymphoblastic leukemia, the most common form of childhood leukemia, achieved a complete response after being treated with immune therapy. Since receiving the treatment, one of those patients remains healthy and cancer-free.

“The Children’s Hospital of Philadelphia is thrilled to be honored with these two awards,” said Philip R. Johnson, MD, chief scientific officer and director of the Research Institute and a new addition to the PA Bio Board of Directors. “They are a testament to the hard work of our investigators and staff, who work every day to improve the health of children.”

Nature Medicine



Discovery.



*Center for Injury
Research and
Prevention*



*"This was the first
randomized clinical trial
of surgery for obstructive
sleep apnea in children."*



*The Wall
Street Journal*

Discovery.

17. Severe Asthma Gene Variant Identified
18. Gut Instinct Establishes Premature Infant Immunity
19. New Methods Needed for Lung Injury Prevention
20. CHOP Expert Advances Next Generation Vaccines
21. Mitochondrial Signaling Response Revealed
22. Children With TBI May Benefit From Continued Care
23. Scientists Try New Approach to Sickle Cell Disease
24. Severe ROP a Predictor of Functional Disability
25. Surgery Improves Outcomes for Pediatric Sleep Apnea
26. Preserving Prepubescent Boys' Fertility

Innovation. >



Severe Asthma Gene Variant Identified

An international scientific team discovered a gene associated with a high risk of severe, recurring childhood asthma, a leading cause of hospitalization in young children. Identifying a risk susceptibility gene linked to this phenotype may lead to more effective, targeted treatments for this type of childhood asthma, said co-lead author of the study, Hakon Hakonarson, MD, PhD, director of the CHOP Center for Applied Genomics (CAG).

The study team, which included collaborators from five countries, performed a genome-wide association study on DNA from Danish national health registries and the Danish National Screening Biobank. In the discovery phase of their study, they compared genomes from 1,173 children aged 2 to 6 years from the Copenhagen Prospective Study on Asthma in Childhood with genomes from 2,522 adult and pediatric control subjects without asthma. The study team replicated their findings using data from other children of both European and non-European ancestry.

The researchers identified a novel gene, *CDHR3*, which is particularly active in epithelial cells lining the surfaces of airways.

“Abnormalities in the epithelial cells may increase a patient’s risk to environmental triggers by exaggerating immune responses and making the airway overreact,” said Dr. Hakonarson, a pediatric pulmonologist. “Because the *CDHR3* gene is related to a family of proteins involved in cell adhesion and cell-to-cell interaction, it is plausible that variations in this gene may disrupt normal functioning in these airway cells and make a child vulnerable to asthma.”

The findings from the study, published in *Nature Genetics*, were consistent with previous investigations by CAG, suggesting that other genes linked to childhood asthma play a role in oversensitive immune reactions. Further research is needed to better understand how the *CDHR3* gene may function in asthma.



Gut Instinct Establishes Premature Infant Immunity

At birth, infants move from a sterile environment to one full of microorganisms. Researchers at Children's Hospital used mouse models to show that changes in microbial colonization of the gastrointestinal tract play a vital role in this transition. Ultimately, this research may lead to potential treatments to restore critically ill newborns' resistance to common pathogens.

"Babies who are born preterm, in addition to them having less ability to fight infection, are more likely to get infected," said Hitesh Deshmukh, MD, PhD, of CHOP's Division of Neonatology.

Dr. Deshmukh and his colleagues found that regulation of postnatal granulocytosis — a burst in production of infection-fighting white blood cells that infants experience within 12 to 24 hours after birth — likely lies within the gut microbiome. Microbial colonization of the gut starts upon an infant's arrival into the world, initiating this immune response. The investigators showed that antibiotics hampered the natural buildup of granulocytes in mice models.

"While some antibiotics may affect the bone marrow directly, we believe these effects are due to the influence of antibiotics on bacteria in the gut," he said. "If you were to replace some of those microbes, you might restore the resistance of the newborn to the infection."

In a study published in *Nature Medicine*, his research team proved this by taking normal intestinal microbiota from mice that were not exposed to antibiotics and transferring them to mice that had received antibiotics. In adult humans, this procedure is called a fecal transplant.

"Fecal transplant could be one of the ways in which you could make sure that babies have more resistance or more power to fight infection," said the study's senior author [G. Scott Worthen, MD](#), a professor of pediatrics in the Division of Neonatology at the [Perelman School of Medicine](#) at the University of Pennsylvania. "One of the things you could do with this mixture is to use it to rapidly reconstitute an infant after they've finished a course of antibiotics."

Dr. Deshmukh's future research will focus on identifying bacterial components that could generate a new microbial community for preterm infants who needed antibiotics and subsequently preserve or restore their resistance to infection.



New Methods Needed for Lung Injury Prevention

Neonatologists commonly use noninvasive nasal ventilation instead of mechanical ventilation via a breathing tube, in hopes of avoiding bronchopulmonary dysplasia (BPD). A study led by CHOP investigator Haresh Kirpalani, BM, showed that current noninvasive techniques for respiratory support are less effective than assumed in reducing the incidence of severe lung injury in very premature infants.

Frequently a byproduct of intubation, BPD — scarring and inflammation of the lungs — is a leading cause of death or neurological injury in infants with extremely low birth weights.

Dr. Kirpalani and his team compared two common forms of noninvasive ventilation used in extremely-low-birth-weight premature infants. Both techniques make breathing easier for the infant by stopping the lungs from collapsing, which over time causes lung inflammation and injury.

The current standard of care, nasal continuous positive airway pressure (CPAP), delivers slightly pressurized air throughout the breathing cycle. In contrast, nasal intermittent positive-pressure ventilation (IPPV), which has become widespread, provides an additional spike of positive pressure when the infant inhales. While more complicated, the hope had been that IPPV was more effective than standard CPAP.

With this study, published in the *New England Journal of Medicine*, Dr. Kirpalani and his team found no significant difference in the primary outcome of either death or survival with BPD at 36 weeks. They also found no significant difference in rates of other neonatal complications.



CHOP Expert Advances Next Generation Vaccines

Most existing vaccines use inactivated viruses or similar particles to stimulate the body's immune system to release infection-fighting antibodies; however, rapidly evolving infectious agents such as HIV can evade traditional vaccine candidates. As a result, vaccine experts have been working to develop next generation vaccines that elicit broadly neutralizing antibodies to strike against hidden vulnerable structures within quick-changing viruses.

An advanced approach to vaccine design could be useful against highly variable viruses that have been difficult to stop using traditional strategies. [Philip R. Johnson, MD](#), chief scientific officer and director of the Research Institute, was among the co-authors of a study published in *Nature* that offers proof-of-principle that a new software application, “Fold from Loops,” can custom-design artificial proteins as vaccine components.

The new strategy uses sophisticated techniques to imitate an epitope — a structure specific to each type of invading virus that is recognized by the immune system. “Fold from Loops” designs flexible protein scaffolds to hold the epitope that induces the immune system to produce protective antibodies.

In the *Nature* study, the research team induced potent antibodies in non-human primates against [respiratory syncytial virus](#) (RSV), a serious childhood infection. The successful experiment demonstrates that this approach is feasible for developing a first RSV vaccine in humans, as well as for accelerating the creation of new vaccines against difficult-to-treat diseases such as HIV, influenza, and hepatitis C.

“Bringing these new types of vaccines into clinical use will take years of work, but this study represents an important first step along the way,” Dr. Johnson said.



Mitochondrial Signaling Response Revealed

Primary mitochondrial diseases directly interfere with the function of the respiratory chain (RC) — the highly conserved sequence of chemical reactions within mitochondria that generate energy from oxygen and nutrients. RC malfunction in mitochondrial disease may cause symptoms such as seizures, strokes, blindness, heart disease, progressive muscle weakness, and vulnerability to infections. No cure exists, and most current treatments for RC diseases are largely ineffective.

CHOP investigators identified a master network of signaling molecules that acts like a “fuse box” to regulate the cellular effects of defective energy flow in mitochondrial RC diseases — a diverse set of difficult-to-treat genetic-based energy disorders. Using that knowledge, they showed that a form of vitamin B3 called nicotinic acid partially restores normal functioning in cells taken from patients with mitochondrial disease.

Marni J. Falk, MD, led the study published in the journal *PLOS ONE* suggesting that the regulatory signaling network may offer a common avenue to target in developing effective, personalized treatments for many mitochondrial energy disorders.

The investigators analyzed cellular responses in human skeletal muscle and skin cell lines, finding that RC disease disrupted crucial biological pathways controlled by a handful of master signaling factors. All of those factors are integral components of cellular signaling networks that sense nutrient availability and regulate growth.

Building on her team’s previous studies, Dr. Falk and colleagues added nicotinic acid to a cell line grown from the skin of a patient with the mitochondrial disease known as Leigh syndrome that causes strokes in young children.

The results were exciting. The nicotinic acid normalized signaling activity across an integrated signaling network, and it also improved overall cellular respiration — the cells’ ability to use oxygen.



Children With TBI May Benefit From Continued Care

Parents and primary care physicians should consider that children with traumatic brain injury (TBI) may need ongoing support to address difficulties with memory, problem solving, and verbal communication when transitioning from inpatient rehabilitation to home and school, according to a study conducted by researchers at Children's Hospital.

The study published in the *Journal of Pediatrics* included data from nearly 14,000 children aged 7 to 18 years with trauma-related injuries who completed inpatient rehabilitation during the period from 2002 to 2011.

The investigators, led by Mark Zonfrillo, MD, MSCE, analyzed the children's cognitive deficits before and after admission to inpatient rehabilitation. Children with TBI had more cognitive disability when entering inpatient rehab than other children with serious injuries, which included spinal cord injury, multiple fractures, amputations, and burns. While all injury groups showed improvements upon discharge, children with TBI had more residual cognitive disability.

These children may continue to improve after discharge, so this transition is a critical point in their care, said Dr. Zonfrillo, who is an investigator at CHOP's Center for Injury Research and Prevention and associate director of research in the Division of Emergency Medicine.

"The goal of this line of research at CHOP is to maximize access to trauma systems and to optimize acute and rehabilitation care for young patients with serious injuries," Dr. Zonfrillo said. "If we have a complete picture of the scale of pediatric traumatic injuries and related long-term needs, as well as the differences between injury patterns and various outcomes, we can predict the type and level of support necessary upon discharge from inpatient rehabilitation."



Scientists Try New Approach to Sickle Cell Disease

Hematologists have long sought to reactivate fetal hemoglobin as a treatment for children and adults with sickle cell disease (SCD), a painful, sometimes life-threatening genetic disorder that deforms red blood cells and disrupts normal circulation.

Shortly after birth, regulatory elements in DNA shift the body from producing the fetal form of hemoglobin to producing the adult form instead. But when patients with SCD undergo this transition, their inherited gene mutation distorts adult hemoglobin, forcing red blood cells to assume a sickle shape.

CHOP hematology researcher Jeremy W. Rupon, MD, PhD, who worked in collaboration with a former postdoctoral fellow, Wulan Deng, PhD, in the laboratory of Gerd Blobel, MD, PhD, reprogrammed gene expression to reverse the biological switch. This caused cells to resume producing fetal hemoglobin, which is not affected by the SCD mutation, and produces normally shaped red blood cells.

“Our study shows the power of a technique called forced chromatin looping in reprogramming gene expression in blood-forming cells,” Dr. Rupon said. “If we can translate this approach to humans, we may enable new treatment options for patients.”

Dr. Blobel’s team demonstrated in previous work that chromatin looping, a tightly regulated interaction between widely separated DNA sequences, drives gene transcription — the conversion of DNA code into RNA messages to carry out biological processes.

In the current study, the investigators custom-designed a genetically engineered zinc finger protein that latched onto a specific DNA site carrying the code for fetal hemoglobin. They attached the zinc finger to another protein that forced a chromatin loop to form. The loop then activated gene expression that produced embryonic hemoglobin in blood-forming cells from adult mice. The team obtained similar results in human adult red blood cells, forcing the cells to produce fetal hemoglobin.



Severe ROP a Predictor of Functional Disability

Retinopathy of prematurity (ROP) is a disorder of the blood vessels of the retina, which are not completely developed until a baby reaches full term, and its incidence has been rising.

“It is therefore important to research the association between this neonatal complication and adverse long-term child development,” said Barbara Schmidt, MD, MSc, an attending neonatologist at Children’s Hospital and also a professor of pediatrics and Kristine Sandberg Knisely Chair in Neonatology, Perelman School of Medicine at the University of Pennsylvania.

Dr. Schmidt led a study that showed infants with severe ROP diagnosed and treated under modern protocols remain at risk of nonvisual disabilities, even if blindness can be averted in most children. This exploratory analysis reported in the Journal of the American Medical Association used data from a cohort of very low-birth-weight infants involved in the Caffeine for Apnea of Prematurity trial.

The study found that motor impairment, cognitive impairment, and severe hearing loss were three to four times more common in children with severe ROP than those without severe ROP. Yet, it remains unclear why there is an association between the development of severe ROP and the presence of nonvisual disabilities.

“We can only speculate,” Dr. Schmidt said. “The retina has been called a ‘window to the brain;’ hence, severe damage to the developing retina in a very immature baby may also indicate damage to the developing brain.”

These findings remind clinicians and parents that while blindness often can be prevented by timely retinal therapy in the neonatal intensive care unit, severe ROP remains a predictor of functional disability. It reinforces the need for long-term visual and developmental follow-up for infants who are diagnosed with severe ROP.



Surgery Improves Outcomes for Pediatric Sleep Apnea

Obstructive sleep apnea syndrome, or OSAS, is a condition of interrupted breathing caused by a narrowing in the throat or upper airway, resulting from enlarged tonsils and adenoids, obesity, or other medical problems. The primary treatment for OSAS in children is adenotonsillectomy, the surgical removal of the adenoids and tonsils. More than half a million U.S. children undergo the surgery each year.

Sleep experts conducted the first multicenter clinical trial of OSAS in children and found that those who underwent adenotonsillectomy had notable improvements in behavior, quality of life, and other symptoms compared to those treated with “watchful waiting” and supportive care. However, the researchers found no difference between treatment groups in attention and executive functioning, as measured by formal neuropsychological tests.

“This was the first randomized clinical trial of surgery for obstructive sleep apnea in children,” said first author Carole L. Marcus, MBBCh, who directs the Sleep Center at Children’s Hospital. “Some previous, smaller studies had found this condition associated with cognitive and behavioral problems, including ADHD, so it was important to do a controlled trial to evaluate the benefits of surgery, which is a common treatment.”

The findings are the result of the Childhood Adenotonsillectomy Trial (CHAT) that involved 464 children, aged 5 to 9 years, at seven academic sleep centers. The CHAT researchers published their findings in the New England Journal of Medicine, in conjunction with a presentation at the American Thoracic Society annual meeting.

Overall, both surgery and watchful waiting were safe in this clinical trial, the researchers noted. Watchful waiting was a reasonable option for parents of children with less severe OSAS who opt not to have surgery, Dr. Marcus said, but clinicians should carefully monitor these children to ensure their condition does not worsen.

“Sleep medicine is a very new field, with many unanswered questions,” Dr. Marcus said. “For instance, we go to sleep each night, yet we don’t even understand the true purpose of sleep. But this study is a great first step in finding some of the answers.”



Preserving Prepubescent Boys' Fertility

The good news is that doctors are able to cure nearly 80 percent of cancer patients, but that does not mean that those pediatric patients who survive cancer stop fighting once treatment ends.

Children's Hospital's [Cancer Survivorship Program](#) "helps patients and families navigate life after cancer, including both the physical and emotional issues they may have." The program, which is led by [Jill P. Ginsberg, MD](#), includes research into the neurobehavioral outcomes of acute lymphoblastic leukemia survivors and key adverse events following childhood cancer.

A research initiative led by Dr. Ginsberg and [Thomas F. Kolon, MD](#), involving prepubescent boys who have been diagnosed with cancer, was the subject of media attention, with articles appearing in [Nature Medicine](#) and [The Wall Street Journal](#).

An estimated 35 percent of prepubescent boys are at risk of sterility following cancer treatment, Dr. Ginsberg said, and because prepubescent boys cannot produce sperm, CHOP's testicular tissue cryopreservation program can offer families hope that their tissue could one day be used to produce viable sperm. Only boys at the highest risk for infertility are approached to take part in the program because the procedure remains experimental.

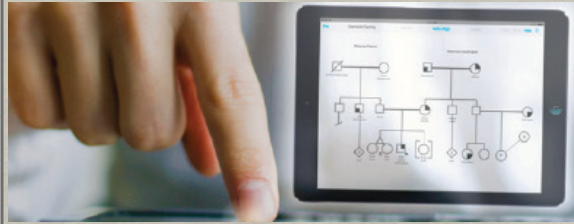
Based on pioneering work by the University of Pennsylvania's [Ralph L. Brinster, PhD](#), the procedure involves the removal of a small amount of testicular tissue containing spermatogonial stem cells. Scientists suggest that one day these cells could either be transplanted back into the boys to grow spermatogonial tissue following cancer treatment or be used to grow sperm in vitro. Though researchers have yet to produce sperm using human spermatogonial tissue, work by Dr. Brinster's lab has shown that the approach works in a mouse model.

A \$125,000 [St. Baldrick's Foundation](#) grant awarded in August 2013 will allow the Testicular Cryopreservation Consortium to expand beyond CHOP to include [Seattle Children's Hospital](#) and Memorial [Sloan-Kettering Cancer Center](#).

"We are hopeful that advances in the laboratory will make it possible for these boys to achieve fertility when they are ready to start a family," said Dr. Ginsberg after the award was announced. "This work could not have been accomplished without the support of St. Baldrick's Foundation."

In addition to its groundbreaking program for prepubescent boys, CHOP is one of few, if not the only, institutions in the country that invite all postpubescent boys set to undergo cancer treatment to participate in a sperm-banking program. About 85 percent of boys agree to bank.

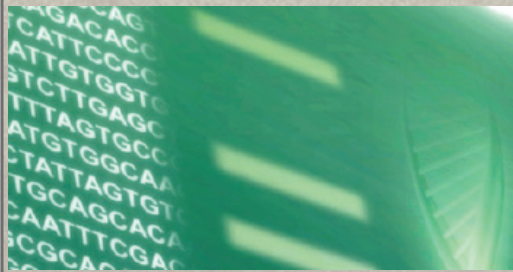
It is "one of the programs here at CHOP that I'm most proud of," Dr. Ginsberg said.



*Department of Biomedical
and Health Informatics*

Innovation.

*CHOP's Open
Canvas Project*



*"This is a new, disruptive
technology, with the potential to
transform research and clinical
practice, in transplantation
and other fields."*



*Center for
Applied Genomics*



Innovation.

- 29. Innovative App, Software Toolkit Help Harness Data
- 31. New Software Aims to Protect Patient Privacy
- 33. Novel Gene Test to Improve Transplantation, Research
- 34. Technology Focuses on Acne Evaluation, Management
- 36. Tech Transfer By the Numbers
- 37. List of Patents

Collaboration. >



Innovative App, Software Toolkit Help Harness Data

Bioinformatics experts, programmers, and application developers in CHOP's Department of Biomedical and Health Informatics (DBHi) build solutions for managing complex biomedical data for both research and clinical use. During fiscal 2013, DBHi's Application Development team released two innovative applications: an iPad app for drawing family genetic histories, and an open source software toolkit that lets software developers build highly interactive data discovery applications for use by researchers and clinicians.

Similar to family trees, human pedigree diagrams are a critical tool for visualizing relationships within families and recording the occurrence of diseases through multiple generations. Genetic counselors use pedigree analysis to study the inheritance of genes and apply this knowledge to patient-care decision-making. Traditionally, counselors have hand-drawn pedigrees, but they now have a new way to create those diagrams, with just a few finger taps.

The Proband app for iPad enables genetic counselors, geneticists, and researchers to construct even the most complex family pedigrees simply and flexibly. Using simple hand gesture, users diagram the family tree with standard pedigree nomenclature and symbols. In addition, edits can be made seamlessly as they gather new information, even after the interview is completed.

"We designed this app so options appear as you need them," said DBHi's Jeff Miller. "Our goal was to make the features contextually relevant, and assist the user as they conduct the interview."

Mindy Li, MD, a clinical genetics and metabolism fellow, tested the app and compared it to reviewing traditional hand-drawn pedigrees. One advantage of the app is that she did not have to decipher someone else's handwriting or idiosyncratic abbreviations. She also enjoyed the convenience of being able to set the iPad on her lap while conducting an interview.

The app can capture any level of detail, without the space limitations of paper. And instead of opening up a file cabinet, users can store the pedigrees in a standardized format and export the diagrams to other applications such as electronic medical records. Proband is available in the iTunes App Store.

"As health technology in general is moving toward electronic data, it's important to have pedigrees that are easy to read and easy to integrate," Dr. Li said.

DBHi's software toolkit, meanwhile, will help researchers confronted with large quantities of information in many forms — including vital signs, blood cell counts, lengthy DNA sequences, bar graphs, MRIs, patient demographics, and so much more. With this toolkit, DBHi specialists sought to answer the question of how researchers should assemble, access, and analyze data without having to become specialized database technicians themselves.

Their answer: an open source, highly interactive framework, known as Harvest, which is designed to allow users to navigate quickly among different types and levels of data. “We want to help researchers explore their data, not their database,” said Byron Ruth, lead developer of Harvest.

A key feature of Harvest is the ability to maneuver smoothly among various levels of data, from individual patient records to aggregated reports of all patients in a database, and to subpopulations in between. Users can construct queries to slice and dice data — grouping subjects, for instance, by age or ethnicity, calling up individual blood test results or MRIs, or including or excluding specific diagnoses.

Harvest, said DBHi's Manager of Translational Informatics Michael J. Italia, “isn't just shrink-wrapped, ready-to-go software.” He estimates that Harvest typically provides 80 percent of the work, leaving it to any institution's software developer to adapt the framework to a project's needs, in collaboration with each project's principal investigator. Harvest is open source, so users have free access, and in fact are encouraged to customize and contribute to the toolkit.



New Software Aims to Protect Patient Privacy

Healthcare organizations are adept at collecting data, from admissions information to vital signs. In a multispecialty care network like [The Children's Hospital of Philadelphia](#) where clinicians see 1 million patients annually in the ambulatory setting alone, the number of users who are accessing this data stored in patients' electronic medical records (EHRs) on any given day is massive.

Federal privacy regulations mandate that healthcare organizations have effective privacy programs in place to monitor EHR access logs to ensure that employees are not mistreating that information. If a hospital employee leaks information about a notable patient to the media, for instance, the hospital system could be subject to fines and legal action.

"The challenge is that hospital information privacy officers around the country don't have the auditing tools they need to look at the volume of data that they're getting from these EHR access logs," said CHOP's Chief Medical Information Officer [Bimal Desai, MD, MBI](#). "It's like trying to drink from a firehouse."

Dr. Desai is developing a software application based on sophisticated algorithms that will allow hospital information privacy and compliance staff to detect security breaches among internal users more intuitively. His concept was selected in the spring for CHOP's Open Canvas project, a one-year program designed to help CHOP employees transform their ideas into accelerated business models.

Currently, hospital information privacy officers use multiple approaches to police access to patients' medical records. On EHRs' front end, they help to construct permissions according to users' roles and profiles. They can build in additional authentication rules and alerts into the EHRs that require providers to attest that they are true participants in a patient's care each time that they request a particular part of patient's record.

On the back end, privacy officers scan the voluminous EHR access logs, but it is extremely difficult for them to derive any meaningful information. For example, a single patient who spent two weeks in CHOP's intensive care unit generated 96,000 rows of data.

"So the task metaphorically becomes looking for the needle in the haystack," Dr. Desai said.

He aptly named the software application that he created, "Haystack." It uses computational techniques to filter the EHR access logs and distinguish between normal clinical behavior patterns and potential privacy breaches categorized as high, medium, or low risk. Instead of a spreadsheet with thousands of rows of data, the software generates interactive graphs that enable privacy professionals to view the network of providers involved in the patient's care and then drill down to investigate any discrepancies.

“Ultimately, it will allow privacy professionals to focus on a very, very small subset of access events that look suspicious,” Dr. Desai said.

“Every patient deserves the highest level of rigor around privacy of their healthcare data, and organizations like CHOP and others have an obligation to help enforce that,” Dr. Desai said. “Every hospital wants to do the right thing; they just need the tools to do it.”



Novel Gene Test to Improve Transplantation, Research

The Children's Hospital of Philadelphia has long been a leader in the world of genomic medicine. CHOP Research investigators regularly publish groundbreaking studies that span the gamut of childhood disease, from those focused on autism to studies of the childhood cancer neuroblastoma, to investigations of common conditions like obesity and more rare diseases.

During fiscal 2013, Children's Hospital immunogenetics experts developed a unique laboratory test to characterize the genes that encode human leukocyte antigen (HLA) molecules, which are complex proteins on cell surfaces that are essential to immune function. By using faster, more comprehensive gene sequencing technology to type HLAs, the new test may improve transplantation outcomes through a more refined assessment of donor compatibility.

"This faster, more thorough technology allows us to better account for subtle genetic differences between individuals," said Dimitri Monos, PhD, director of the Immunogenetics Laboratory in the Division of Genomic Diagnostics. "We expect this knowledge to yield clinical benefits, by facilitating more precise matches between transplant donors and recipients, and assessing the significance of mismatches in genomic regions of the HLAs that were previously uncharacterized."

HLA genes are the most complex gene family in the entire human genome, and current tests often provide ambiguous and limited results. In addition, preliminary HLA testing must often be followed by a second level of testing, adding expense and time to the process. However, the new CHOP test — a single, comprehensive test — will provide the highest resolution possible by covering the full HLA genomic region, Dr. Monos said. CHOP is the first hospital to offer this new comprehensive HLA-typing test, based on extensive research by Dr. Monos and colleagues.

In addition to allowing for refined assessments of donor compatibility, the test also will expedite the donor selection process from bone marrow registries. And it provides an advanced tool for research in immunological diseases, infectious diseases, and pharmacogenomics — the field that studies the influence of genetic variations on drug efficacy and toxicity.

Indeed, "by focusing on fine details of immune responses, this technology can advance our understanding of how specific individuals respond to infectious diseases, to vaccinations, and to particular drugs. This test represents a potentially powerful tool in personalized medicine," Dr. Monos said.

"This is a new, disruptive technology, with the potential to transform research and clinical practice, in transplantation and other fields," said Robert Doms, MD, PhD, pathologist-in-chief at CHOP.



Technology Focuses on Acne Evaluation, Management

It is challenging for clinicians who are treating a patient with acne to accurately measure disease activity from visit to visit. Often, they must rely on personal memory and the patient's perspective to determine if the skin problem is improving, which can be an imprecise and time-intensive process.

In the U.S., it is estimated that 60 million people have acne, and one-fourth will seek out medical services; however, pediatric dermatology services are particularly difficult for patients to access with referral wait periods that can exceed more than three months.

Albert Yan, MD, Section Chief of the Division of Dermatology at The Children's Hospital of Philadelphia, and co-developers Elena Bernardis, PhD, and Jianbo Shi, PhD, are creating a software program using sophisticated computer vision algorithms that will expedite clinical visits for acne and allow physicians to spend more valuable time on patient education.

"We are excited about this project because of the great potential to streamline the efficiency of primary care management of this disease in a way that adheres to accepted evidence-based guidelines and reduces unnecessary referrals of less severe disease to specialists," Dr. Yan said.

First, patients will complete an electronic survey to update their clinical history and current symptoms. In the exam room, clinicians will take pictures of the patient's skin lesions using an inexpensive smartphone or smart device, and then send those images to the software system that Dr. Yan named COMEDO, a clever acronym for "computer optimized management and evaluation of disease outcomes." The term also carries the double meaning of blackhead or whitehead, so COMEDO represents the initiative's target disease as well.

COMEDO will analyze the images and generate an overall assessment of acne severity. Next, it will produce a treatment plan based on a set of standardized pediatric acne guidelines that Dr. Yan helped to author for the American Acne and Rosacea Society.

"Formulating an acne treatment plan can be challenging for primary care clinicians because we all have to navigate myriad medications out there," Dr. Yan said. "When you consider all of the topical and oral medications available, there are literally thousands of different combinations that you can come up with for any individual patient. This system will take into account patients' skin types, medication history, etc., and then it will create treatment recommendations that are customized to that particular patient."

At subsequent patient visits, COMEDO will update the acne assessment and treatment recommendations data. In doing so, it also will actively compile information based on the cumulative experience of all patients in the system.

“The idea is to make it a smart system that continues to get smarter as time goes on,” Dr. Yan said. “We’re going to build a big data repository of clinical response to disease, and as we accumulate that data, it will inform the system and make it smarter in terms of predicting what are going to be the best available treatments and what improvements clinicians should expect to see for their patients.”

In addition to helping pediatricians and primary care clinicians who grapple with assigning acne treatment plans on a daily basis, COMEDO’s database could spark interest from insurance company representatives who decide how to prioritize medications for their formularies or from pharmacies to help patients find appropriate over-the-counter products while patients are in the store. Eventually, patients could use COMEDO to provide symptom updates in between visits, allowing physicians to provide immediate feedback and encouragement to stay on track with the treatment plan.

Dr. Yan anticipates that a pilot prototype of COMEDO will be available in six to 12 months to be used in clinical trials within CHOP’s primary care practices that will compare the system’s accuracy with expert clinicians to establish good concordance. The development team also is working closely with the Food and Drug Administration to ensure that the device is compliant with the agency’s latest guidelines for medical apps.

The COMEDO project received start-up funds and helpful institutional resources through CHOP’s Chair’s Initiatives, which awards two-year internal grants to support the piloting of different care models to deliver accessible, high quality care at lower cost and coordinate complex, accountable care across disciplines.



93

**Invention Disclosures
Received**

23

**U.S. Patent Application Filed
(Utility and Nationalized PCT)**

27

**U.S. Patent Application
Filed (Provisional)**

9

**U.S. Patents Issued
to CHOP**

50

**International Patents
Issued**



U.S. Patent No. 8,497,285

Mark I. Greene, MD, PhD; Wayne W. Hancock, MBBS, PhD; Makoto Katsumata, PhD; and Yan Xiao, PhD

This invention is in the fields of immunology and autoimmunity. More particularly, it concerns methods of treating patients with compounds, which are useful agents for inhibiting the functions of TIP60 in the treatment of an individual suffering, for example, from ulcerative colitis and other irritable bowel diseases.

U.S. Patent No. 8,557,762

Rodney M. Camire, PhD, and Mettine H. A. Bos, PhD

Compositions and methods for the treatment of coagulation disorders using Factor V variants are provided. Preferred disorders include hemophilia A and B.

U.S. Patent No. 8,569,229

Michael M. Grunstein, MD, PhD

Compositions and methods for the treatment of asthma and inflammatory ocular disorders are disclosed.

U.S. Patent No. 8,580,545

Ivan S. Alferiev, PhD; Robert J. Levy, MD; and Ilia Fishbein, MD, PhD

A method and a composition for delivery of a biomaterial to an animal cell or a tissue. The composition includes (a) a biomaterial; (b) a biodegradable cross-linker portion having a hydrolyzable bond, wherein the biodegradable cross-linker portion is covalently bound to the biomaterial; and (c) a substrate, wherein the substrate is covalently bound to the biodegradable cross-linker portion, provided that the biodegradable cross-linker is adapted to hydrolyze by breaking the hydrolyzable bond and thereby release and deliver the biomaterial. A process of making the composition is also provided.

U.S. Patent No. 8,575,120

Hakon Hakonarson, MD, PhD; Struan F. A. Grant, PhD; Jonathan P. Bradfield, BS; and Constantin Polychronakos, MD

Compositions and methods for the detection and treatment of T1D are provided.

U.S. Patent No. 8,562,505

Robert J. Levy, MD; Boris Polyak, PhD; Michael Chorny, PhD; Ivan S. Alferiev, PhD; Gennady Friedman, PhD; Darryl Williams, PhD; and Ilia Fishbein, MD, PhD

Systems and methods for magnetic targeting of therapeutic particles are provided. Therapeutic particles comprise one or more magnetic or magnetizable materials and at least one therapeutic agent. Therapeutic particles are specifically targeted using uniform magnetic fields capable of magnetizing magnetizable materials, and can be targeted to particular locations in the body, or can be targeted for capture, containment, and removal. Also provided are bioresorbable nanoparticles prepared without the use of organic solvents, and methods for therapeutically using such bioresorbable nanoparticles.

U.S. Patent No. 8,618,242

Robert J. Levy, MD; Ivan S. Alferiev, PhD; and Stanley J. Stachelek, PhD

Heart valve disease affects millions, and at this time can only be treated by valve replacement or repair surgery. Cardiac valve prostheses have not significantly improved in decades, and one problem is a progressive decline in performance of heart valve replacements over 10 to 15 years after implant, necessitating additional surgery or resulting in morbidity and mortality. Additionally, valve prostheses prepared from polymeric materials, typically polyurethanes, have limited ability to bond to the living tissue to which they are attached. Therefore, methods of providing replacement valves having good longevity in vivo, including effective attachment to living tissues, would be of considerable medical value.

U.S. Patent No. 8,642,265

Carolyn A. Felix, MD; and Donald A Baldwin, PhD

Compositions, methods, and kits for detecting DNA topoisomerase II-DNA complexes are disclosed.

U.S. Patent No. 8,703,733

John H. Wolfe, VMD, PhD; and Carlos Gay-Antaki, BS

Compositions and methods for treating neurological diseases and disorders are disclosed.

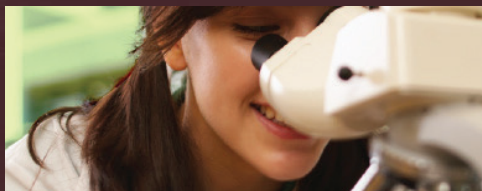
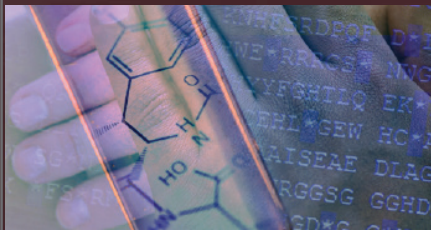
Dream Teams



Collaboration.



*National Institute of
Neurological
Disorders and Stroke*



“This partnership offers a mechanism to move our Hospital’s innovative research into the marketplace and better provide health benefits to children and families worldwide.”

Collaboration.

- 41. Center of Emphasis on Clinical Pharmacology Launches
- 43. Reaching Across Borders to Expand Pediatric Research
- 44. Consortium Boosts Pediatric Medical Device Pipeline
- 45. New Friedreich's Ataxia Center of Excellence Created
- 47. Partnership Speeds Research to the Marketplace
- 48. CHOP, High School Join Forces to Promote Science

Dedication. >



Established to speed research from the bench to the bedside, The Children's Hospital of Philadelphia Research Institute's Centers of Emphasis concentrate investigator efforts and resources. Bringing together many of the most pioneering researchers in the U.S., CHOP Research's Centers of Emphasis have become well known for their consistently excellent, forward-thinking investigations.

During fiscal 2013 the Institute's current Centers — which include the Center for Applied Genomics, the Center for Childhood Cancer Research, PolicyLab, and the Center for Injury Research and Prevention — were joined by a new Center of Emphasis, the Center for Clinical Pharmacology (CCP).

Led by Athena F. Zuppa, MD, MSCE, the CCP offers pharmacological training, bioanalytical and pharmacostatistical support, and study design services. By "restructuring and rebuilding" on previously existent resources, the new Center of Emphasis provides a single, consolidated resource for investigators across the Institute, according to Dr. Zuppa.

Dr. Zuppa joined CHOP in 1996 as an intern after receiving her medical degree from SUNY Stony Brook. She was named an assistant professor of Anesthesia and Pediatric Critical Care Medicine Pediatrics in 2002, and — in addition to her new role leading the CCP — is now an associate professor of Anesthesiology and Critical Care at the Hospital of the University of Pennsylvania and CHOP as well as associate director of Children's Hospital's PICU Fellowship Program. Dr. Zuppa has an active research program, and she is currently supported by a number of grants, including an R01 that is funding her investigation of the impact of hypothermia on the pharmacokinetics of midazolam (used for sedation) and the painkiller morphine (pain control) in children following cardiac arrest.

As Dr. Zuppa sees it, the CCP's overarching structure will be supported by three pillars: training in clinical pharmacology, bioanalytical services, and pharmacostatistical support.

"If there are investigators who want to do a pharmacology study, they can come to us, and we can help them with study design, implementation, quantitative analysis of the biologic specimens, wrap that up into a database, and then actually interpret the data," she said.

Dr. Zuppa also noted that along with Thomas Jefferson University, CHOP has applied for a T32 award to support a training program in clinical pharmacology. If approved, the joint CHOP-Thomas Jefferson training program would "be one, if not the first, pediatric and adult clinical pharmacology training programs bridging pediatrics and adults," she said.

In addition to Dr. Zuppa, other CHOP staff who will be contributing to the CCP include Director of the Bioanalytical Core Ganesh Moorthy, PhD; pharmacometrician Chee Ng, PharmD, PhD; pediatric intensivist Adam S. Himebauch, MD; pediatric oncologist and Chair of the Children's Oncology Group Peter C. Adamson, MD; director of clinical research in the Center for Childhood Cancer Research Frank M. Balis, MD; and pediatric oncologist and pharmacologist Elizabeth Fox, MD, head of the Developmental Therapeutics Program in the Division of Oncology. Dr. Zuppa noted that she is also actively looking to expand the new Center's faculty and staff.



Reaching Across Borders to Expand Pediatric Research

A trade mission to Israel led by Philadelphia Mayor Michael A. Nutter during fiscal 2013 led to a new research agreement between The Children's Hospital of Philadelphia, Drexel University, and The Hebrew University of Jerusalem. The partnership — which is focused on pediatric translational research and moving investigations from the bench to the bedside — stimulated a January conference hosted by CHOP that gave researchers from all three institutions the chance to connect and share ideas.

"I am proud to see two great Philadelphia institutions, CHOP and Drexel University, expand their research overseas," said Mayor Nutter when the agreement was signed in a ceremony at Jerusalem's City Hall, Nov. 11, 2013.

Prior to the signing of the research agreement, Drexel University and Hebrew University already had a partnership in place, the Joint Drexel-Hebrew University Institute for Drug Research Hub. The new collaboration with CHOP will "address unmet needs in pediatrics through innovative commercial pediatric therapeutics and diagnostics," said John A. Fry, president of Drexel University.

The collaborative research symposium, hosted by the Research Institute, brought together investigators from all three institutions for presentations and discussions aimed at fostering cooperation and teamwork. One of the goals of the symposium was to form collaborative "Dream Teams" of investigators who would unite to craft innovative solutions to challenges.

The symposium featured sessions on everything from the nervous system to orphan diseases to pediatric cancers and drug discovery. For example, during the session "Transformative Approaches to Diseases and Disorders of Childhood," Philip R. Johnson, MD, chief scientific officer and director of the Research Institute, said that defining the future of pediatric medicine "is a tall challenge." But Dr. Johnson nonetheless challenged researchers to consider novel ways to advance pediatric care.

Participants also were given the opportunity to meet privately for one-on-one discussions. These meetings allowed investigators to follow up on presentations and discussions, and served as the first step in the development of new collaborations.

"The symposium really exceeded our expectations," said CHOP Research's Deputy Scientific Director Tom Curran, PhD, FRS, who led the organization of the symposium. "It set the tone for us to work together, transcending traditional boundaries, and forming unique collaborations with the common theme of improving the health and welfare of children."



Consortium Boosts Pediatric Medical Device Pipeline

For medical devices, as with many medicines, the market for children is a small fraction of the adult market, and there are far fewer child-sized devices. But the need for pediatric medical devices exists, even if proper devices may not, and a collaborative, multi-institution consortium led by CHOP experts is looking to address this need.

“It’s not simply a matter of scaling down adult equipment for pediatric use,” said Children’s Hospital bioengineer Matthew Maltese, PhD. “Pediatricians have long known that children are not just small adults, and adults are not just big children.”

Dr. Maltese is the principal investigator of the Philadelphia Regional Pediatric Medical Device Consortium (PPDC), which brings engineers and biomedical researchers from CHOP, Drexel University, and the University of Pennsylvania to address the shortage of medical devices designed for children. During fiscal 2013 the PPDC received a \$1.5 million, five-year grant from the U.S. Food and Drug Administration (FDA).

This multi-institution consortium will provide clinical, business, and regulatory expertise, as well as seed funding, to help translate innovative ideas into commercial devices for use in young patients. As the center of the nation’s largest pediatric care network, CHOP offers a large, diverse pool of pediatric patients, allowing for carefully regulated clinical trials to test potential medical devices.

Co-principal investigator of the PPDC Robert Levy, MD, sees opportunities to help children, saying that the consortium “will help to address unmet needs for pediatric medical devices.” Dr. Levy’s medical device experience is reflected in his 35 issued U.S. patents that have led to extensive licensing activities, both to established medical device companies and to startups.

In addition, the PPDC will benefit from Dr. Maltese’s own experience adapting medical devices for children in his position in Critical Care Medicine at CHOP. The Hospital is currently collaborating with industry partners to develop pediatric versions of existing FDA-approved cardiopulmonary resuscitation (CPR) quality feedback tools developed for adults. These smartphone-sized devices measure motion and force on a patient’s chest during CPR to rapidly produce sound and visual prompts that improve the quality of CPR and save lives.

“For a variety of reasons, it is difficult to advance pediatric medical devices beyond the idea stage,” Dr. Maltese said. The PPDC provides “innovators with the support they need to transform concepts into practical and available medical devices that benefit children,” he added.



New Friedreich's Ataxia Center of Excellence Created

Clinicians and researchers at [The Children's Hospital of Philadelphia](#) and [Penn Medicine](#) have developed remarkable expertise in [Friedreich's Ataxia](#) (FA), a rare, progressive neurodegenerative condition that is heavily disabling because it affects a variety of body systems.

A [new Penn Medicine/CHOP Friedreich's Ataxia Center of Excellence](#) opened in March to advance this work under the direction of [David Lynch, MD, PhD](#), FA program director at CHOP, and [Robert B. Wilson, MD, PhD](#), professor of pathology and laboratory medicine at the Perelman School of Medicine. The establishment of the Center was catalyzed by a \$3.25 million gift from the Friedreich's Ataxia Research Alliance (FARA), in partnership with the Hamilton and Finneran families.

"We are the center for research on FA for the world," Dr. Lynch said.

FA is a genetic mitochondrial disease found in approximately one in 50,000 people worldwide. Symptoms usually begin in childhood, and most patients are confined to a wheelchair by their mid-to-late 20s. People diagnosed with FA experience general unsteadiness, motor speech problems, increased heart wall thickness, and a higher tendency to develop diabetes over time. Myocardial failure and/or arrhythmias are the most common cause of premature death. Currently there are no approved drugs to treat FA.

For the past 16 years CHOP, Penn Medicine, and FARA, a nonprofit organization dedicated to curing FA, have collaborated to provide and enhance the care needed by FA patients. The three longtime allies also have shared in research and clinical trials that have elucidated the metabolic dysfunction underlying FA.

One of the Center's first goals was to establish a biomarker development program with the expertise of [Ian Blair, PhD](#), of the Perelman School of Medicine. This collaboration is the focus of a [National Institute of Neurological Disorders and Stroke](#) grant awarded to Dr. Lynch.

"A unique aspect of this grant is our chance to partner on a technique that not only may be useful for understanding the mitochondrial abnormalities that are proposed in FA, but also for monitoring it and related diseases in clinical trials," Dr. Lynch said.

If successful, this new approach could allow investigators to know within days if a chosen therapy reverses the intracellular mechanisms that go awry in FA and other more common secondary mitochondrial disorders such as Parkinson's disease and Alzheimer's.

Another objective for the center was to add cardiac expertise in FA research and clinical care under the leadership of Kimberly Y. Lin, MD, a cardiologist at CHOP with board certification in pediatrics, internal medicine, and pediatric cardiology.

“Integrating cardiac expertise into the care of patients is one major step forward this gift allows us to pursue,” said Philip R. Johnson, MD, chief scientific officer and director of the Research Institute. “Rare diseases are often an area where philanthropy can make a difference, and the generosity of these donors will make a significant impact.”



Partnership Speeds Research to the Marketplace

Investigators at Children's Hospital work tirelessly to uncover the inner workings of biological systems and the causes of diseases. But making discoveries is only part of the challenge; the next set of challenges often lies in taking the new knowledge from discoveries and working with outside partners to bring promising new therapeutics and treatments to patients.

A new partnership launched in 2013 between Children's Hospital and the venture capital fund Osage University Partners (OUP) will expand the opportunities to commercialize the research done at Children's Hospital, moving the potential for new treatments even closer to patients' bedsides.

OUP invests exclusively in startup companies that commercialize academic research. It shares part of the resulting profits with those institutions to further promote entrepreneurial opportunities within those centers.

OUP is part of Osage Partners, a family of venture capital funds based in Bala Cynwyd, Pa. OUP has research partnerships with more than 60 universities and research centers, including the University of Pennsylvania, Johns Hopkins University, Carnegie-Mellon University, Drexel University, and Duke University.

The company invests in life sciences, biopharma, and medical devices and diagnostics, in addition to other industries such as those involved in information technology, energy, and materials technology. It typically co-invests in conjunction with other venture companies.

"This partnership offers a mechanism to move our Hospital's innovative research into the marketplace and better provide health benefits to children and families worldwide," said Philip R. Johnson, MD, chief scientific officer and director of the Research Institute.



CHOP, High School Join Forces to Promote Science

The Children's Hospital of Philadelphia engages with the community around it in myriad ways, from collaborating with social organizations to organizing fundraisers to working to prevent and reduce violence.

During fiscal 2013 CHOP Research and the Science Leadership Academy (SLA), a Philadelphia public high school focused on the sciences, formed a novel partnership under which SLA students worked in CHOP labs. By being mentored by CHOP investigators, SLA students contributed to a variety of studies while also getting a feel for the daily work and benefits of a career in science.

SLA is a partnership high school with The Franklin Institute that "provides a rigorous, college-preparatory curriculum with a focus on science, technology, mathematics and entrepreneurship." SLA students have been accepted at prestigious colleges around the country, including the University of Pennsylvania, Princeton University, and Oberlin College, according to the school's website.

The students worked at CHOP Research through SLA's Individualized Learning Plan program, which prepares students for adulthood by giving them the chance to work in various organizations around Philadelphia. Students are placed in an array of Philadelphia institutions, from the Academy of Natural Sciences to the Philadelphia Zoo.

CHOP's SLA partnership is administered by Raymond Colliton, MS, director of CHOP Research's Office of Research Safety; Wendy Williams, PhD; and Jodi Leckrone, MEd, director and assistant director, respectively, of the Office of Responsible Research Training.

Six SLA students were paired with five Children's Hospital investigators from a number of disciplines. Pathologist Yair Argon, PhD; geneticist Ian Krantz, MD; cartilage and bone researcher Motomi Enomoto-Iwamoto, DDS, PhD; gastroenterologist Randy Matthews, MD, PhD; and anesthesiologist Francis McGowan, MD; all hosted SLA students. The students, who began working in October 2013, helped in the researchers' labs for two to five hours one day a week, Leckrone said.

"By exposing these students to research at CHOP, we hope to not only provide them with practical, applicable laboratory skills but also foster an interest in science, research, and medicine," Dr. Williams said.



*Center for Cellular and
Molecular Therapeutics*

Dedication.



*“The research is moving into
the community and making
an impact on care.”*



*Children's
Oncology Group*



Dedication.

- 51. CHOP Leader Examines Host-Pathogen Interactions
- 53. Prominent Gene Therapy Expert Joins CHOP
- 54. New Leadership Fortifies Center's Success
- 56. Neonatologist Elected to Institute of Medicine
- 57. Novel Immunotherapy Work Leads to Honors
- 59. Awards Celebrate Oncologists' Distinguished Careers

Leadership. >

A close-up portrait of a middle-aged man with grey hair, smiling. He is wearing a dark suit jacket over a light blue shirt. The background is blurred, showing green foliage and a white vertical structure.

CHOP Leader Examines Host-Pathogen Interactions

Fiscal 2013 saw a change in leadership at The Children’s Hospital of Philadelphia: Noted microbiologist and Children’s Hospital alumnus Joseph W. St. Geme, III, MD, was named physician-in-chief and chair of the [Department of Pediatrics at the University of Pennsylvania](#). Dr. St. Geme succeeds [Alan R. Cohen, MD](#), who held the post of physician-in-chief for 12 years.

After receiving his medical degree from Harvard, Dr. St. Geme served his residency and chief residency at Children’s Hospital from 1984-88. He later performed postdoctoral research under [Stanley Falkow, PhD](#), at Stanford, and in 1992 joined the faculty of the [School of Medicine at Washington University in St. Louis](#). A progression of appointments followed, and in 2005 Dr. St. Geme moved to Duke University, where he served as chairman of the Department of Pediatrics and Chief Medical Officer of [Duke Children’s Hospital](#).

Dr. St. Geme said his great respect and fondness for CHOP led him to return to Philadelphia. He called the opportunity to serve at the site of his medical training “very appealing and ultimately irresistible.” Since joining CHOP, Dr. Geme has continued his active research program examining host-pathogen interactions.

In particular, he has spent much of his career working to better understand why commensal microbes (which normally live in perfect harmony with our own cells) cause disease. The human body is a crowded place; while there are many types of human cells — numbering approximately 37.2 trillion, according to an [Annals of Human Biology](#) study — there are many more microbial cells that live in our bodies. Indeed, the NIH’s [Human Microbiome Project](#) notes “microbial cells are estimated to outnumber human cells 10 to one.” But sometimes these microbes can cause disease, such as when they leave their normal environment and enter the circulatory system.

For many years, Dr. St. Geme’s investigations were focused on the bacterium [Haemophilus influenzae](#). Despite its somewhat misleading name, *H. influenzae* does not cause influenza, but is instead associated with invasive infections and localized respiratory tract disease. And more recently, Dr. St. Geme has been investigating [Kingella kingae](#), an emerging cause of bone and joint infections in young children.

“In many ways the thrusts of the two projects, the two general themes, are similar,” Dr. St. Geme said. Both are investigations of “host-pathogen interactions, and understanding how organisms that are common, commensal organisms, common colonizers usually not associated with disease do, in some circumstances, produce disease.”

CHOP researchers Katherine Rempe, Brad Kern, and Eric Porsch (who all moved to CHOP from Duke with Dr. St. Geme), as well as Duke's Sue Grass, Jessica McCann, and Kim Starr have contributed to the *H. influenzae* and *K. kingae* work. At the 2014 Scientific Symposium in May, Dr. St. Geme gave an in-depth talk on his research as the Symposium's internal keynote speaker.

Saying he was "very pleased" that Dr. St. Geme had agreed to join CHOP, Children's Hospital's CEO Steven M. Altschuler, MD, noted he is "a distinguished researcher and member of the Institute of Medicine and is recognized nationally for his outstanding leadership at Duke."

"In many respects CHOP sets the standard in pediatrics as a leading children's hospital nationally and internationally, and I'm excited to participate in establishing the standards in pediatric clinical care, education, and research as a member of the CHOP community," Dr. St. Geme said.



Many investigators at The Children's Hospital of Philadelphia Research Institute are leaders in their fields, regularly making groundbreaking contributions to medical science. Children's Hospital's gene therapy researchers are no exception, as their work has led to advances in treating diseases such as hemophilia and congenital blindness.

During fiscal 2013, the Research Institute added another gene therapy specialist to its fold, welcoming Beverly L. Davidson, PhD, a nationally prominent expert in gene therapy. In addition to serving as the new director of the Center for Cellular and Molecular Therapeutics (CCMT), Dr. Davidson also joins the Hospital's Department of Pathology and Laboratory Medicine.

By assuming the role of director of the CCMT, Dr. Davidson succeeds the Center's inaugural director, [Katherine A. High, MD, HHMI](#). The CCMT is "dedicated to the understanding, development, and application of gene and related cell and nucleic acid therapies, and the promotion of professional public education," according to its website.

"I am thrilled that we have been able to recruit one of the premier translational investigators in the U.S. to serve as the next director of the Center," Dr. High said. "I have led the Center for the last 10 years, and I eagerly look forward to the innovations of the next decade under Dr. Davidson's leadership."

In addition to her new roles at CHOP, Dr. Davidson is currently a member of the [Scientific Advisory Board of the Hereditary Disease Foundation](#), and is chair of [Medical Sciences Section of the American Association for the Advancement of Science](#). She is also a scientific co-founder and advisor at the gene therapy company [Spark Therapeutics](#), which launched in late 2013 with a \$50 million capital commitment from CHOP.

Dr. Davidson's research has been concentrated on inherited genetic diseases that attack the central nervous system, with a particular focus on [childhood-onset neurodegenerative diseases](#).

And although much of Dr. Davidson's work has centered on delivering beneficial genes to the central nervous system, the novel methods she has developed are applicable to other organs and tissues — for example, in gene therapy directed to the lungs or the liver.

Dr. Davidson "will greatly enhance our abilities to translate important biological discoveries into pioneering treatments for deadly diseases," said [Robert W. Doms, MD, PhD](#), CHOP's pathologist-in-chief.

A portrait of Theoklis Zaoutis, MD, MSCE, a man with glasses and a beard, smiling. The text "New Leadership Fortifies Center's Success" is overlaid on the left side of the image.

New Leadership Fortifies Center's Success

The Center for Pediatric Clinical Effectiveness (CPCE) at Children's Hospital diligently works to discover and spread knowledge about the best practices to treat pediatric diseases. It is a tremendous and important effort to advance the health and well-being of children, and the CPCE's efforts are fortified by new leadership at the helm.

As the new CPCE director, Theoklis Zaoutis, MD, MSCE, does what he enjoys most — creating, developing, and building new ideas. Dr. Zaoutis co-founded the CPCE, a Center of Emphasis within the Research Institute. The Center provides critical infrastructure for training in and the performance of clinical effectiveness research, which is aimed at understanding the best ways to prevent, diagnose, and treat diseases in children.

One of his first priorities as director centers on “outreach to increase awareness of the CPCE by developing collaborations and synergies with other researchers,” Dr. Zaoutis said.

He sees tremendous opportunity for population level research to cross over to projects being conducted by bench scientists and translational researchers. “The link between these two can be phenomenally strong,” he said.

As Dr. Zaoutis describes it, the CPCE is an “intellectual home” for clinical researchers. In the same way that scientists learn essential skills at the bench, the CPCE uses a laboratory model to teach junior faculty and other interested clinicians the elements of good clinical research design, implementation, and practices.

“The CPCE has grown tremendously in the six years that it's been in existence,” said Dr. Zaoutis, who previously served as its associate director of research, and during those half-dozen years the CPCE's total grant funding has exceeded \$71 million. In addition to providing a database of funded grants for investigators to use as examples of effective grant submissions, the CPCE established the Healthcare Analytics Unit, which has expertise in using large datasets to answer research questions.

Dr. Zaoutis is enthusiastic about taking the Center's success to the next level. He envisions more partnership with the Hospital to create pathways and guidelines that are real-world applications of the CPCE's research.

A recent example is a study led by CPCE faculty member Jeffrey S. Gerber, MD, PhD, assistant professor of pediatrics in the Division of Infectious Diseases at CHOP, published in the *Journal of the American Medical Association* that described an intervention to improve antibiotic prescribing at outpatient practices.

“The research is moving into the community and making an impact on care,” Dr. Zaoutis said, who added that he feels well-prepared to expand his responsibilities after working closely with the CPCE’s former director, Ron Keren, MD, MPH, who in fiscal 2013 was appointed CHOP’s vice president of quality and chief quality officer. In his new role, Dr. Keren will be a bridge for the CPCE to disseminate and implement research findings about best practices and safety, Dr. Zaoutis said.

“We have the unique advantage that Dr. Keren’s been on the research side creating this knowledge, and now we have a natural partnership to fulfill the CPCE’s whole mission,” Dr. Zaoutis said.

Dr. Zaoutis is also the Thomas Frederick McNair Scott Professor of Pediatrics and Epidemiology at the Perelman School of Medicine at the University of Pennsylvania and associate chief in the Division of Infectious Diseases at CHOP.

A close-up portrait of Dr. Phyllis A. Dennery, a woman with short, curly brown hair, smiling warmly at the camera. She is wearing a light-colored blazer and a small earring. The background is a neutral, light gray.

Neonatologist Elected to Institute of Medicine

An internationally prominent neonatologist and researcher, [Phyllis A. Dennery, MD, FAAP](#), has received numerous awards and honors throughout her illustrious career. In fiscal 2013, she added another accolade to her roster when she was elected to the prestigious [Institute of Medicine](#) (IOM).

Dr. Dennery, chief of the Division of Neonatology and Newborn Services at Children's Hospital and holder of the Werner and Gertrude Henle Endowed Chair in Pediatrics, was one of 70 new members elected to the IOM in recognition of their major contributions to the advancement of the medical sciences, healthcare, and public health.

The focus of her work centers on oxidative stress-mediated neonatal lung gene regulation and on the biology of lung injury and repair. She runs a [National Institutes of Health](#)-funded laboratory and has published her findings in highly respected peer-reviewed journals such as the *Journal of Biological Chemistry*, *New England Journal of Medicine*, and *Blood*, among others. Her clinical interests are in neonatal jaundice, bronchopulmonary dysplasia, and the long-term consequences of prematurity.

Throughout her career, Dr. Dennery has received the [Andrew Mellon Fellowship](#), the Alfred Stengel Health System Champion Award from the [Perelman School of Medicine](#) at the University of Pennsylvania, and the Mentor of the Year Award from the Eastern Society of Pediatrics, among other awards and honors.

In 2010, she was appointed to the [U.S. Secretary of Health and Human Services Advisory Committee on Infant Mortality](#), and she also has served on the Community Action Team of the [Medical Examiner's Office in Philadelphia](#) focused on infant mortality.

After receiving her medical degree from Howard University College of Medicine, Dr. Dennery completed her residency at Children's National Medical Center and a fellowship in neonatology at Rainbow Babies and Children's Hospital. She was on the faculty at Stanford University where she served as director of Neonatology Research and associate division chief, before coming to Children's Hospital in 2003 to assume the role of division chief of Neonatology.

The [National Academy of Sciences](#) established the IOM in 1970 to honor professional achievement in the health sciences and serves as a national resource for independent analysis and recommendations on issues related to medicine, biomedical sciences, and health. Current members of the Institute elect new members from a slate of candidates nominated for their professional achievement.

A portrait of Dr. Stephan A. Grupp, a man with glasses and a mustache, wearing a white lab coat. The background is a blurred laboratory setting.

Novel Immunotherapy Work Leads to Honors

The Children's Hospital of Philadelphia's [Stephan A. Grupp, MD, PhD](#), the director of Translational Research at the [Center for Childhood Cancer Research](#), received a number of awards and honors for his groundbreaking immune therapy work during fiscal 2013. Dr. Grupp's research was featured at the American Society of Hematology annual meeting, was honored by WebMD, and received awards from several professional societies.

Dr. Grupp has received a great deal of attention for his investigation of using cell therapy (known as CART19 or CTL019 therapy) to treat an aggressive form of childhood leukemia, acute lymphoblastic leukemia (ALL). The most common form of leukemia found in children, ALL is largely curable, with a roughly 85 percent cure rate. However, the remaining 15 percent of ALL cases resist standard therapy.

Last year his work — conducted in partnership with the University of Pennsylvania's [Carl June, MD](#) — led to [dramatic, extraordinary results](#) published in the [New England Journal of Medicine](#): Two children with chemotherapy-resistant ALL achieved a complete response after being treated with immune therapy, and since receiving the treatment, one of those patients remains healthy and cancer-free two years later.

At the [American Society of Hematology \(ASH\) Annual Meeting](#), Dr. Grupp co-chaired a special session on immunotherapy and gave a talk on his ALL investigation. And Dr. Grupp and colleagues presented exciting follow-up results of their T cell clinical trial: Of the 24 pediatric and adult patients who have been treated for ALL, 18 had ongoing complete responses at a median of 2.6 months after treatment.

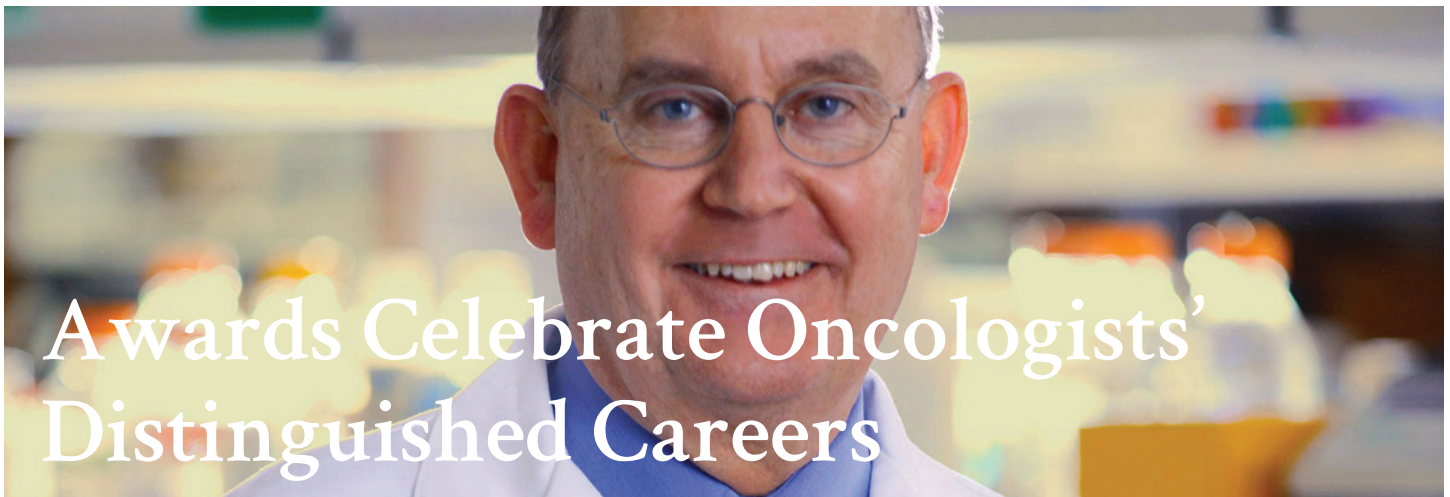
"Our results serve as another important milestone in demonstrating the potential of this cell therapy for patients who have no other therapeutic options," said Dr. Grupp at ASH.

More recently, The Children's Hospital of Philadelphia and the University of Pennsylvania received the Patient Impact Award from [Pennsylvania Bio](#) for their joint immune therapy research. Dr. Grupp also received the 2014 Herbert Pardes Clinical Research Excellence Award from the [Clinical Research Forum](#), and a team of researchers led by Dr. Grupp received the 2014 van Bekkum Award from the [European Society for Blood and Marrow Transplantation \(EBMT\)](#).

The data presented at the Clinical Research Forum and EBMT updated the data published in the *New England Journal of Medicine*. "Our group has now treated 25 kids and five adults with relapsed/refractory ALL," Dr. Grupp said. "We have seen unexpectedly high rates of complete remission: 90 percent in this group of patients, many of whom had no other treatment options. These results are leading to a phase 2 trial at six pediatric hospitals, with CHOP as the lead site."

And last — but certainly not least — Dr. Grupp, along with his young patient Emily Whitehead, were named [2013 WebMD Health Heroes](#). When Emily came to Dr. Grupp, her ALL had relapsed for the second time and was resistant to chemotherapy. In April of 2012 she became the first pediatric patient to receive the engineered T cells. And though the treatment led to a life-threatening illness, Emily eventually recovered after Dr. Grupp and his team were able to treat her symptoms. Since receiving the T cells, Emily remains healthy and cancer-free.

“It’s an honor to have our cell therapy research recognized by such prestigious organizations,” Dr. Grupp said. “This is potentially revolutionary work, but its success to date — and going forward — would not have been possible without multidisciplinary, truly collaborative input from investigators across CHOP and Penn. I cannot thank my colleagues enough.”



The Children's Hospital of Philadelphia Research Institute has long had a reputation for being home to world-class investigators, from those focused on genetics to behavioral specialists and childhood cancer experts. That reputation was strengthened during fiscal 2013 by the news that two CHOP oncologists received awards celebrating their careers.

Neuroblastoma expert Garret M. Brodeur, MD, received an award from the Advances in Neuroblastoma Research Association (ANRA), while Beverly J. Lange, MD, was honored by the American Society of Pediatric Hematology/Oncology (ASPHO).

Dr. Brodeur's award singles out a researcher who has achieved worldwide scientific prominence in investigating neuroblastoma over the course of an exceptional career. The ANRA Lifetime Achievement Award, given at ANRA's international meeting, is the association's highest honor.

Over his career, Dr. Brodeur has focused on identifying the genes, proteins, and biological pathways that give rise to neuroblastoma and drive its clinical behavior. He has also built on this knowledge to help develop more effective and less toxic treatments for children.

Dr. Brodeur helped discover important neuroblastoma-related genetic changes, collaborating with other CHOP researchers who identified the ALK gene as the gene responsible for most cases of hereditary neuroblastoma. Another major focus of his research regards the role of TRK receptor tyrosine kinases, which control the clinical behavior of neuroblastomas. His work led to a clinical trial with a novel drug that selectively blocks these signals.

Dr. Brodeur has been a member of the CHOP medical staff since 1993 and holds the Audrey E. Evans Endowed Chair in Pediatric Oncology at the Hospital. He is also a professor of Pediatrics in the Perelman School of Medicine at the University of Pennsylvania where he is an associate director of the Abramson Cancer Center.

Meanwhile, Dr. Lange's ASPHO award is given to a professional whose career "has had a major impact on the subspecialty through some combination of research, education, patient care, and advocacy." She received the award in recognition of her more than 40 years of outstanding contributions to the care of children with cancer.

Over the course of her career, Dr. Lange worked on numerous aspects of pediatric oncology, including spending many years focusing on acute myelogenous leukemia (AML). While AML is the second most common form of leukemia in adults, leading to roughly 15,000 new cases and 10,000 deaths every year in the U.S., the disease is rare in children, with only 500 to 600 children diagnosed per year. Since Dr. Lange began working on the disease, AML survival rates have greatly increased, with the five-year survival rate now around 85 percent.

Dr. Lange served as a senior physician and director of clinical affairs in the Division of Oncology at CHOP, where she worked from 1976 until her retirement in 2013. Over the course of her career, Dr. Lange published extensively in top-tier scientific journals, contributed expertise to professional organizations such as ASPHO and the multicenter Children's Oncology Group, and mentored countless numbers of young investigators.



Office of Clinical and Translational Research



Leadership.



*“We have bedside learning from
clinical practice intermixing with
and informing health services
and epidemiological research.”*

Pediatrics



International Society for Traumatic Stress Studies



Leadership.

63. Dennis Durbin Joins Institute's Executive Leadership

64. New Hospital-wide Initiative: Violence Prevention

66. Engaging Patients to Help Inform National Policy

68. Campaign Raises Awareness of Palliative Care

70. Gaining Ground on Sports-related Concussions

72. Nancy Kassam-Adams Furthers Trauma Research

Commitment. >

A portrait of Dennis Durbin, a middle-aged man with short brown hair, smiling. He is wearing a brown blazer over a light blue shirt. The background is a solid light blue.

Dennis Durbin Joins Institute's Executive Leadership

Fulfilling the mission and vision of The Children's Hospital of Philadelphia Research Institute requires thoughtful and innovative leadership, with particular expertise in navigating the ever-changing waters of biomedical research.

The Research Institute's leadership was bolstered in June 2014 as seasoned investigator Dennis Durbin, MD, MSCE, became the new director of the Institute's Office of Clinical and Translational Research (OCTR). Before assuming his new role, he served as the co-scientific director of the Center for Injury Research Prevention.

The OCTR "assists clinical and translational investigators in identifying scientific opportunities and in forging productive collaborations" across both CHOP and the University of Pennsylvania. Dr. Durbin took over the office's leadership reigns from Mary Leonard, MD, MSCE, who, after nearly a quarter-century at Children's Hospital and the University of Pennsylvania, left CHOP to pursue other exciting research endeavors at Stanford University.

A professor of Pediatrics at CHOP and Penn, Dr. Durbin is a member of the Division of Emergency Medicine and an associate scholar at the Center for Clinical Epidemiology and Biostatistics. An internationally renowned leader in pediatric injury prevention research, Dr. Durbin has particularly focused on the prevention of motor vehicle occupant injuries to children and the prevention of teen driver crashes.

He served as the co-principal investigator of Partners for Child Passenger Safety, a partnership between CHOP and State Farm Insurance Companies that resulted in the world's largest child-focused motor vehicle crash surveillance system.

Dr. Durbin has also served on various local and national committees including the Committee for Injury, Violence and Poison Prevention of the American Academy of Pediatrics.



More than 40 percent of children in the U.S. are exposed to some form of violence, which has become a public health epidemic with significant health and psychosocial consequences. Some of those possible consequences include poor physical, emotional, and developmental health; long-term physiologic and brain changes; school failure, drug abuse, and delinquency; and the possibility of more violence.

In an effort to reduce the severity and impact of violence and aggression on children and families not only in Philadelphia communities but also across the country, The Children's Hospital of Philadelphia launched the [Violence Prevention Initiative](#) (VPI).

"As an institution that exists to promote the health and well-being of children and as the nation's leading pediatric hospital, it is our responsibility to find ways to prevent this epidemic from spreading," said Steven M. Altschuler, MD, the Hospital's chief executive officer.

VPI is led by psychologist [Stephen Leff, PhD](#), and emergency physician [Joel Fein, MD, MPH](#), and includes a multidisciplinary team made up of some of the nation's foremost [experts](#) in hospital-based violence intervention, evidence-based anti-bullying methods, and trauma-informed care. Through the strength of its longtime partnerships with community organizations, CHOP's VPI builds on years of rigorous public health research to address and prevent ongoing concerns such as bullying in schools, intimate partner violence (IPV) in the home, and assaults in the community.

The VPI [programs](#) concentrate CHOP's medical training, mental health programs, provider training, research expertise, and knowledge of public health policies to interrupt violence while ensuring that limited resources are spent efficiently with the greatest chance for impact. Interventions occur at locations that are relevant to CHOP patients — within schools, primary care, and hospital sites.

The majority of children reached by VPI may never be CHOP patients, but witness violence in their schools or communities. VPI works within schools to provide evidence-based, whole-school approaches to bullying prevention for children in third through eighth grade. These programs address the multiple forms that aggression and bullying can take, including physical, social (such as gossiping and threatening to withdraw friendships), and cyber-bullying. This training gives them tools to handle and avoid more dire forms of violence as they grow older.

In addition, IPV counselors support clinical staff in screening for and addressing IPV and teen dating violence in CHOP's patient population. This is a partnership with [Lutheran Settlement House](#), with the goal of minimizing the adverse effects of childhood IPV exposure. Healthcare provider training and parenting education is provided as well.

And children aged 8 through 18 years who arrive in CHOP's Emergency Department with injuries from an assault receive long-term intensive support from a violence prevention counselor in the hospital and after discharge to reduce re-injury or retaliation and to promote physical and emotional healing.

"VPI programs reach beyond the hospital and doctors office into schools, homes, neighborhoods, and recreation centers by empowering and training kids and adults to interrupt the cycle of violence," said Dr. Fein, who added that the initiative "aims to become a national model for hospital-led youth violence prevention."



Engaging Patients to Help Inform National Policy

Now that electronic health records (EHRs) are more prevalent in clinical settings, doctors and other healthcare workers increasingly use the technology during patient visits. EHRs are valuable not only for improving healthcare, but also for enhancing patient safety and confidentiality, coordinating care, and engaging patients and their families.

But the use of EHRs is not limited to healthcare workers who manage and coordinate patient care. More and more, families are being encouraged to spend some screen time on their own entering health-related preferences and goals. Providing information on these goals helps providers tailor treatments and respond to patients' most pressing concerns.

The ability of patients to submit health information and actively participate in their healthcare is a main focus of Meaningful Use Stage 3 (MU3) criteria. The federal government allocated \$27 billion to fund a staged program to boost the meaningful use of EHRs. A phased approach to participation helps eligible providers move from creating information in Stage 1, to exchanging health information in Stage 2, to focusing on improved outcomes in Stage 3.

Yet a knowledge gap remains on the best ways to accomplish MU3's objectives, so the Agency for Healthcare Research and Quality funded 12 research projects to provide real-world evidence to inform MU3 policy development and implementation. Alexander G. Fiks, MD, MSCE, who co-directs the Pediatric Research Consortium (PeRC), leads one of those studies at Children's Hospital that aims to help policymakers understand the feasibility of using patient portals linked to EHRs to foster patient engagement in pediatrics.

"Data is lacking on which Meaningful Use goals can be reasonably achieved in pediatric primary care settings," Dr. Fiks said. "We are on track to potentially shape what the expectations should be about using patient portals and these types of tools to collect patient reported outcome data as Stage 3 is rolled out."

The study will use the patient portal "MyAsthma," which provides asthma education, collects patient-reported outcomes, evaluates medication use and side effects, and tracks parents' preferences and goals. The portal transmits information entered by parents to the clinician's office, which allows the medical team to address immediate problems and adjust treatment if needed.

Asthma is well-suited to the study of patient portals because it has a high prevalence, affecting more than 7 million children in the U.S., especially in socioeconomically disadvantaged communities. It requires symptoms to be tracked over time, and it poses a significant burden on patients' and families' quality of life. Patients with persistent asthma regularly use controller medications, so patient portals also may help in medication management for this population.

"On a monthly basis, families check in," Dr. Fiks said, "so their healthcare isn't just tied to office visits. There is ongoing monitoring of how kids with this condition are doing."

A unique aspect of the study is its approach to primary care research across two networks. The American Academy of Pediatrics electronic subnetwork of Pediatric Research in Office Settings (ePROS) is collaborating with PeRC. This is enabling the researchers to evaluate two types of patient portals used across multiple EHR vendors in varied pediatric primary care settings with at least 20 percent Medicaid patients.

"Little is known about the effectiveness of meaningful use policy, and even less is known about how it applies to pediatrics," Dr. Fiks said. "Most meaningful use research has primarily been structured within adult healthcare settings. Being able to inform how the process works within pediatric settings is important because the needs of children are different."

Dr. Fiks anticipates a rapid turnaround time for study results. The majority of data from parent surveys were collected over the summer, followed by individual interviews of parents and practitioners to describe any factors that facilitated or posed barriers to patient portal adoption. He expects to identify strategies that will directly inform national healthcare priorities for MU3, which are scheduled to take effect in 2017.

CHOP's Department of Biomedical and Health Informatics, Center for Pediatric Clinical Effectiveness, and PolicyLab also are contributing to the study, bringing together CHOP's health service research, policy, and technological expertise.



Campaign Raises Awareness of Palliative Care

A nationally esteemed [Pediatric Advanced Care Team](#) (PACT) at The Children's Hospital of Philadelphia provides comprehensive pediatric palliative care services that can help to reduce a child's pain, manage other distressing symptoms, and provide emotional support. Yet many families and caregivers elsewhere are not as familiar with palliative care's benefits, and healthcare providers hesitate to recommend palliative care for their youngest patients.

The [National Institute of Nursing Research](#) (NINR) last year launched a national campaign, "[Palliative Care: Conversations Matter](#)," to raise awareness of palliative care and increase its use within the pediatric population. Campaign materials include informational video vignettes and tear-off pads of patient education sheets that guide providers in how to engage in interactive palliative care discussions.

CHOP's [Chris Feudtner, MD, PhD, MPH](#), director of research for PACT, was involved in planning the NINR campaign and has had several research studies funded by NINR grants, including an ongoing two-year cohort study focusing on decision-making in advanced pediatric care.

"Palliative care is not exclusive to patients who are no longer seeking cure or no longer seeking life-prolonging therapy," Dr. Feudtner said. "It can be in addition to those types of therapies. The campaign can help physicians provide a more clear explanation of what palliative care is and allay fears."

An important part of implementing the campaign is having skilled staff as ambassadors at the bedside to collaborate with parents and incorporate their perspectives into the palliative care plan, Dr. Feudtner said. CHOP's PACT, for example, helps families understand their children's underlying disease process and prognosis, optimize symptom control, establish a comforting environment, and promote their highest quality of life.

A study Dr. Feudtner published in [Pediatrics](#) showed an explosion in the number of palliative care teams over the past 10 years in the U.S. Of 162 children's hospitals that provided data for the study, 69 percent reported having a pediatric palliative care program.

"You need to have high quality palliative care teams in place in order to make a bad situation as good as possible," Dr. Feudtner said.

Dr. Feudtner's [current research](#) aims to improve understanding of how parents make extremely difficult medical decisions for children with life-threatening complex chronic conditions. The findings of his previous studies have emphasized the importance of psychology and the emotional realities involved in this daunting challenge.

“Our team and our experience at CHOP have helped us to heed the potential of what palliative care can do from many different angles,” Dr. Feudtner said. “And our research is taking us further. We have bedside learning from clinical practice intermixing with and informing health services and epidemiological research.”



Gaining Ground on Sports-related Concussions

A concussion is a mild traumatic brain injury caused by a blow or jolt to the head or body that causes the brain to shake, and it is a common occurrence in young athletes. Some concussion symptoms may appear immediately after the injury, while others may not show up for several days. They can include headache, nausea, dizziness, sleep problems, difficulty concentrating, and moodiness.

The clinical demand for concussion care throughout The Children's Hospital of Philadelphia's system remains high, with a total of about 12,800 concussion visits in 2013 alone. Consequently, the need for pediatric research in the area of concussion prevention and care is great.

The Center for Injury Research and Prevention's Kristy Arbogast, PhD, and the University of Pennsylvania's Susan S. Margulies, PhD, contributed to an Institute of Medicine report (IOM) in 2013 that revealed many gaps in researchers' understanding of the causes and consequences of sports-related concussions. The report's authors also found that despite increased awareness of concussions, there remains a culture "that resists both the self-reporting of concussions and compliance with appropriate concussion management plans."

The IOM report generated national attention that even reached President Obama's podium, as he cited its findings during the first-ever White House Healthy Kids & Safe Sports Concussion Summit, where key stakeholders gathered in May to promote new efforts that will increase research to expand knowledge of concussions.

Pediatric sports medicine specialist Christina Master, MD, and CHOP President and Chief Operating Officer Madeline Bell were in attendance at the summit as it was announced that the Hospital will begin development of a database about pediatric and adolescent concussion cases to inform scientific research to improve care. The registry is a result of a Department of Pediatrics Chair's Initiative project at CHOP called Minds Matter that involved a multidisciplinary team led by Dr. Arbogast and Dr. Master who set out to create tools to standardize and streamline concussion diagnosis and management across the CHOP Care Network.

As fundamental science about concussions is changing quickly, finding the best way to translate that research into evidence-based advocacy is the next challenge that Dr. Arbogast will tackle as a new member of the National Council on Youth Sports Safety. David Satcher, MD, former U.S. Surgeon General, and Eliot Sorel, MD, a global health expert from George Washington University School of Public Health and Health Services, convened a multidisciplinary panel of experts to form the national council.

Council members plan to visit about 10 localities and host town hall-like events that will feature innovative practices and approaches to concussion prevention, diagnosis, treatment, and management. While the spotlight will be on sharing knowledge, they anticipate some sports players will lend their star power to help change society's norms.

"Its mission is to raise awareness and apply an integrative approach to create a culture of prevention and reduce the number of injuries that children sustain in sports," Dr. Arbogast said. "We want to think about youth sports in a way that children can gain the benefits of physical activity, leadership, and character development while ensuring that they are as safe as possible while they play."

A portrait of Nancy Kassam-Adams, a woman with short blonde hair and red-rimmed glasses, smiling. The background is a warm, out-of-focus orange-brown.

Nancy Kassam-Adams Furthers Trauma Research

Children's Hospital investigators are taking on an increasing number of leadership positions while maintaining their vibrant programs at The Children's Hospital of Philadelphia Research Institute, a testament to their influence and the impact of their endeavors.

One example is [Nancy Kassam-Adams, PhD](#), who plans to reach out across the globe to advance trauma stress research and practice as she takes on the role of president of the [International Society for Traumatic Stress Studies \(ISTSS\)](#).

Traumatic stress occurs in significant numbers of children and parents after unintentional injuries like concussions, interpersonal violence, and other difficult medical events.

Founded 29 years ago, ISTSS is an international, interdisciplinary professional organization that includes researchers, psychiatrists, psychologists, social workers, nurses, and others with an interest in the study and treatment of traumatic stress. Dr. Kassam-Adams, associate director for behavioral research at CHOP's [Center for Injury Research and Prevention \(CIRP\)](#), has been an ISTSS member for more than 20 years.

In her term as ISTSS president, Dr. Kassam-Adams is advancing the Society's strategic goals by fostering mutual scientific exchange and engaging ISTSS' broad international membership. ISTSS hosted a conference in Norway, and also appeared in Singapore, China, and Chile, among other places.

The Society's Past President Karestan C. Koenen, PhD, described Dr. Kassam-Adams as having a "rare combination of passion, intelligence, and kindness. She will be successful because she will motivate ISTSS members through her passion to improve the lives of traumatized children, employ ISTSS resources intelligently, and listen to our members and make sure their views are represented."

Dr. Koenen added that Dr. Kassam-Adams' willingness to take risks will make the ISTSS a better organization. For example, she instituted a Spanish track at the [ISTSS Annual Meeting](#) in November that enabled the society to expand its reach to new attendees and allow greater interchange among researchers and clinicians in the U.S., Latin America, and Spain.

CHOP research over the past several decades has been at the forefront of understanding the [impact of pediatric medical events](#) (illness and injury) for children and their families through the lens of traumatic stress. Dr. Kassam-Adams has completed several large prospective studies of traumatic stress in children and youth in medical settings. With colleagues at CHOP, she developed innovative [web-based tools for parents](#) that promote secondary prevention of traumatic stress in ill or injured children.

“I see my involvement and leadership roles in ISTSS as mutually beneficial for ongoing CHOP research in this area, helping to tie us in with the larger field of traumatic stress and promoting mutual exchange of ideas with colleagues around the world who are doing very interesting work in related areas,” Dr. Kassam-Adams said.



*National
Science
Foundation*



*Center for Mitochondrial
and Epigenomic Medicine*



*“We’re giving these kids
a voice where they didn’t
have one, an opportunity
to speak about their
life experiences.”*

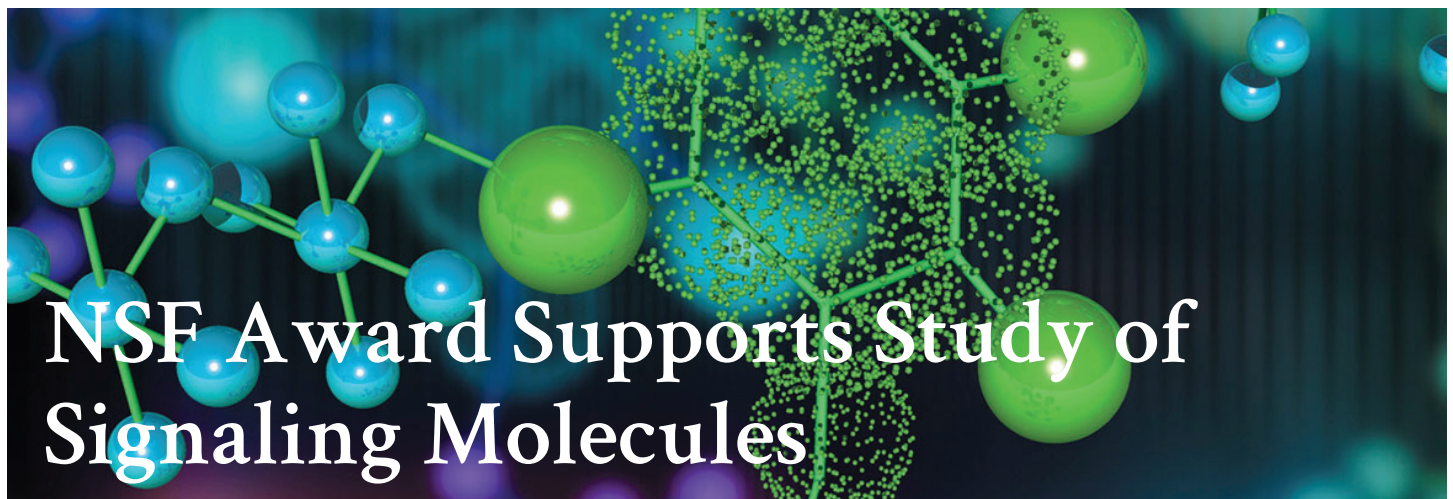
Commitment.



Commitment.

- 76. NSF Award Supports Study of Signaling Molecules
- 77. Study to Expand Understanding of Tumor Development
- 78. CURE Funds Investigation of Novel Epilepsy Therapies
- 79. Scientist Pursue Molecular Mechanisms of Aging
- 80. Researchers Begin Advanced Transplant Study
- 81. Children's Feedback Used to Measure to Adversity

Inspiration. >



The National Science Foundation (NSF) gave CHOP molecular biologist Adam Resnick, PhD, a five-year award to study inositol pyrophosphates, a new class of signaling molecules. Dr. Resnick's award is one of only a handful of active NSF awards given to Children's Hospital investigators.

Found in all eukaryotic cells, inositol pyrophosphates "play roles in diverse processes," said Dr. Resnick, an assistant professor of neurosurgery at the University of Pennsylvania School of Medicine. "They do novel things — they modify proteins in new ways."

Dr. Resnick and Phillip B. "Jay" Storm, MD, chief of neurosurgery, study cell signaling in pediatric brain tumors, working to better understand tumors at a molecular and genetic level.

The inositol pyrophosphate project is a good fit for the NSF, Dr. Resnick said, because his lab conducts a fundamental level of research, while at the same time it is committed to translational research. After all, in order to perform translational research, scientists first have to know how cells work, he added.

The project will feature specific opportunities for undergraduate, graduate, and medical school students to receive basic research training in the context of the laboratory's translational science endeavors. Students will have the chance to get a "real authentic view of the importance of basic, fundamental research in the context of a children's hospital setting," Dr. Resnick said.



Beckwith-Wiedemann Syndrome (BWS) occurs in approximately 1 out of 13,700 births and is associated with an increased risk of childhood cancers, in particular the kidney cancer Wilms' tumor and hepatoblastoma, a form of liver cancer.

“Up to 25 percent of children with BWS develop tumors, but we do not have a good understanding of why they do,” said Jennifer Kalish, MD, PhD, an attending physician in the Division of Genetics.

In an attempt to understand why only some children with BWS develop tumors, and to work to develop better screening markers, Dr. Kalish is conducting a two-part study. She is simultaneously developing a mouse model of the disease, as well as deriving induced pluripotent stem cells from BWS patients' fibroblasts.

The focus of the mouse model will be on the role particular genes play in BWS and tumor development. Dr. Kalish's investigations will focus on chromosome 11, as several genes' expression there is altered in BWS and other cancers, including neuroblastoma, a form of childhood cancer that is responsible for 10 to 15 percent of all childhood cancer-related deaths.

“This region is dysregulated in other cancers, outside of BWS cancers, so there is clearly something about this region that is leading to tumors,” Dr. Kalish said, pointing out that the new investigation, coupled with the fact that she has been receiving BWS referrals from throughout the country and the world, could give researchers the ability to take a more comprehensive look at BWS patients' long-term health and tumor risk.

“Ultimately, we would like to have better markers to screen for, a better understanding of why these children get tumors, but most importantly possible treatments,” she said.



CURE Funds Investigation of Novel Epilepsy Therapies

The epilepsy advocacy organization [Citizens United for Research in Epilepsy](#) (CURE) gave a “Taking Flight” award to a Children’s Hospital neurologist to study how transplanted cells could be used to treat [epilepsy](#).

[Ethan Goldberg, MD, PhD](#), was one of three researchers to receive a one-year grant of up to \$100,000 designed to “promote the careers of young investigators and support them as they develop an independent research focus,” according to CURE.

A brain disorder marked by seizures of varying intensity and type, epilepsy affects approximately 2 million Americans. With this investigation, Dr. Goldberg seeks novel treatments for forms of epilepsy that are resistant to standard medication. Using a mouse model, his research team will assess the “functional integration of transplanted interneurons” as well as whether transplanted cells can reduce or eliminate seizures in patients with epilepsy.

“Cell-based therapies offer hope of a future cure for our patients who are in greatest need, although significant additional basic science research is required to realize this potential,” Dr. Goldberg said. “This generous grant from CURE will greatly assist in getting this project off the ground and pushing it forward.”

Children’s Hospital has a robust epilepsy treatment and research program. Part of its Division of Neurology, the Pediatric Regional Epilepsy Program’s multidisciplinary team of clinicians, nurse practitioners, and researchers collaborate with families to design personalized treatment plans that best control epilepsy with as few side effects as possible.



Scientist Pursue Molecular Mechanisms of Aging

The National Institute on Aging awarded a Children's Hospital researcher a four-year grant to investigate the role biological errors play in age-related diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and Amyotrophic Lateral Sclerosis.

The NIA grant will support Marc Vermulst, PhD, of the Center for Mitochondrial and Epigenomic Medicine, in his investigation of the role non-genetic errors made during cell transcription and translation play in age-related diseases.

This is a new, "non-DNA centric way to understand how aging results ultimately in age-related diseases," Dr. Vermulst said. He has developed a number of novel assays to conduct this research, which he hopes may significantly deepen the understanding of aging and age-related pathology and help identify new targets for treatments or prevention strategies in the clinic.

In their experiments, Dr. Vermulst and his team increased the error rate of transcription in living cells and found features that are indicative of accelerated aging. For example, he pointed out that some age-related diseases are caused by an aggregation of proteins. As the researchers increased the error rate of transcription, they also increased the rate at which these proteins aggregated, which suggests that a link exists between transcription errors and age-related diseases.

While his investigation is basic and clinical applications of the work remain in the future, Dr. Vermulst said the project's focus on establishing a better understanding of the mechanisms of aging could lead to future treatment strategies.



A Department of Defense (DoD) grant to The Children’s Hospital of Philadelphia will fund a new study focused on vascularized composite allotransplantation, a type of transplantation in which multiple tissues — such as an entire hand — are transplanted as a functional unit.

With this four-year, \$2 million grant, CHOP and the University of Pennsylvania join a consortium of institutions — including the University of Maryland and the Christine M. Kleinert Institute for Hand and Microsurgery — led by Emory University that will examine advanced transplantation techniques through the DoD’s Restorative Transplantation Research program. Overall, the research program seeks to make a significant impact on improving the function, wellness, and overall quality of life for wounded members of the military

Wayne Hancock, MBBS, PhD, chief of CHOP’s Division of Transplant Immunology, will be the study’s principal investigator, and his aim is to develop new approaches to immunosuppression.

L. Scott Levin, MD, FACS, the Paul B. Magnuson Professor of Bone and Joint Surgery at the University of Pennsylvania, will lead Penn’s efforts. Matthew H. Levine, MD, PhD, assistant professor of surgery at the University of Pennsylvania, will contribute to the investigation.



Children's Feedback Used to Measure to Adversity

Children who have experienced adversity are the true experts in understanding which childhood exposures were stressful and traumatic for them. A Children's Hospital of Philadelphia researcher has been striving to incorporate these children's voices into public health measures.

With the support of the Philadelphia-based [Stoneleigh Foundation](#), the work of [Roy Wade, Jr., MD, PhD, MPH](#), an attending physician and public health researcher, will build on the results of a major study published in [Pediatrics](#), which sought to add the perspectives of low-income inner-city youth to measures of adverse childhood experiences (ACEs).

A [previous study](#) showed that ACEs such as abuse, neglect, and household dysfunction are major risk factors for leading causes of illness and death as well as poor quality of life in the U.S.; however, that research did not consider chronic ACEs that affect disadvantaged youth such as pervasive community violence, economic hardship, and racial discrimination.

In the *Pediatrics* study, alongside Children's Hospital's [Joanne Wood, MD, MSHP](#), and [David Rubin, MD, MSCE](#), as well as the University of Pennsylvania's [Judy A. Shea, PhD](#), Dr. Wade conducted a series of focus groups with low-income inner-city young adults 18 to 26 years old to get their perspectives on ACEs. After meeting with a total of 105 participants, the researchers found that stress related to family relationships (such as domestic substance abuse and domestic violence) was the most common ACE cited. The second most commonly cited area was community stressors, including "neighborhood violence, crime, and death."

Overall, Dr. Wade and his team concluded that assessments of childhood adversity "should include experiences relevant to the target population," and ACE research "should be broadened to include stressors experienced by youth in low-income urban settings."

That is precisely what Dr. Wade's current project, funded both by the Stoneleigh Foundation as well as the Perelman School of Medicine's [Center of Excellence for Diversity in Health Education and Research](#), aims to do. Over the course of this three-year project, Dr. Wade will be working "to build a youth-informed measure of childhood adversity that is informed by kids but also informed by the organizations that actually use the instrument," he said.

He is gathering input from organizations across healthcare, social service, and youth mentoring groups to create the measure, which will eventually be adopted by the partner organizations. Dr. Wade then plans to gauge the impact of the tool and adversity assessment on each organization's work, seeking to measure how it changes practice "in unforeseen ways," he said.

In contrast to the *Pediatrics* study, with this project Dr. Wade is looking to recruit children as young as 8 years old. The measure itself will be a series of questions, as part of interviews that will validate the framework of areas of concern established by the *Pediatrics* study.

“We’re giving these kids a voice where they didn’t have one,” he said, adding that the project will allow children who have experienced adversity “an opportunity to speak about their life experiences.”

Dr. Wade’s hope is that by creating an assessment tool and promoting its use, he and the organizations involved will create a dialogue between children, their families, and providers that facilitates open discussion of trauma.

Inspiration

“We want to capitalize on this window of time during the transition to adulthood when health behaviors are being solidified, and provide guidance on how they value their health and how they fit health into their identity as it’s being developed.”

- Dr. Lisa Schwartz





Young Girls Help Inform Breast Cancer Prevention

With a megawatt smile and adventurous spirit, Marlena Penn, 16, is a high school junior, master scuba diver, and talented underwater photographer. She has been eye-to-eye with an octopus and captured its spectacular changes in color. Evidently, her bravery and glossy, auburn curls come from her mother, Norma Roth, who is a writer, speaker, volunteer extraordinaire, and breast cancer survivor.

Put them together in an interview room, and you can feel the girl power about to burst through the door.

Even though they have a packed schedule, twice a year the pair travels from Cherry Hill, N.J., to visit The Children's Hospital of Philadelphia as participants in the "Lessons in Epidemiology and Genetics of Adult Cancer from Youth" (LEGACY Girls Study).

Funded by the National Cancer Institute, the LEGACY study is unique in its focus on healthy, young girls and how their habits and development are related to breast health. LEGACY researchers hope to identify risk factors and lifestyle modifications that could potentially be addressed early enough to prevent or diminish the effects of cancer.

BRIDGE TO FUTURE

Norma and Marlena come from three generations of breast cancer. Marlena is named after her grandmother, Marlene, who died of breast cancer many years before she was born. Marlena's grandmother had three aunts, a sister, and several cousins who also were devastated by breast cancer diagnoses. It is estimated that 5 to 10 percent of breast cancer cases result directly from gene defects — usually a mutation in the *BRCA1* and *BRCA2* genes — so Norma underwent genetic testing to see if she had inherited them from a parent.

Although the results were negative, she discovered in 2004 at age 40 that she indeed had breast cancer. Marlena was only 5 years old and does not remember her mom being sick, but Norma had many talks with her two other young children, now 19 and 22, to reassure them that recent breast cancer advances had made it more curable than ever before.

"We've seen a lot of death on both sides of my mother's family from breast cancer, but as detection and treatment has advanced, we've seen better outcomes," Norma said. "I always thought there also was some kind of environmental link. So it was interesting to me to see that the LEGACY study was tracking the health and diet of young girls to see what effects it might have on breast cancer development in the future."

Three years ago, Norma received a study recruitment letter looking for girls to participate in LEGACY. She was hopeful that Marlena would want to join, but she left the decision up to her then 13-year-old daughter.

“I knew that from my family’s past, I might as well do it,” Marlena said. “Two visits a year is not that big of a commitment, and what I give could be really helpful to other families.”

UP CLOSE AND PERSONAL WITH RESEARCH

The biggest selling point for Marlena was that bloodwork would not be performed at every visit. While she has no problems with close encounters with sharks and eels baring their sharp teeth, needlesticks make her a “hysterical mess.”

Entering its fifth year, the LEGACY study enrolled 1,040 girls ages 6 to 13 at five sites in North America. The Philadelphia site includes the University of Pennsylvania, Fox Chase Cancer Center and The Children’s Hospital of Philadelphia, where the data collection is performed. Coordinators of the Philadelphia cohort reached a milestone in 2013 when their 150th participant enrolled.

The study teams measure the girls’ growth and development, obtain either blood or saliva samples, and conduct surveys about their knowledge and perceptions of breast cancer, their health and risk behaviors, and psychosocial adjustment. The mothers also answer survey questions along the lines of, “What did you daughter eat this week?” or “Choose the picture that best illustrates your daughter’s body type.” Norma schedules their LEGACY visits to take place during school winter break and the beginning of summer, so that they do not interfere with homework or after school activities.

“The visits are easy,” Marlena said. “And it’s a nice group of people that run it. I’ve learned about how consistent everything must be in a research study. Whenever you get measured, it’s not just once, it’s five times, to make sure that everything is precise and accurate.”

Participating in the research study already has helped Marlena to think more about keeping her body healthy. Over the past few years, for example, she has answered study questions about drinking water. These raised her awareness about the importance of staying hydrated, especially when she is away on diving vacations. She is drinking only water at school this year, instead of juices, which is a big change for her.

GIRLS’ RESPONSE TO BREAST CANCER RISK

Half the girls participating in the LEGACY study come from families with a history of breast cancer, like Marlena. They are among the first generation where women are routinely tested for genetic mutations that may increase their risk for breast cancer. Yet little research has been completed that explores how adolescents respond to learning about their familial breast cancer risk.

While none of the girls in the LEGACY study will be tested for the breast cancer genes, the researchers will assess whether genomic DNA methylation levels are modified by early-life exposures, pubertal development, and other endpoints relevant to breast cancer etiology. DNA methylation is a mechanism that cells use to switch genes on and off.

Lisa A. Schwartz, PhD, a psychologist in the Division of Oncology at CHOP, is a LEGACY co-investigator who collaborates with adult breast cancer specialists to find ways for girls from high-risk families to navigate the nuances of how growing up with knowledge of their families' breast cancer history affects their well-being and health behaviors. She works closely with co-principal investigators Angela R. Bradbury, MD, an assistant professor of medicine in the Division of Hematology-Oncology at the Perelman School of Medicine at the University of Pennsylvania, and Mary B. Daly, MD, PhD, at Fox Chase Cancer Center.

"We want to capitalize on this window of time during the transition to adulthood when health behaviors are being solidified, and provide guidance on how they value their health and how they fit health into their identity as it's being developed," Dr. Schwartz said.

Communicating with her family members about their risk of breast cancer was not a difficult choice for Norma, who believes that knowledge is power and wrote a book, "Pink Ribbon Journey" that chronicles the breast cancer experiences of her family and other women of varying ages, faiths, and backgrounds.

"Way before the *BRCA* genes were discovered, the women in my family truly thought something in their DNA was killing them, and they felt helpless," Norma said. "Today we have better mammograms, we have MRIs, and we have genetic testing. All of these tools are very empowering for my generation. I think the more you know, the better you can control things and change the history in your life. That's why I really wanted Marlena to be part of the LEGACY study. It's great, and it will be interesting to see what they do with the information in the end."

As the LEGACY study moves into its final year, the collaborators are planning to seek additional funding to continue to follow this cohort from a biological, developmental, and behavioral standpoint.

Facts & FIGURES

88.

FINANCIALS.



90.

WHO'S WHO.



95.

CREDITS.



96.

LINKS.



Financials

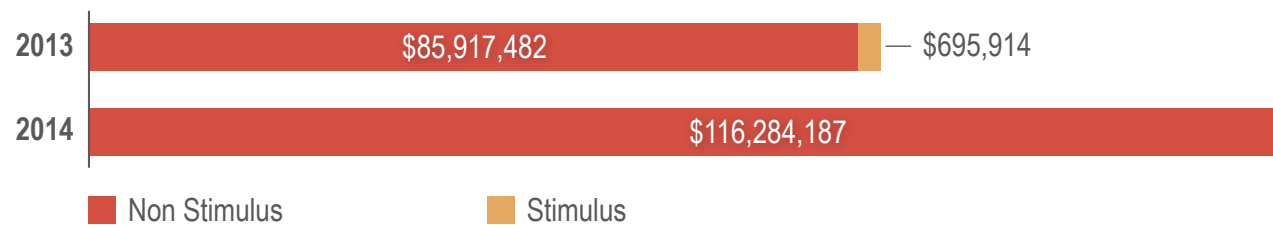
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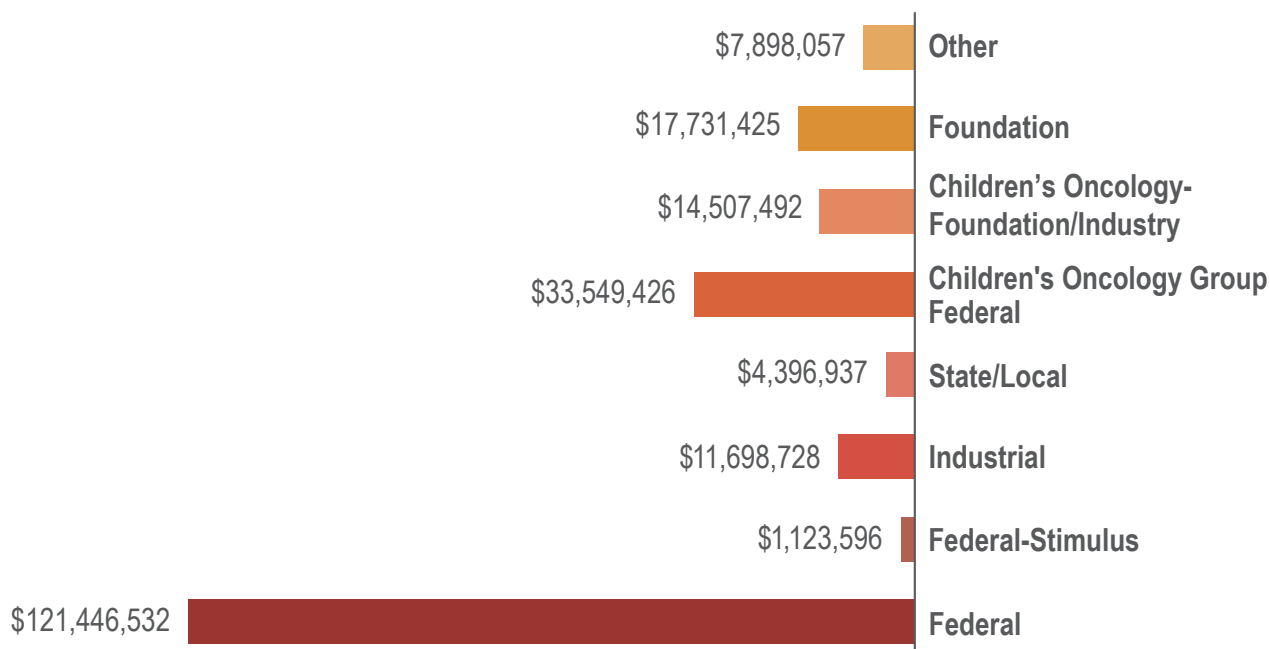
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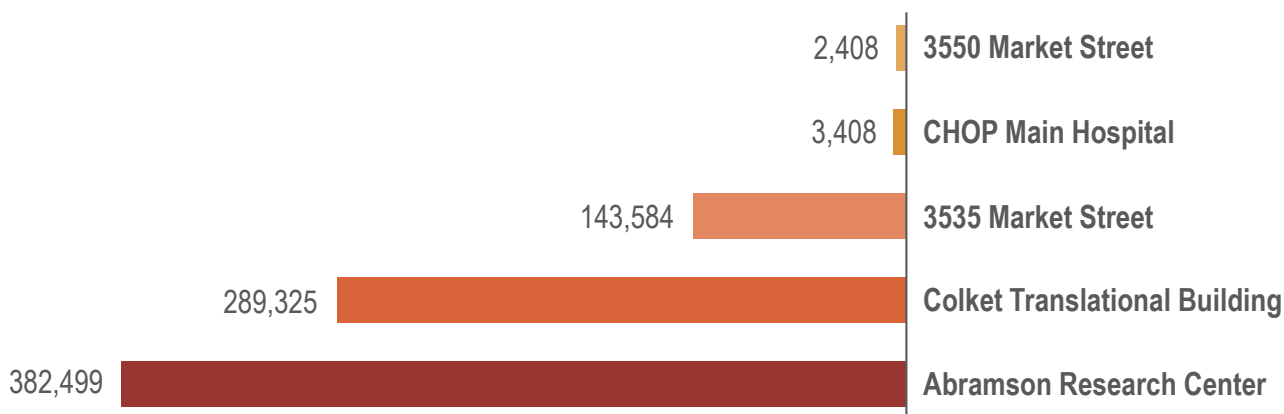
Sources of External Grants and Contracts.



Publications.



Total Research Space - Gross Sq Ft.



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Michael Bennett, PhD

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

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

Buck Family Endowed Chair in Hematology Research
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Daniel B. Burke Endowed Chair for Diabetes Research
Pending Appointment

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Susan E. Levy, MD

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

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Francis McGowan, MD

Children's Hospital of Philadelphia Endowed Chair in Pediatric Anesthesiology and Critical Care Medicine
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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 Pediatric Neuroradiology
Robert Zimmerman, MD

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Pending Appointment

Children's Hospital of Philadelphia Endowed Chair in Pediatric Orthopaedic Surgery
Pending Appointment

Children's Hospital of Philadelphia Endowed Chair in Pediatric Otolaryngology
Ken Kazahaya, MD

Children's Hospital of Philadelphia Endowed Chair in Pediatric Otolaryngology and Pediatric Airway Disorders
Ian N. Jacobs, MD

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

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

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

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
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Distinguished Chair in the Department of Pediatrics
Carole Marcus, MD

Distinguished Chair in the Department of Pediatrics
Peter Adamson, MD

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William J. Greeley, MD, MBA

Mary Downs Endowed Chair in Pediatric Craniofacial Treatment and Research
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Garrett M. Brodeur, MD

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James S. Meyer, MD

Kwame Ohene-Frempong Endowed Chair in Pediatric Hematology
Pending Appointment

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Mitch Weiss, MD

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Christopher Feudtner, MD, PhD, MPH

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Jack Rychik, MD

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Paul Offit, MD

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Susan Furth, MD

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Monte Mills, MD

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Brenda Banwell, MD

Stephen Ludwig Endowed Chair in Medical Education
Lisa Zaoutis, MD

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Arthur Vincent Meigs Endowed Chair in Pediatrics
Beverly Davidson, PhD

Jeffrey Modell Endowed Chair in Pediatric Immunology Research
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Julian Allen, MD

Thomas Moshang Endowed Chair in Endocrinology
Craig Alter, MD

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

Edmond F. Notebaert Endowed Chair in Pediatric Research
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Louis M. Bell, MD

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William Potsic Endowed Chair in Pediatric Otolaryngology and
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Regional Autism Center Endowed Chair
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Bryan Wolf, MD, PhD

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Janis Burkhardt, PhD

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

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Brigid Czyszczin, Assistant Director
Robert Denight, Assistant Director

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Technology Transfer
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Madeline Bell
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Executive Vice President, Translational Medicine and Science
Director, The Children's Hospital of Philadelphia Research Institute

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