2015 RESEARCH ANNUAL REPORT

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The Children's Hospital *of* Philadelphia[®] **RESEARCH INSTITUTE**



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DISCOVERY >

New Leadership Ushers in the Future of Research

Every day, countless children worldwide are living to see longer, brighter futures thanks to discoveries at the <u>The Children's Hospital of Philadelphia Research Institute</u>. The 2015 Annual Report places the spotlight on the collaborations, innovations, and breakthroughs that are shaping the health of generations to come.

Leading the Research Institute into the next era of pediatric healthcare is <u>Bryan A. Wolf, MD, PhD</u>, who took on the role of Chief Scientific Officer (CSO) and Director of the Research Institute in April. Dr. Wolf, a diabetes researcher, served as pathologist-in-chief and chair of the Department of Pathology and Laboratory Medicine from 2001 to 2008 and was most recently CHOP's chief information officer and senior vice president.

Building upon CHOP's legacy as one of the preeminent pediatric research institutions in the world, Dr. Wolf began in spring 2015 an ambitious, faculty-led strategic planning process to make the most of the Research Institute's talent, intellect, and energy to ensure continued success every step along the way to improve the health of children.

"I believe this is the ideal time for us to see how far we've come at The Children's Hospital of Philadelphia Research Institute, and to look ahead to where we'd like to go, while paying careful attention to the bumps we've encountered in the road and to resources and opportunities now within reach," Dr. Wolf said.

The strategic plan will ultimately illuminate the next stretch of the Research Institute's trailblazing path and, in the process, identify and support a handful of transformative research initiatives that will produce the most knowledge and clinical impact.

The future is here, as we create breakthroughs and advance the best in pediatric care to ensure that all children's lives are full of possibilities.

THE FUTURE MENUI

Collaboration Empowers Microbiome Exploration

During doctors' visits a few years from now, your physician might not only ask how you are feeling but also inquire about how your giant collection of bugs — your microbiome — is doing.

Scientists participating in the new <u>PennCHOP Microbiome Program</u> have extraordinary research opportunities to explore the trillions of organisms that are within us — or on us — and how these microscopic communities can sway our health. The microbiome may play pivotal roles in the likelihood of acquiring conditions such as obesity, gastrointestinal disorders, and autism, and how our bodies respond to those states.

"If we take advantage of what they're trying to tell us, it's going to change medicine in the future," said Microbiome Program Co-director <u>Robert Baldassano, MD</u>, a pediatric gastroenterologist who also directs the <u>Center for Pediatric Inflammatory Bowel Disease</u> at T<u>he Children's Hospital of Philadelphia</u>. Dr. Baldassano also is a professor of Pediatrics at the <u>Perelman School of Medicine at the University of</u> <u>Pennsylvania</u>.

One hundred billion bacterial and microbial cells fit into a gram of gut material, but despite their tiny size, the microbiome produces metabolites that can have a big voice. Gut bacteria, for instance, help to create about 95 percent of your body's serotonin, which influences mood, depression, and behavior. Microbes that are associated with your body also help make vitamins, aid digestion, and set your immune tone.

Advancements in deep DNA sequencing technology over the last five to 10 years have made it possible for researchers to characterize the bacterial, fungal, and viral members of the human microbiome. When the Microbiome Program launched in August as a Center of Emphasis at CHOP, it became the only pediatric center in the world with such state-of-the-art facilities and assets, Dr. Baldassano said. The Center gives researchers the ability to identify, measure, and monitor microbiota communities within pediatric biosamples from multiple body sites, including gut, airway, and skin.

These methods generate enormous amounts of sequencing data. Our microbiota contain at least 100 times more bacterial genes than our own bodies have human genes. The program offers bioinformatics and analytical tools from CHOP's <u>Department of Biomedical and Health Informatics</u> that allow researchers to identify microbes, and pinpoint and interpret genetic differences in nearly identical organisms.

Research teams at CHOP and the <u>Perelman School of Medicine at the University of Pennsylvania</u> share all of the Microbiome Program's resources, including a population of germ-free (gnotobiotic) mice that are available as animal models. The research collaboration facilitates a diverse range of basic, translational, and clinical research that provides a lifetime perspective on the microbiome from infancy into adulthood. Microbial colonization begins at birth and continues to develop in early childhood. These formative years for microbiome communities depend on multiple factors such as where you live, your household environment, what you eat, the medications you take, and your genetic composition.

"Many studies suggest that the most important time for the impact of these organisms is during the first few years of life, so this is a significant pediatric issue that will allow us to intervene in disease processes," Dr. Baldassano said.

The Microbiome Program's focus on designing human interventions makes it unique, agreed Co-director <u>Frederic Bushman, MD</u>, an adjunct faculty member at CHOP and a chair and professor of Microbiology at the Perelman School of Medicine. As researchers begin to identify microbiome environments that are associated with wellness, they can figure out how to push the microbiome in healthy directions, such as by changes in diet. Scientists also are testing ways to manipulate or engineer microbial populations to influence different disease states.

"We are gathering this kind of data to circle back to patients," Dr. Bushman said. "We can use this knowledge to try experimental therapies to improve patient welfare."

Dr. Bushman also sees future applications for metagenomic analysis of the microbiome in diagnostics. For example, if an immunocompromised patient has been sick for a long time, and nobody can determine why, deep sequencing could allow clinicians to identify outgrowths of opportunistic bugs that they may not have previously considered.

In a recent research project, Dr. Baldassano, Dr. Bushman, and colleagues James Lewis, MD, MSCE, and Gary Wu, MD, at Penn showed that dysbiosis — when the variety and balance of microorganisms in the microbiome are disrupted — appears to lead to the perpetuation of pediatric chronic inflammatory bowel diseases. They collected half a trillion bases of sequencing information from the biosamples of 90 pediatric patients and documented that multiple environmental stressors altered these children's microbiota. The researchers anticipate that the biomarkers they found will be useful in devising new diagnostic approaches and therapeutic targets.

Endless other possibilities exist at the Microbiome Program for investigators to discover the microbiome's true potential. "Everybody finds this incredibly exciting, and many, many people are coming by," Dr. Baldassano said. "We can empower them to expand their current research interests into the microbiome and further science."

Beyond Imagining: New Frontiers for Pediatric HIV

The HIV epidemic in 2015 and beyond is a dramatically different one than ever seen or imagined during the height of the AIDS crisis in the 1980s and '90s.

"In the early days, up to a quarter of all infants born to women with HIV became infected. Now it's less than one percent," said <u>Richard Rutstein, MD</u>, an HIV clinical research leader and medical director of the Special Immunology Service at <u>The Children's Hospital of Philadelphia</u> since its inception in 1989. "For those infected, HIV has changed from a rapidly fatal disease to a chronic illness." Dr. Rutstein is also a professor of Pediatrics at the <u>Perelman School of Medicine at the University of Pennsylvania</u>.

At the front line of this evolution, CHOP researchers are helping infected pregnant women, infants, children, and youth around the world live full, productive lives.

PEDIATRIC HIV CARE GROWS UP

In past decades, a major focus of pediatric HIV research was blocking viral transmission to infants before and after birth. Now that successful therapeutic strategies are available to prevent perinatal transmission, there is a new frontier in pediatric HIV research: Adolescents. HIV/AIDS is among the leading causes of death in adolescents worldwide, and mortality in this group has <u>tripled since the turn of the century</u>.

One major group of high-need adolescents is in sub-Saharan Africa, home to 90 percent of children with HIV. Most were infected perinatally, and many grow up managing the infection well until normal adolescent behaviors — independence-seeking and risk-taking — upset the balance. CHOP research is showing that parents may miss this cue to add support.

"Without understanding that that developmental transition is normal, some families are going to miss the need that's there," said <u>Elizabeth Lowenthal, MD, MSCE</u>, research director for CHOP Global Health, who has led <u>research</u> along with other CHOP investigators and international partners on the role of <u>parental</u> <u>involvement</u> and education in supporting these aging-up teens with HIV. Their work has deepened understanding of how this support and disclosure of a youth's HIV status affects health outcomes and treatment adherence. Dr. Lowenthal is also an assistant professor of Pediatrics and Epidemiology at the Perelman School of Medicine.

In the U.S., getting infected with HIV during adolescence, as opposed to growing up with the infection, is a more frequent and growing challenge, especially affecting teens in stigmatized and disadvantaged groups including LGBT youth and youth of color. Adolescents represent more than a quarter of new infections in the U.S., and most do not know they are infected.

<u>Nadia Dowshen, MD</u>, director of adolescent HIV services at CHOP, leads research identifying barriers to routine adolescent HIV testing, using social media to encourage teens to get tested, and developing an app to improve medication adherence among youth with HIV. Her team is also studying factors affecting HIV prevention, diagnosis, and care among young transgender women. Transgender women are 50 times more likely to become infected with HIV than other individuals. Dr. Dowshen is co-founder and co-director of CHOP's <u>Gender and Sexuality Development Clinic</u>, among only a handful of such specialized pediatric centers in the country. Dr. Dowshen is also an assistant professor of Pediatrics at the Perelman School of Medicine.

HALTING HIV'S IMPACT ON AND IN THE BRAIN

Whether children grow up with HIV or become infected as adolescents, keeping them healthy includes managing and understanding their risk for complications, including neurologic ones. A broad and advanced array of research approaches at CHOP is illuminating the complex interconnections between HIV and the brain — and pointing toward interventions to prevent damage.

"HIV probably enters your central nervous system very soon after initial infection. Once there, the virus appears to both infect certain cells, as well as trigger an inflammatory reaction that causes a lot of secondary cellular and neuronal damage," said <u>Jennifer McGuire, MD, MSCE</u>, whose <u>research focuses</u> <u>on the neurological impact of acquired infection</u>. She also is linking immune biomarkers to neuronal injury in these youth and combining this work with neuroimaging data. Dr. McGuire is also an instructor of Neurology at the Perelman School of Medicine.

<u>David Bearden, MD</u>, also a CHOP neurologist, is pursuing parallel questions about immune biomarkers in the brain, primarily in younger, perinatally infected children in Africa.

"Neurologic complications are very common in children with HIV, especially in low-resource settings where therapy may be delayed," he said. Complications result from a combination of factors including direct and indirect effects of HIV on the brain, socioeconomic factors, in utero exposure to toxins, and inflammation.

Meanwhile, a <u>CHOP-Penn team is looking at depression</u> — a common co-occurrence with HIV, and a concern that often arises in adolescence. Depression, immune dysregulation, and susceptibility to HIV infection are all associated, the researchers have reported in adult studies led by <u>Dwight Evans</u>, <u>MD</u>, chair of Psychiatry at Penn. Immune function also improves when depression does, according to the team, which includes <u>Tami Benton</u>, <u>MD</u>, chief of Psychiatry at CHOP, <u>Steven D. Douglas</u>, <u>MD</u>, chief of the Section of Immunology at CHOP, and a professor of Pediatrics at the Perelman School of Medicine and other CHOP and Penn psychiatrists and neurologists.

Now turning their attention to teens, "We are examining the mechanisms of this relationship, specifically, does depression impact your immune system in a way that allows HIV infection to occur and to progress to AIDS?" Dr. Benton said.

RETHINKING AND REENGINEERING HIV ERADICATION

Part of the effort to address HIV in the brain is to eradicate the virus itself from its hiding places there. Dr. Douglas, who also leads several NIH HIV/ADS centers, clinical trials groups, and domestic and international networks, is pursuing this approach in a <u>collaborative effort with Temple University funded by a NeuroAIDS grant</u>.

Dr. Douglas' <u>internationally recognized work</u> in <u>NIH-supported programs</u> targets a receptor on macrophages that changes the state of these cells from harboring virus in the body to potentially restoring immunity against HIV/AIDS. This tactic may decrease the body's HIV reservoir and lead to a functional cure for HIV/AIDS.

Meanwhile, another unimagined vista is emerging in preventing HIV infection from taking hold the body. Decades of effort have focused on educating the body's immune system about how to handle HIV — in other words, developing traditional vaccines. These efforts have largely come up short, with the immune system regularly getting a few too many questions wrong to pass its exam. A new approach is skipping the lecture and giving the immune system a cheat sheet for the test.

Immunoprophylaxis by gene transfer (IGT) was pioneered by CHOP's former chief scientific officer <u>Philip R. Johnson, MD</u>, and first reported successful in monkeys in a 2009 paper in <u>Nature Medicine</u>. It is a method of genetically engineering the body to produce virus-fighting defenses on its own. This year, the International AIDS Vaccine Initiative partnered with CHOP to launch the <u>first phase 1 clinical trial of the</u> <u>IGT method</u>. More IGT-based trials are being planned around the globe.

This is among the many ways that, as CHOP researchers tackle the new everyday challenges that HIV presents, they continue exploring novel strategies to wipe out the disease.

Gene Therapy Aims to Thwart Ruthless Disease

As a bright-eyed toddler, Noah VanHoutan walked and talked. He giggled and twirled. Then, around age 3, he began experiencing seizures, and within a few months his physical, thinking, and language skills were fading mysteriously.

The eventual diagnosis three years later was Late Infantile Neuronal Ceroid Lipofuscinosis (LINCL), known as <u>Batten disease</u>. A recessively inherited brain disease, the disease robs children of their capabilities, leaving them blind, bedridden, and unable to communicate. It is fatal by age 12

Noah's family received yet another devastating blow when they learned that his then 5-year-old sister, Laine, also had LINCL-Batten disease, but her twin, Emily, was unaffected. Their parents, Jennifer and Tracy, quickly calculated that 40 percent of their family were expected to die in less than a decade. They turned to researchers like <u>Beverly Davidson, PhD</u>, director of the <u>Raymond G. Perelman Center for</u> <u>Cellular & Molecular Therapeutics</u> at <u>The Children's Hospital of Philadelphia</u>, to help ensure that future young families facing LINCL-Batten disease start off with better odds.

"Our family and our entire patient community are grateful for Dr. Davidson's efforts to combat this devastating and cruel disease," said Tracy VanHoutan, who helps to raise Batten disease awareness and research funding through the <u>Noah's Hope</u> foundation and also serves as vice president of the <u>Batten</u> <u>Disease Support & Research Association</u>. "Without research, both basic and translational, affected children and their families would have no hope. Our patient community now has hope that this research will soon translate into the clinic."

LINCL-Batten disease is within a group of disorders called lysosomal storage diseases that part of <u>Dr. Davidson's lab</u> focuses on. Although individually rare, cumulatively lysosomal storage diseases occur in one in 10,000 children. Fewer than 450 children in the U.S. have LINCL-Batten disease. It is caused by mutations in the *TPP1* gene, which encodes the lysosomal enzyme TPP1 that every brain cell needs in order to get rid of waste.

"We try to understand what is going wrong in the absence of these proteins and how we can develop new therapies to treat these children," said Dr. Davidson, who also is professor of Pathology and Laboratory Medicine at the <u>Perelman School of Medicine at the University of Pennsylvania</u>. "Our research is really getting close to being translated to the clinic."

One approach that Dr. Davidson and her team have been working on for many years is using gene transfer vectors to supply the enzyme directly to the brain. They modify the nonpathogenic adeno-associated virus as a vehicle to deliver the gene to ependymal cells that line cavities in the brain called ventricles. These cells then produce and circulate the enzyme within the cerebrospinal fluid so that it bathes the entire brain.

"The missing protein now has the ability to get into the cells and correct the disease," Dr. Davidson said. "These cells that are secreting the protein are very, very long lived. This gene therapy should last the life of the individual."

In mouse and dog models, preliminary data shows that a <u>gene therapy approach to enzyme replacement</u> <u>therapy has a beneficial effect on disease onset and progression</u>. Recognizing the disease at an early stage and starting treatment promptly will be critical to delaying the brain decay, Dr. Davidson said, but a "big unknown" is whether it will be possible to regain any brain function.

Dr. Davidson envisions that children could be treated with a relatively simple 30-minute surgical procedure performed by CHOP neurosurgeons to infuse the vector into the brain. In comparison, another experimental method involves putting the enzyme, rather than the gene, into the brain. Enzyme replacement therapy requires an indwelling device and delivery to the brain every two weeks in the setting of an intensive care unit. If the genetic version of enzyme replacement therapy proves to be successful, it could obviate the need for such an arduous routine.

"We hope to save their lives but at a minimum provide them with greatly improved quality of life with improved functional abilities," Dr. Davidson said.

CChIPS Paves the Way to a Safer Future

The <u>Center for Child Injury Prevention Studies</u> (CChIPS), a <u>National Science Foundation</u> (NSF) Industry/ University Cooperative Research Center (I/UCRC), is celebrating 10 years of being on the road to safety, and it has been a fantastic ride.

In a unique partnership, CChIPS researchers from <u>The Children's Hospital of Philadelphia's Center for</u> <u>Injury Research and Prevention</u> (CIRP), <u>The University of Pennsylvania</u> (Penn), and <u>The Ohio State</u> <u>University</u> work side by side with industry members to prevent pediatric injury. The 20-member CChIPS Industry Advisory Board (IAB) funds research, establishes investigative priorities, and advises on the Center's strategic direction. The IAB is comprised of the top five auto manufacturers, two of the top three juvenile product manufacturers, the only anthropomorphic test device (ATD) manufacturer, the U.S. auto safety regulatory agency, and the U.S. national aviation authority, among other organizations invested in child safety.

Currently, CChIPS research is primarily focused on preventing traffic injuries, the leading cause of injury and death for children, youth, and young adults. Let's take a look in the rearview mirror at how CChIPS has navigated some of these important research challenges over the last decade:

TEEN DRIVING DATA LINKAGE

The New Jersey Traffic Safety Outcome Program, led by <u>Allison Curry, PhD, MPH</u>, CIRP director of Epidemiology and Biostatistics, linked teen driver crash, citation, and licensing data for all N.J. drivers. This data became the foundation for a first-of-its-kind analysis of N.J.'s Kyleigh's Law, which requires youth 16 to 20 years holding a learner's permit or intermediate license to display a decal on the license plates of their vehicle. The <u>results</u> published in November 2014 showed crash involvement of an estimated 3,197 intermediate drivers was prevented in the first two years after the decal's implementation.

"Decal provisions now have the support of science," Dr. Curry said. "The provision may encourage safer driving behaviors, both among teens and other drivers sharing the road with them."

DIAGNOSING DRIVING

The purchase of an advanced <u>driving simulator</u> from IAB member company Realtime Technologies Inc. in 2010 opened new doors for CChIPS to systematically evaluate realistic behavior of drivers in a safe environment. Several lines of CChIPS research, led by <u>Yi-Ching Lee, PhD</u>, human factors researcher at CIRP, have utilized the simulator to observe the <u>impact of distractions</u> such as peer passengers and technology on young drivers' behavior.

An emerging line of teen driving simulator research being pioneered at CChIPS utilizes machine learning models, where state-of-the-art experimental and analytical techniques are used to create accurate <u>models</u> <u>of teenage drivers' behavior</u>. Although this research is geared toward the young driver population, it ultimately can be used beyond teens to assist other vulnerable driving populations such as the elderly or drivers with ADHD or other medical conditions.

"What our research tells us is that a validated simulated driving test could be used to assess the driving skills needed to avoid crashes," said <u>Catherine McDonald, PhD, RN</u>, a teen driver safety researcher at the <u>Penn School of Nursing</u> and CIRP. "If we can identify driving skill deficits in a safe, simulated environment, then we can tell families and driving instructors what to focus on during supervised practice drives or how to help those with citations or crashes who are already licensed."

IMPROVING DESIGN OF PEDIATRIC CRASH TEST DUMMIES

Since its inception, CChIPS has been committed to improving pediatric ATDs, or crash test dummies. To be an effective tool, pediatric ATDs must accurately mimic how child occupants move and respond to the forces of a vehicle crash. The research being conducted through CChIPS is delivering the fundamental data needed to improve the design of pediatric ATDs and to develop innovative restraint products to make vehicles safer for children in the future.

In 2006, CChIPS researchers, led by <u>Kristy Arbogast, PhD</u>, co-scientific director and director of Engineering for CIRP, and research associate professor of Pediatrics at the Perelman School of Medicine, with founding CChIPS IAB member TK Holdings Inc. (Takata Corp.), Rowan University, and University of Virginia researchers developed a low-speed human volunteer sled to mimic the crash experienced by children and adults when they ride an amusement park bumper car. This allowed CChIPS to collect the only known data on the kinematics and kinetics of restrained 6- to 14-year-old pediatric human volunteers in low speed impacts. The crash sled has been used in several CChIPS studies to compare child and adult volunteers' heads, necks, and spines during a bumper car's safe crash, as well as the same body regions on pediatric ATDs.

Since 2005, CChIPS has conducted <u>more than 106 research projects</u>, and the research team continues to gain momentum and explore new areas of study related to child injury prevention as it enters its next fiveyear phase of NSF support. Buckle up!



A future free from the toughest and most challenging pediatric illnesses grows closer every day. New fuel to accelerate that journey at <u>The Children's Hospital of Philadelphia</u> now comes from an extraordinary \$50 million gift, <u>equal to the largest ever received by CHOP</u>, from Philadelphia philanthropist Raymond G. Perelman.

"We know first-hand the tremendous resource that CHOP represents to families in the Philadelphia region, across the country, and around the world," Perelman said. "This gift will help to ensure that critically important pediatric research, conducted on this campus, remains second to none; in addition to making a tangible difference in the lives of children around the globe for many years to come, it is my hope and expectation that advances in medical research funded by this gift will benefit us all."

The gift, announced in January, establishes CHOP as a global center for innovative pediatric study and provides direct support for a wide range of <u>pediatric research</u>:

- **Raymond G. Perelman** Center for Cellular & Molecular Therapeutics, designed to re-engineer the body's immune system to fight and defeat cancer, metabolic diseases, and other catastrophic illnesses through the efforts of the world's leading experts in immunotherapy and molecular therapy.
- **Perelman Scholars**, two new tenure-track faculty positions at CHOP to be filled by candidates from among the world's finest pediatric researchers.
- **Perelman Fund for Research Innovation**, a permanent source of reliable funding for the CHOP Research Institute to strategically identify and support new pilot research initiatives.
- **Perelman Endowed Chair in Pediatric Ophthalmology** to support a highly skilled researcher and physician-scientist seeking to break new ground and forge novel paths critical to understanding and treating ophthalmologic diseases in children.
- **Research support** for general research activities of the <u>CHOP Research Institute</u>.

"The significant research funding associated with this gift underscores the commitment of Raymond Perelman to world-class pediatric research and medicine," said Mortimer J. Buckley, chair, Board of Trustees at The Children's Hospital of Philadelphia. In recognition of this generous gift for research, CHOP also established the Raymond G. Perelman Campus, an eight-acre area just south of the main hospital that will serve as a hub of pediatric research and clinical innovation at CHOP. The campus encompasses CHOP's most state-of-the-art research and clinical centers, including the <u>Ruth and Tristram Colket</u>, Jr. <u>Translational Research Building</u>, which opened in 2009; the new <u>Buerger Center for Advanced Pediatric Care</u>, which opened in July 2015; and a 2.6-acre landscaped plaza.



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INNOVATION >

New Approach to Gene Therapy for Hemophilia Tested

For more than two decades, research teams have investigated gene therapy strategies that deliver DNA sequences carrying genetic code to produce clotting factor in patients with hemophilia, an inherited bleeding disorder. However, this approach has been frustrated by the body's immune response against vectors — the non-disease-causing viruses used to transport the DNA.

<u>Valder R. Arruda, MD, PhD</u>, a hematology researcher at <u>The Children's Hospital of Philadelphia</u> and an associate professor of Pediatrics at the <u>Perelman School of Medicine at the University of Pennsylvania</u>, and colleagues therefore investigated gene therapy that used lower dosages of vector to produce a "turbocharged" potent clotting factor — a variant protein called FIX-Padua that is hyperfunctional. It clots blood 8 to 12 times more strongly than normal, wild-type factor IX, a clotting protein. It also eliminated pre-existing antibodies that often weaken conventional treatments for people with hemophilia.

"Our findings may provide a new approach to gene therapy for hemophilia and perhaps other genetic diseases that have similar complications from inhibiting antibodies," Dr. Arruda said.

The investigators tested the safety of FIX-Padua in three dogs, all with naturally occurring types of hemophilia B very similar to that found in people. Two of the dogs had never been exposed to clotting factor and had never developed antibodies. The gene therapy injections changed their hemophilia from severe to mild, with no bleeding episodes for up to two years. They did not develop inhibitory antibodies, nor was there evidence of thrombosis.

The third dog, named Wiley, already had inhibitory antibodies before receiving the gene therapy. Wiley also experienced safe and effective treatment of hemophilia, persisting over a sustained period of three years. The treatment also eradicated the inhibitory antibodies, the first time this occurred in an animal model with pre-existing antibodies.

Another set of preclinical safety studies in mice supported the safety and efficacy of gene therapy using FIX-Padua. Dr. Arruda published the findings in the journal <u>Blood</u> and added that additional studies are needed to confirm these encouraging early results.

Investigator Explores Mitochondrial DNA Mutations

<u>Mitochondria</u> are tiny energy-producing structures within our cells that contain their own DNA. Although mitochondrial DNA (mtDNA) holds far fewer genes than nuclear DNA, mtDNA exchanges signals with nuclear DNA and participates in complicated networks of biochemical reactions essential to life. New research shows that small changes in the ratio of mutant to normal mtDNA can cause abrupt changes in the expression of numerous genes within cells' nuclear DNA.

"The findings in this study provide strong support for the concept that common metabolic diseases such as diabetes and obesity, heart and muscle diseases, and neurodegenerative diseases have underpinnings in energy deficiencies from malfunctioning mitochondria," said <u>Douglas C. Wallace, PhD</u>, director of the <u>Center for Mitochondrial and Epigenomic Medicine</u> at <u>The Children's Hospital of Philadelphia</u>.

Dr. Wallace's team investigated the impacts of steadily increasing levels of a pathogenic mutation in one particular base of mtDNA. Researchers already knew that if 10 to 30 percent of a person's mtDNA has this mutation, a person has diabetes and sometimes autism. Individuals with an mtDNA mutation level of 50 to 90 percent have other multisystem diseases, particularly MELAS syndrome, a severe condition that involves brain and muscle impairments. Above the 90 percent level, patients die in infancy.

In the current study, conducted in cultured human cells, Dr. Wallace and colleagues analyzed cells with different levels of this pathogenic mtDNA mutation to determine the effects on the cell's gene expression. The researchers measured variations in cellular structure and function, nuclear gene expression, and production of different proteins.

"By showing that subtle changes in the cellular proportion of the same mitochondrial DNA mutation can result in a wide range of different clinical manifestations, these findings challenge the traditional model that a single mutation causes a single disease," Dr. Wallace said.

While Dr. Wallace's paradigm-shifting hypotheses remain controversial in biomedicine, the study, published in the *Proceedings of the National Academy of Sciences*, reinforces the argument that he has presented over the course of his career: Mitochondria play a central, largely under-recognized role in all common human diseases.

Antibiotics Early in Life Associated With Obesity Risk

Investigators at <u>The Children's Hospital of Philadelphia</u> want to identify ways to avert the lifetime of medical, developmental, and social problems associated with obesity. They are intrigued by the emerging idea that the microbial population that begins to colonize in infants' intestines shortly after birth, known as the microbiome, plays an important role in establishing energy metabolism.

"As pediatricians, we're interested in whether there is anything happening early in life that resets this 'thermostat' and has a long-term effect on how your body regulates its weight," said <u>L. Charles Bailey,</u> <u>MD, PhD</u>, lead author of a retrospective study based on electronic health records that looked at how tendencies toward obesity develop early in life. "The thought is that the microbiome may be critically dependent on what is going on during infancy."

Dr. Bailey is an attending physician at CHOP and an assistant professor of Pediatrics at the <u>Perelman</u> <u>School of Medicine at the University of Pennsylvania</u>.

Previous studies have shown that antibiotic exposure influences the microbiome's diversity and composition. With these findings in mind, Dr. Bailey and colleagues analyzed electronic health records from 2001 to 2013 of 64,580 children with annual visits at ages 0 to 23 months, as well as one or more visits at ages 24 to 59 months within the network of primary care practices affiliated with CHOP. They assessed the relationships between antibiotic prescription and related diagnoses before age 24 months and the development of obesity in the following three years.

The results showed an increased risk of obesity with greater antibiotic use, particularly for children with four or more exposures to broad-spectrum antibiotics in early childhood, but they reported no significant association between obesity and narrow-spectrum drugs.

"What we think we're seeing here with these associations is that the more we choose to use narrowspectrum antibiotics, the less likely it may be that we're doing something that will affect a patient's risk of obesity later on," Dr. Bailey said.

<u>Christopher Forrest, MD, PhD;</u> Peixin Zhang, PhD; Thomas M. Richards, MS; Alice Livshits, BS; and <u>Patricia DeRusso, MD, MS</u>; contributed to the article published in <u>JAMA Pediatrics</u>.

Warming Planet May Increase Risk of Kidney Stones

A painful condition that brings half a million patients a year to U.S. emergency rooms, kidney stones have increased in prevalence markedly in the past three decades, especially in children. When stones do not pass on their own, surgery may be necessary.

<u>Gregory E. Tasian, MD, MSc, MSCE</u>, a pediatric urologist and epidemiologist at <u>The Children's Hospital</u> <u>of Philadelphia</u>, along with <u>Ron Keren, MD, MPH</u>, of the <u>Center for Pediatric Clinical Effectiveness</u>, conducted a research study that found as daily temperatures increase, so does the number of patients seeking treatment for kidney stones.

"With some experts predicting that extreme temperatures will become the norm in 30 years, children will bear the brunt of climate change," predicted <u>Dr. Tasian</u>, who is also an assistant professor of Urology in Surgery at the <u>Perelman School of Medicine at the University of Pennsylvania</u>.

The investigators analyzed medical records of more than 60,000 adults and children with kidney stones between 2005 and 2011 in Atlanta, Chicago, Dallas, Los Angeles, and Philadelphia, in connection with weather data. The delay between high daily temperatures and kidney stone presentation was short, peaking within three days of exposure to hot days.

The researchers suggest that the number of hot days in a given year may better predict kidney stone risk in those people predisposed to stone formation than the mean annual temperature. Dehydration leads to higher concentrations of calcium and other minerals in the urine that promote the growth of kidney stones.

The researchers also found that very low outdoor temperatures increased the risk of kidney stones in three cities: Atlanta, Chicago, and Philadelphia. The authors suggest that as frigid weather keeps people indoors more, higher indoor temperatures, changes in diet, and decreased physical activity may increase their risk of kidney stones.

Dr. Tasian added that while the five U.S. cities have climates representative of those found throughout the world, future studies should analyze how risk patterns vary in different populations, including among children, who were represented by a small sample size in the current study.

The study team published its findings in *Environmental Health Perspectives*, the journal of the <u>National</u> <u>Institute of Environmental Health Sciences</u>.

Forced Looping May Switch Off Sickle Cell Disease

Sickle cell disease is an inherited condition that distorts the red blood cells into a sickle shape, like the letter "C," that blocks blood flow and damages blood vessels and many organs. A sickle cell gene mutation tells the body to make a defective type of hemoglobin, which is the oxygen transport protein in red blood cells.

Pre-empting the effects of this sickle cell gene mutation has been a focus of Children's Hospital of Philadelphia hematology researcher <u>Gerd A. Blobel, MD, PhD</u>, and the <u>August 2014 edition of *Cell*</u> reported his novel findings. Dr. Blobel and his co-authors described how they altered the genetic architecture behind a developmentally controlled process called hemoglobin switching, in which adult hemoglobin (HbA) almost completely replaces fetal hemoglobin (HbF) within six months after birth.

"A major driver in the field for many years has been to understand the molecular basis and the machinery that controls that switch," Dr. Blobel said. "The goal is ultimately to overcome the silencing of the fetal globin genes and turn them back on."

His research team's strategy was to manipulate gene expression in order to elevate the amount of HbF and also downregulate the amount of faulty HbA, thereby reducing the sickle cell inducing properties of the mutated form of HbA. They employed artificial zinc finger protein technology that Dr. Blobel and colleagues adapted for use in hemoglobin regulation and <u>described in *Cell*</u> two years ago.

Dr. Blobel's team designed zinc fingers in a way that they would promote looped contacts between the locus control region and the fetal genes in adult red blood cells. This approach worked well and indeed enhanced the expression of fetal genes and reduced the level of the adult-type genes. In the context of sickle cell disease, this would be a double benefit since both high fetal gene expression and low levels of the mutated toxic form of adult hemoglobin would ameliorate the disease.

"This is a novel way to manipulate gene expression via altering chromatin architecture," Dr. Blobel said.

Autism Risk Difficult to Detect During Short Visit

Results of a study <u>published in *Pediatrics*</u> suggest that short 10- to 20-minute observations, such as an office visit, may be insufficient when it comes to assessing autism risk.

Led by Judith S. Miller PhD, MS, a senior scientist at the <u>Center for Autism Research</u> (CAR) at <u>The</u> <u>Children's Hospital of Philadelphia</u>, the researchers studied a group of children age 15 to 33 months with autism, speech delays, and typical development. The researchers asked two licensed psychologists with toddler and autism expertise — who were unaware of the study participants' status — to analyze two 10-minute video samples of the participants' autism evaluations. The experts measured five behaviors, including responding, initiating, vocalizing, play, and response to name.

The researchers found the experts missed referrals for 39 percent of the children in the autism group. Detecting autism risk based on the brief observations alone was challenging because the children who had autism showed more typical behavior (89 percent of the time) than atypical behavior (11 percent) during that short window.

In March of 2014, the <u>Centers for Disease Control and Prevention</u> announced that one in 68 children in the U.S. has an autism spectrum disorder (ASD) — a 29 percent increase over the 2012 rate of one in 88. The seemingly growing prevalence of ASD demonstrates the need for accurate autism referral decisions. This decision-making process should include parent observations, developmental testing, a detailed history, and autism screening tools, in addition to clinical judgment, the research team concluded.

A description of the diagnostic tests and other information on how parents can spot the developmental delays associated with ASD is available in the diagnosis section of <u>Autism Roadmap</u>, an online resource developed by the CAR. The roadmap provides directories of service providers, community resources, government programs, ideas for various stages of childhood and beyond, and explanations of the latest research on ASD treatments and interventions.

Gene Mutation in Blood Disorder Discovered

Studying a family in which three generations had blood disorders, researchers discovered a defect in a gene that regulates telomeres, complex chromosomal structures with crucial roles in normal cell function.

Telomeres are made of DNA and protein that are located on the end of chromosomes, where they protect the chromosomes' stability. They are sometimes compared to plastic tips at the end of shoelaces. Certain inherited and acquired disorders may shorten telomeres and injure rapidly dividing blood-forming cells produced in bone marrow. This leads to bone marrow failure, one example of which is <u>aplastic anemia</u>.

<u>Hakon Hakonarson, MD, PhD</u>, director of the <u>Center for Applied Genomics</u> at <u>The Children's Hospital</u> <u>of Philadelphia</u>, and a number of other CHOP investigators collaborated with Australian scientists on the study that focused on an Australian family with aplastic anemia and other blood disorders, including leukemia. The investigators performed whole-exome sequencing on DNA from the families and identified an inherited mutation on the *ACD* gene, which codes for the telomere-binding protein TPP1. They determined that the mutation shortened telomeres and interrupted their ability to attract the enzyme telomerase, which counteracts telomere shortening and thus protects cells.

"Identifying this causal defect may help suggest future molecular-based treatments that bypass the gene defect and restore blood cell production," Dr. Hakonarson said.

Nine other genes were previously found to play a role in bone marrow failure disorders. The current study, which appeared in the journal <u>Blood</u>, adds ACD to the list, the first time the gene has been shown to have a disease-causing role.

Chromosome Deletion Linked to Language Delay

Children born with a DNA abnormality on chromosome 16, which already has been linked to neurodevelopmental problems, show measurable delays in processing sound and language, according to a team of radiologists and psychologists led by an expert from <u>The Children's Hospital of Philadelphia</u>.

"This <u>study</u> shows an important connection between gene differences and differences in neurophysiology," said the study's leader, <u>Timothy P.L. Roberts, PhD</u>, vice chair of <u>Radiology</u> Research at CHOP and a researcher at CHOP's <u>Center for Autism Research</u>. Dr. Roberts is also a professor of Radiology at the <u>Perelman School of Medicine at the University of Pennsylvania</u>.

The researchers examined 115 children with some neurological or learning disabilities who had copy number variants — either deletions or duplications of DNA — at the genetic site 16p11.2. Previous researchers had found that this location on chromosome 16 was associated with a subset of autism spectrum disorders (ASDs) and with language impairments and developmental delays.

The researchers used magnetoencephalography (MEG), which detects magnetic fields in the brain, just as electroencephalography (EEG) detects electrical fields. As each child heard a series of tones, the MEG machine analyzed changing magnetic fields in the child's brain, measuring an auditory processing delay called the M100 response latency.

In children with the deletion, the researchers found a significant delay: 23 milliseconds, about one-fortieth of a second, a figure that Dr. Roberts called "stunningly high" compared to the healthy children. There was no such delay among children with the duplication, who actually had a non-significant tendency to process sounds faster than the control subjects.

Because the severity of neurodevelopmental symptoms did not correlate with the length of the auditory processing delay, the M100 delay may not become a clear-cut diagnostic biomarker in neurological disorders, but it may be a clue to an important common pathway in neurobiology, Dr. Roberts said. Further studies will investigate other genes previously implicated ASDs and other psychiatric disorders, to determine whether they also involve M100 response delays.

"Our goal is to unify diverse genes along a few common pathways, some of which may be treatable with specific therapies," Dr. Roberts said.

Antipsychotics May Increase Diabetes Risk in Children

Initiating antipsychotics may elevate a child's risk not only for significant weight gain, but also for Type II diabetes by nearly 50 percent, according to a study conducted by researchers from <u>PolicyLab</u> at <u>The</u> <u>Children's Hospital of Philadelphia</u>.

Moreover, among children who are also receiving antidepressants, the risk may double. Previous PolicyLab research showed that one in three youth receiving antidepressants in the Medicaid program were receiving an antipsychotic at the same time.

"These new findings should give us pause," wrote PolicyLab Director <u>David Rubin, MD, MSCE</u>, in a <u>blog post about the study</u>. "With such vast numbers of children being exposed to these medications, the implications for potential long-lasting harm can be jarring." Dr Rubin is also a professor of Pediatrics at the <u>Perelman School of Medicine at the University of Pennsylvania</u>.

Traditionally, antipsychotics have been narrowly prescribed to children with a diagnosis of schizophrenia or bipolar disorder, or to those with significant developmental delays who were displaying aggressive behaviors that were potentially injurious to themselves or others.

In recent years, however, antipsychotics are increasingly being prescribed in the absence of strong supporting safety and efficacy data to treat healthier children and adolescents with disruptive behaviors, such as those who are diagnosed with <u>attention-deficit/hyperactivity disorder</u>. Despite the number of children being exposed to antipsychotics, the researchers remain cautious about over-reacting to these findings.

"We need to incorporate these new revelations about the risk for diabetes into a more thoughtful consideration of the true risks and benefits of prescribing an antipsychotic to a child," Dr. Rubin said. "Yes, we should try, by all means possible, to minimize the numbers of children and adolescents exposed to these powerful medications. But for some children in immediate crisis, we must also concede that the benefit of the antipsychotic for acute management may still outweigh the risk."

The study's authors recommend that clinicians and families who are making medication decisions periodically revisit the treatment strategy to address challenging behaviors. For example, when planning to prescribe antipsychotics to a child, professional organizations recommend beginning cautiously with the lowest dose possible, while strictly monitoring for early evidence of weight gain or abnormal lab tests that often predict later onset of diabetes.

The study's results appeared in JAMA Pediatrics.

Prevention Strategies Cut Monthly Infection Rate in Half

Catheter-associated urinary tract infections (CAUTIs) have received national attention as a highpriority, preventable hospital-acquired condition because they are common and costly. Yet, most of the research on CAUTI epidemiology and evidence-based prevention guidelines focused on adults, until the multidisciplinary "Prevent CAUTI" team at <u>The Children's Hospital of Philadelphia</u> published an observational study in <u>Pediatrics</u> that established a plan to reduce the infection in a pediatric setting.

In July 2010, the team initiated a bundle of quality-improvement practices that focused on placing indwelling urinary catheters only when indicated, using sterile techniques at all points of care, and reviewing catheter necessity daily. A crucial part of the intervention was institution-wide training on proper urinary catheter insertion technique and maintenance practices. In all, about 1,500 clinicians over a three-month period received training on the CAUTI prevention bundle.

"It was an incredible example of multidisciplinary work," said <u>Katherine Finn Davis, PhD, RN, CPNP</u>, a nurse researcher for CHOP's Center for Pediatric Nursing Research and Evidence-Based Practice who helped to lead the CAUTI team. "People from different aspects of the clinical world drew on their strengths and worked together toward a common goal to get our rate down."

Dr. Davis and her colleagues conducted a retrospective, observational analysis that compared CHOP's hospital-wide CAUTI rates before and after implementation of the quality improvement project. Using data from July 2009 to June 2012, they found that the multifaceted intervention was associated with a 50 percent reduction in the hospital's monthly CAUTI rate.

"That reduction was impressive," Dr. Davis said. "After analysis, we also determined that the children getting catheters were still the right kids — everyone had an indication. The usage rate of catheters did not decrease during that time period, but we were using them appropriately."

In addition to understanding better which children are at risk for CAUTIs, Dr. Davis said the study is important because it is one of the first to provide information to healthcare institutions on how to prevent CAUTIs from a pediatric perspective. Other pediatric institutions can assess their CAUTI rates and then use CHOP's tools to implement similar CAUTI prevention bundles.

Gene Crucial to Immune Defense Revealed

Researchers suspect that mutations in the genes associated with <u>common variable immunodeficiency</u> (CVID) result in a shortage of antibodies that leaves the body <u>vulnerable to infections</u> from bacteria and viruses. Children with CVID experience recurrent respiratory infections that can lead to chronic lung disease, and they also may have joint inflammation, stomach and bowel disorders, and a higher risk of cancers.

A study team from the <u>Center for Applied Genomics</u> (CAG) at <u>The Children's Hospital of Philadelphia</u> performed an association analysis that focused on immune-related genes in a cohort of 360 CVID patients and 21,610 healthy controls. They compared regions of the genome using a genotyping chip specialized to search for gene variants previously implicated in autoimmune and inflammatory diseases.

The researchers found 11 single <u>nucleotide polymorphisms</u> (SNPs) associated with CVID on the 16p11.2 locus of chromosome 16. SNPs are changes in a single DNA building block (A, T, C, or G), compared to the more typical sequence in a certain stretch of DNA. Of particular interest, the study team found variants in the gene <u>ITGAM</u>, which carries codes for an integrin protein that regulates cellular contact and adhesion.

"This association is of high biological relevance because *ITGAM* plays an important role in normal immune responses," said <u>Hakon Hakonarson, MD, PhD</u>, director of the CAG, who led the study team. "Other researchers have shown that mice in which this gene has been knocked out have immune deficiencies."

The new findings may promote better understanding of *ITGAM's* functional role and eventually lead to targeted therapies for patients with CVID. Dr. Hakonarson added that the research, published in the *Journal of Allergy and Clinical Immunology*, may have broader implications for other patients who do not have these novel gene variants because the integrin protein affects many important pathways in immune function.

NTRK3 Gene Mutation Could Contribute to Heart Defects

<u>One in 125 babies</u> in the U.S. is not born with a perfect heart. For example, a heart defect called <u>ventricular septal defect</u> (VSD) involves an opening in the dividing wall between the two lower chambers of the heart. The hole allows an extra volume of blood to be pumped into the lungs, creating increased pressure, stress, and congestion.

At <u>The Children's Hospital of Philadelphia</u>, investigators reported that mutations in the gene <u>NTRK3</u> may be involved in the development of VSDs. *NTRK3* regulates cell survival and encodes a protein called neurotrophic tyrosine kinase receptor C (TrkC).

"We picked *NTRK3* as a candidate gene because deletion of this gene in mice will result in heart defects, and we had identified a patient with a VSD that had a large deletion encompassing *NTRK3*," said Petra Werner, DVM, PhD, a senior research associate in the laboratory of <u>Elizabeth Goldmuntz, MD</u>, professor of pediatrics in the <u>Division of Cardiology</u>.

In an article published in <u>Human Mutation</u>, Dr. Werner and colleagues described how they screened 467 patients with related heart defects for *NTRK3* mutations. They identified four of those patients with VSDs who had a <u>missense mutation</u>, which means an amino acid substitution occurred in the TrkC protein made by the gene that may modify how it works.

Next, the study team conducted experiments to see if the mutated TrkC lost any function. As a receptor, TrkC sits on cells' membranes and waits for a signal from its ligand, a protein called neurotrophin-3 (NT-3). The results showed that one of the mutations significantly reduced TrkC's ability to respond to the ligand, and subsequently TrkC failed to activate essential downstream signaling pathways. In addition, the investigators found that cells expressing mutant TrkC showed altered cell growth.

Dr. Werner and her colleagues hypothesize that if TrkC's function is impaired and allows the wrong heart cells to differentiate and migrate, then flaws could occur during the rapid remodeling of embryonic heart development.

"They may end up in the wrong location in the heart and be missed in other locations, resulting in malformations or holes," Dr. Werner said. "But much more research must be done before we fully understand all of TrkC's functions."



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Game Teaches Coping Skills to Kids Exposed to Irauma

"Mwa-ha-ha-haaaa!" laughs General Malaise, a character in a game-like, online tool under development called "Coping Coach" designed to be played by school-age children who have experienced a traumatic event. The web-based intervention is based on areas that researchers at <u>The Children's Hospital of</u> <u>Philadelphia</u> and others have shown to be important in lowering the severity of pediatric <u>post-traumatic stress</u>.

These include teaching children to recognize helpful or unhelpful thoughts and behaviors and how not to rely on avoidance as a coping response. For example, General Malaise goes on to zap the town, leaving the townspeople without any feelings, and then the player must identify different emotions in order to advance to the next module.

"Each module includes carefully selected intervention targets based in empirical evidence on how posttraumatic stress develops in children," said <u>Meghan Marsac, PhD</u>, a CHOP psychologist at the <u>Center</u> <u>for Injury Research and Prevention</u> (CIRP) and research assistant professor at the Perelman School of Medicine at the University of Pennsylvania, who has co-led the development and evaluation of Coping Coach. "We have applied what we know about the treatment of post-traumatic stress to prevention."

A study team tested Coping Coach's feasibility in a randomized controlled trial of 72 children ages 8 to 12 who had been admitted to the hospital for an acute medical event. They invited one group of children to log in and play the game within six weeks after being admitted to the hospital. A second group was assigned to a wait list and given the same instructions to complete the online activities at 12 weeks.

Both groups completed research assessments over the phone at six, 12, and 18 weeks so that the researchers could track their symptoms and coping skills over time. They concluded that both groups benefited from Coping Coach participation, which suggests its recommended timing can be flexible. The investigators reported their results in the *Journal of Pediatric Psychology*.

The next step is to test Coping Coach in a bigger trial, said <u>Nancy Kassam-Adams, PhD</u>, a CHOP psychologist and associate director of Behavioral Research at CIRP, who was the lead author of the study. Once the researchers have enough data to validate Coping Coach's effectiveness, she anticipates that it could be publicly available within the next five years. Since the number of school-age children who could benefit from a low-cost, web-based post-traumatic stress intervention is enormous, she envisions Coping Coach as a way to fill the gap in resources available to support them during their recovery.

"It's a different way of engaging kids," Dr. Kassam-Adams said. "We've worked hard to build in items that are useful and therapeutic while keeping it fun. It doesn't substitute for full-blown mental health treatment. This is for the early days after they've been through something difficult, and it teaches kids skills to recover well."

Researchers Expand Evidence for Reprogrammed T Cell Therapy

Since the <u>news broke</u> of the first pediatric patient receiving an investigational immune cell therapy at <u>The Children's Hospital of Philadelphia</u> in 2012, for leukemia that had relapsed twice after conventional treatments, the researchers continue to learn more from each clinical study participant who undergoes <u>CTL019</u> treatment.

The investigational approach developed by a team at CHOP and the <u>University of Pennsylvania</u> is a personalized cell therapy that reprograms a patient's own immune system to fight specific types of cancer cells. At the heart of the therapy are bioengineered T cells called <u>CTL019</u> cells that potentially seek and destroy B-cells, including tumor cells, that express the antigen CD19, a protein essential to cell processes that appears on the cells' surface.

"Our results show that these engineered cells greatly expand in patients, producing complete response rates over 90 percent," said study leader <u>Stephan A. Grupp, MD, PhD</u>, a pediatric oncologist at CHOP and professor of Pediatrics at the <u>Perelman School of Medicine</u> at the University of Pennsylvania. "Just as important, the cells are persisting in patients, potentially allowing for long-term disease control."

The Food and Drug Administration designated the CTL019 approach as a <u>Breakthrough Therapy</u> in July 2014. It is the first personalized cellular therapy under development for the treatment of cancer to receive this important classification, which helps to expedite its progress into broader clinical trials.

Multi-site <u>Phase II clinical trials</u> in pediatric <u>acute lymphoblastic leukemia</u> (ALL) are already underway to test this experimental cell therapy in more patients in several hospitals around the world, including CHOP. The trials are sponsored by Novartis Pharmaceuticals, which acquired exclusive rights to CTL019 from Penn in 2012.

Most recently, at the annual meeting of the American Society of Hematology in December 2015, the CHOP/Penn team reported that 55 of 59 children (93 percent) who received the treatment at CHOP experienced a complete remission. They reported that 18 patients had continuous remissions for more than one year, and nine patients for more than two years. At one year, 79 percent of these children with highly resistant ALL were still surviving.

"As we follow these patients for longer periods, we are seeing some patients stay in remission without further therapy," said <u>Shannon Maude, MD, PhD</u>, a pediatric oncologist at CHOP and an assistant professor of Pediatrics at Penn. "We are continuing to learn about this therapy, and from this, hope to continue to improve."

Most (88 percent) of the patients developed cytokine-release syndrome, a systemic inflammatory response ranging from mild forms, which may include fever and muscle aches, to severe forms, which may be life-threatening. A subset of patients experienced neurologic toxic effects ranging from delirium accompanying high temperature to global encephalopathy with additional symptoms, with these effects lasting over two to three days and fully resolved in all patients.

The CHOP study team had reported similar results in October 2014 in the <u>New England Journal of</u> <u>Medicine</u>.

"The patients who participated in these trials had relapsed as many as four times, including 60 percent whose cancers came back even after stem cell transplants," Dr. Grupp said. "The durable responses we have observed with CTL019 therapy are unprecedented."

Financial support for cell therapy research is helping to get new studies on line, including a \$100,000 gift over the winter from <u>Curing Kids Cancer</u> to support cell therapy directed at an alternative target (CD22) in ALL, as well as a grant from <u>Solving Kids Cancer</u> to support cell therapy treatments for neuroblastoma.

"Support like this allows us to test these new treatments in kids, who are often at the back of the line for new cancer therapies," Dr. Grupp said. "Given that drug companies usually target the adult market, it's amazing that Novartis is planning to go for FDA approval in pediatric ALL."

Ongoing research is vital because many questions remain unanswered, and the treatment is not yet proven.

"It's so important to understand that, while we know so much more than we did starting out three years ago, this is still a limited group of patients," Dr. Grupp said, adding that it is not yet known whether CTL019 represents a long-term solution or cure for the disease.



Discovery is in the air. New matchmaking approaches to explore genomic data are an alluring way for physician scientists to find connections, start conversations, and launch beautiful breakthroughs.

A curious researcher contemplating a seemingly unsolvable patient case can reach out to another investigator on the opposite side of the world studying a patient with a similar genetic makeup. Working together, in a matter of minutes they can pinpoint the genetic mutations that may explain the rare disease that their patients have in common.

"It is an important, new way of thinking about collaborative science and reaching beyond your own research studies to deepen your understanding," said <u>Marni Falk, MD</u>, an attending physician and director of the <u>Mitochondrial-Genetic Disease Clinic</u> at <u>The Children's Hospital of Philadelphia</u>.

Dr. Falk helped form the <u>Mitochondrial Disease Sequence Data Resource</u> (MSeqDR), a secure webbased portal that pools genomic information and is integrated with a real-time data analysis engine called <u>GENESIS</u>. The technologies' user-driven data sharing capabilities enable scientists anywhere to gain novel insights into genes, variants, and phenotypes.

A researcher can submit a patient's sequence data information — from a solitary gene to an entire genome — and then they can query it within the systems' intuitive tools and shared databases, Dr. Falk explained. It lets investigators directly ask clinically meaningful questions: Show me mutations that are new in this person. Show me ones that they got from their mother. Show me ones that are in this particular biological pathway.

"The interface is so straightforward that it's like clicking on Google as opposed to typing computer code," Dr. Falk said. "Everything is provided in an interactive format so that the investigator can analyze their patient's data by herself."

Next-generation sequencing has evolved so rapidly that researchers have an unprecedented and vast amount of genomic information to comb through. For example, scientists who study mitochondrial diseases have identified more than 1,000 genes that are involved with making proteins that work in the mitochondria. Plus, mitochondria have their own DNA that also harbors disease-causing mutations. Subsequently, hundreds of genetic causes already have been implicated in <u>mitochondrial diseases</u>.

"It is a very computationally heavy field," Dr. Falk said. "Most of the clinical world and the research world do not have the bioinformatics capabilities to facilely manipulate, explore, and share the data necessary to make new discoveries."

That is why robust genomic data resources that are secure, user-friendly, quick, and economical — MSeqDR and GENESIS are free to academic users — are essential for accurate sequence variant annotation, analysis, sharing, and interpretation. Dr. Falk has led seminars across the globe, including in Japan, Spain, Finland, and Italy, to train clinicians and researchers alike on how to use these tools to curate and analyze genomic data without needing to rely on a bioinformatician. She was the organizer and co-leader of MSeqDR's development since it began as a grassroots effort in 2012 facilitated by the United Mitochondrial Disease Foundation, the North American Mitochondrial Disease Consortium, and the National Institutes of Health.

As the MSeqDR project gained momentum in the mitochondrial disease research community, Dr. Falk and colleagues began working in 2013 with the creators of GENESIS, including <u>Stephan Zuchner</u>, <u>MD, PhD</u>, chair of Genetics at the University of Miami Miller School of Medicine, to expand and integrate the collaborative analysis tools. Originally called GEM.app, GENESIS' initial purpose was to interrogate genomic sequencing data related to neurologic disease. Since many patients with suspected mitochondrial disorders have neurological manifestations, the two initiatives meshed handsomely.

In articles published in the journals <u>Molecular Genetics and Metabolism</u> and <u>Human Mutation</u>, Dr. Falk and her co-authors describe the projects and how their efforts have grown beyond mitochondrial and neurological diseases. GENESIS has about 600 registered users from 44 countries. So far they have revealed more than 70 novel gene disorders.

Even if a patient's mutation is found to be in a gene already known to cause disease, tools like this enable researchers to prove a correct diagnosis and better understand the disease scope or range of severity. For clinicians, directly probing their patients' genomic data over time could help to determine the best drug to prescribe a patient if he has a genetic variance that could slow down or speed up his drug metabolism.

"This type of resource takes advantage of vast number of whole-exome and whole-genome datasets that are being generated to harness their power for gene discovery, better understanding of the disease, and better understanding and treatment of the patient," Dr. Falk said.

After meeting with a patient one afternoon, Dr. Falk logged into MSeqDR and GENESIS to trace a genetic variant that seemed to be running through the family. Genetic sequencing had suggested that her patient had two variants of unknown significance within one gene. She suspected these variants were the cause of an inherited disease, but she could not be certain because genetic samples from the patients' parents were not available.

Dr. Falk looked in the databases and found two other people who each had these same two variants. She contacted the investigator who had input their data, and was speaking to him by telephone the next day. It turned out the cases were a father and daughter who each were affected with an undiagnosed medical condition that was identical to that of Dr. Falk's patient.

The other researcher was not aware that the patients had variants in this gene and was extremely grateful to know this information. Now, he had a diagnosis for that family, and Dr. Falk knew that she probably had in hand the right diagnosis for her patient and did not have to look any further.

"All the time now, we're solving complex cases," Dr. Falk said. "New gene disorders are being discovered literally every day. It is awesome. There has never before been anything like this resource for scientific investigators."

Graphene Microelectrodes Give Dynamic Look at Seizures

One of the most common disorders of the nervous system, <u>epilepsy</u> affects 2.7 million Americans of all ages, races, and ethnic backgrounds. An epileptic seizure takes place when spontaneous high-frequency bursting of neural networks temporarily interrupts normal electrical brain function. Pinpointing those neurons' locations and plotting the intensity of their activity in real time has been difficult for researchers.

An <u>electroencephalogram</u> (EEG), which is a recording of brain activity, traditionally requires metal electrodes that cause interference when used in conjunction with sophisticated, multicellular <u>calcium</u> <u>imaging techniques</u> that investigators couple with high-speed microscopes to see and record when neurons are firing. Neuroscience researcher <u>Hajime Takano, PhD</u>, who works in <u>Douglas Coulter, PhD's</u> epilepsy research laboratory at <u>The Children's Hospital of Philadelphia</u>, collaborated with researchers from the University of Pennsylvania's <u>School of Engineering</u> to test a new type of transparent, flexible microelectrode that they developed to solve this problem.

"The idea of applying this technology to basic neuroscience for brain recording is something new and very exciting," said Dr. Takano, who also has an engineering background and is a research assistant professor in the <u>Neurology Department</u> at the <u>Perelman School of Medicine</u> at the University of Pennsylvania.

It is made of the strongest material known to man: graphene, a two-dimensional form of carbon only one atom thick. Because it is see-through, the graphene microelectrode allows for simultaneous optical imaging and electrophysiological recordings of neural circuits that can provide valuable information on individual cells, while at the same time probing the regions that they may span.

In a study published in Nature Communications, Dr. Takano; senior author <u>Brian Litt, PhD</u>; Penn Engineering postdoc <u>Duygu Kuzum, PhD</u>; and colleagues described how they were able to use the graphene microelectrode technology in combination with calcium imaging involving confocal and two-photon microscopy to observe seizure-like activity that they induced in neural tissue from rats. The investigators were able to obtain both high spatial and temporal resolution, which is the ability to discriminate between two points in space and time.

"By monitoring a seizure with the transparent electrodes and imaging individual neurons at the same time, we can try to pinpoint where a seizure started," Dr. Takano said. "If there are repeated seizures, we can see if the seizure-initiating cell is always the same or not. And if there is an initiating cell, what is different about it?"

Development of the transparent microelectrode technology involved a multidisciplinary effort from Penn's new Center for NeuroEngineering and Therapeutics, Penn's departments of <u>Neuroscience</u>, <u>Pediatrics</u>, and <u>Materials Science</u>, and the <u>Division of Neurology</u> at CHOP.



How important are communication methods for the families of children being treated for <u>attention-deficit/</u><u>hyperactivity disorder</u> (ADHD)? Investigators at <u>The Children's Hospital of Philadelphia</u> intend to find out.

Parents of children with ADHD are key decision makers regarding their treatment plans, but families may not know how to express their preferences and goals to physicians. Researchers at CHOP received a <u>\$2.1 million award</u> from the <u>Patient-Centered Outcomes Research Institute</u> (PCORI) to test how an electronic portal could be used to facilitate family participation in shared clinical decision-making.

ADHD occurs in 5 to 8 percent of school-age children, and they often have difficulties at school and home due to a short attention span, impulsivity, and/or hyperactivity. Stimulant or non-stimulant medication and behavior management training are ADHD treatments that parents often seem reluctant to discuss with physicians or to communicate any concerns about safety and efficacy.

<u>Alexander G. Fiks, MD, MSCE</u>, a co-investigator on the PCORI project, has been developing the electronic ADHD portal based on a questionnaire called the <u>ADHD Preferences and Goals Instrument</u> created by CHOP's <u>PolicyLab</u>. The patient engagement tool is intended to be used in a primary care setting to help doctors and families work together to choose effective, culturally sensitive treatment plans for ADHD that are acceptable to each family and result in improved treatment outcomes. Dr. Fiks is a PolicyLab faculty member, an urban primary care pediatrician at CHOP, and an assistant professor of Pediatrics at the <u>Perelman School of Medicine at the University of Pennsylvania</u>.

<u>James Guevara, MD, MPH</u>, an attending physician at CHOP, will lead the study, which will be conducted in 15 primary care facilities across <u>Children's Hospital's Care Network</u>. The study team plans to assess the effectiveness of the ADHD portal versus the ADHD portal in combination with a care manager in communicating patients' and families' treatment goals. The researchers expect to enroll roughly 300 children between the ages of 5 to 12 years, who will be randomized to one of the two groups. Parents will complete ADHD outcome measures at zero, three, six, and nine months.

Dr. Guevara and colleagues also plan on using feedback to improve the study. They will ask various stakeholders — including clinicians, parents, and teachers of children with ADHD — to advise the research team on study questions, the investigation's design, and how the results are disseminated.

"Findings from this study will inform the use of communication strategies to share family preferences and goals among parents, teachers, and clinicians of children with ADHD," said Dr. Guevara, who also is an associate professor of Pediatrics and Epidemiology at Penn, and a founding member of PolicyLab.

Established by 2010's Affordable Care Act, PCORI funds comparative effectiveness research, with an eye toward improving "the quality and relevance of evidence available to help patients, caregivers, clinicians, employers, insurers, and policy makers make informed health decisions," according to the PCORI website.

Tech Transfer By the Numbers

58 Disclosures Received

U.S. Patent Applications Filed (Provisional)



(15

U.S. Patent Applications Filed (Utility and Nationalized PCT)



U.S. Patents Issued To CHOP

International Patent Applications Filed (PCT and Foreign)

International Patents Issued



United States Patent No. 8,846,632

Linda B. Couto

Nucleic Acids for Targeting Multiple Regions of the HCV Genome Compositions and methods effective for modulating Hepatitis C viral infection are provided.

United States Patent No. 8,816,054

Valder Arruda; Rodney Camire; Nicholas Iacobelli

Compositions and Methods for Enhancing Coagulation Factor VIII Function Factor VIII variants and methods of use thereof are disclosed.

United States Patent No. 8,889,742

Peter Gruber

Use of HDAC and/or DNMT Inhibitors for Treatment of Ischemic Injury

The present invention provides methods of ameliorating or reducing the extent of ischemic injury, reperfusion injury, and myocardial infarction, by administering an inhibitor of histone deacetylase enzyme (HDAC) or an inhibitor of DNA methyltransferase enzyme (DNMT).

United States Patent No. 8,999,322

Sriram Krishnaswamy

Compositions and Methods for Modulating Hemostasis

Novel thrombin/prothrombin protease/zymogen variants which have anticoagulation activity and methods of use thereof are disclosed.

United States Patent No. 8,852,879

Harry Ischiropoulos

Materials and Methods for the Detection of Nitrated Fibrinogen

Compositions are disclosed for detecting a patient's risk for coronary artery disease. The compositions can determine the presence of nitrated fibrinogen which is linked with coronary artery disease. Kits for the detection of coronary artery disease are also provided.



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DEDICATION >

Philadelphia, Israeli Team Refining Cardiac Devices

The future of medical devices that correct heart problems in infants and children lies in Philadelphia and Israel. At least, that's the goal of a new, groundbreaking research agreement.

Philadelphia's former Mayor Michael A. Nutter and Jerusalem's Mayor Nir Barkat witnessed the signing of a research collaboration among <u>The Children's Hospital of Philadelphia</u>, Drexel University and <u>The Hebrew University of Jerusalem</u>. The initiative will explore ways to improve problematic medical devices for infants and children with heart defects and congenital heart disease (CHD).

The agreement, signed in Jerusalem by former CHOP CEO Steven M. Altschuler, MD, Drexel President John A. Fry, and The Hebrew University of Jerusalem President Menahem Ben-Sasson in November 2014, established a research consortium and the creation of two interdisciplinary "dream teams" of investigators. The three institutions are contributing \$250,000 over two years to each team, demonstrating their entrepreneurial spirit and commitment to the collaboration. Outside investors interested in the commercial viability of advancing pediatric translational research are also being recruited.

One "dream team" is based at CHOP and is conducting a research project entitled "Pediatric Transcatheter Valve Replacements: Preventing Device Failure Due to Structural Degeneration." The team, led by CHOP's <u>Robert J. Levy, MD</u>, is focusing on <u>Tetralogy of Fallot</u> (TOF), a rare condition caused by the combination of four heart defects. Infants with TOF are known as "blue babies" because their blood doesn't contain enough oxygen as a result of the cardiac defects.

Repairing TOF requires cardiac surgery early in life, but the procedure leaves the young patients with a chronic malfunction of their pulmonary valve. Currently, the best option to treat the malfunction is transcatheter pulmonary valve (TPV) therapy, in which an artificial heart valve is implanted to replace the defective one. Unfortunately, CHOP researchers have found that the device is prone to oxidative damage and structural failure.

The team is charged with gaining a better understanding of what causes the oxidative and structural damage, as well as what's behind the early inflammatory responses to the TPV. The researchers hope to use their findings to modify the TPV material with an antioxidant to prevent damage.

Joining Dr. Levy, who is also a professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania, are Matthew Gillespie, MD, of CHOP and Joseph H. Gorman, MD, and Robert C. Gorman, MD, of the University of Pennsylvania. Also on the team are Kenneth Barbee, PhD, and Kara Spiller, PhD, of Drexel, and Gershon Golomb of The Hebrew University.

Consortium Links Mutated Genes to Severe Epilepsy

The largest collaborative study to date on the genetic roots of childhood epilepsies is bringing new hope to sufferers of the most severe forms of the central nervous system disorder. An international team of researchers, including pediatric neurologist <u>Dennis Dlugos, MD</u>, director of the <u>Pediatric Regional</u> <u>Epilepsy Program</u> at <u>The Children's Hospital of Philadelphia</u>, and a professor of Neurology at the Perelman School of Medicine at the University of Pennsylvania, have identified specific gene mutations that cause difficult-to-treat forms of epilepsy.

"This research represents a paradigm shift in epilepsy research, giving us a new target on which to focus treatment strategies," Dr. Dlugos said. "There is tremendous potential for new drug development and personalized treatment strategies, which is our task for the years to come."

For many patients with severe epilepsies, the cause of the seizures cannot be identified but increasing evidence indicates that genetic factors may play a role. Epilepsies affect up to 3 million patients in the U.S. and up to one-third of all epilepsies are resistant to treatment with antiepileptic medication.

In a study released in November 2014 and reported in <u>*The American Journal of Human Genetics,*</u> researchers identified gene mutations associated with severe epilepsy syndromes called epileptic encephalopathies, which disrupt functioning in the brain's synapses, the junctions at which nerve cells communicate with one another. The research team pinpointed the gene mutations by sequencing the exomes contained in the human genomes of 356 patients with severe childhood epilepsies as well as the exomes of their parents. An exome is made up of the human genome's exons, which are the coding parts of the genes.

Using family-based exome sequencing, the researchers identified 429 mutations that appeared in affected children, but not in their parents. Such mutations are called "*de novo*" mutations. It's important to note that, while *de novo* changes are increasingly recognized as the genetic cause for severe seizure disorders, not all *de novo* changes necessarily cause disease.

Perhaps the most surprising and promising finding, researchers discovered that a mutated version of a gene called *DNM1* present in five of the patients had a clear connection to the way the patients' synapses functioned. This finding, said Dr. Dlugos, provides important information about the functional roles of the genes that were identified. "We knew that synaptic genes were important but not to this extent," he noted.

Multiple researchers from the U.S. and Europe participated in the project. Two international research consortia collaborated on the study: the Epi4K/EPGP Consortium, funded by the <u>National Institute of Neurological Disorders and Stroke</u>, and the <u>European EuroEPINOMICS consortium</u>.

Access to Groundbreaking HLA Genotyping Tool Expands

<u>The Children's Hospital of Philadelphia</u> has become the first hospital in the world to offer human leukocyte antigen (HLA) genotyping, an advanced research tool with the potential to change how immunological and infectious diseases are treated. CHOP is making the test available through a new partnership with <u>ARUP</u> <u>Laboratories</u> of Salt Lake City, Utah, which will provide HLA testing using next-generation sequencing (NGS) methods to its customers.

In February 2014, CHOP researchers announced the development of a unique laboratory test to characterize the genes that encode HLA molecules. HLAs are complex, highly variable proteins on the surfaces of cells that are essential to immune function. HLA genes are the most complex gene family in the entire human genome, which presented challenges for previous testing methods.

The new procedure provides a cutting-edge tool for research in immunological diseases, infectious diseases, and pharmacogenomics, and may help improve transplantation. ARUP, a nonprofit enterprise of the University of Utah's Department of Pathology, will use the test to help aid decisions in bone marrow transplantation. ARUP offers more than 3,000 tests and test combinations, ranging from routine screening tests to highly esoteric molecular and genetic assays," according to its website.

HLA genotyping "addresses a 60-year old problem," said <u>Dimitri S. Monos, PhD</u>, director of CHOP's Immunogenetics Laboratory and professor of Pathology and Laboratory Medicine at the Perelman School_ of Medicine at the University of Pennsylvania. Since the discovery of HLAs in the early 1950s, it has been a challenge to accurately and thoroughly characterize HLA gene sequences. We have now used NGS tools to significantly advance HLA genotyping. This is the first technology that gives results free of any current or future ambiguities.

<u>Robert W. Doms, MD, PhD</u>, CHOP's pathologist-in-chief, who is also a professor of Pathology and Laboratory Medicine at Penn, added, "We are pleased to be able to provide this test to ARUP Laboratories' customers. It allows us to provide greater access to our tests."

Registry for Pediatric Pulmonary Hypertension Underway

Adults of all ages suffer from pulmonary hypertension (PH), a serious condition that results from high blood pressure in the arteries of the lungs. Over time, the pulmonary arteries narrow, making the right side of the heart work harder. PH also complicates a number of different disease processes, including congenital heart disease, chronic lung disease of prematurity, and genetic disorders. In other cases, the cause of PH may be unknown.

PH doesn't sound like a condition that would affect children. Indeed, PH is a relatively rare problem in pediatrics, but the frequency of the diagnosis in children and PH-related hospitalizations is actually rising. <u>The Children's Hospital of Philadelphia's pulmonary hypertension program</u> follows more than 650 children and adolescents with PH.

Unfortunately, there is currently no cure or FDA-approved therapy for pediatric PH. However, a grant from the <u>National Heart, Lung, and Blood Institute</u> in April 2015 positions CHOP at the forefront of efforts to advance pediatric PH research and change the future for children with PH and their families.

CHOP is one of nine pediatric centers, all members of the <u>Pediatric Pulmonary Hypertension Network</u> (PPHNet), to receive the grant in order to build a much-needed informatics registry of children with PH. The grant's purpose is significant because many of the current care practices for children with PH are based on findings from adult studies. For example, clinicians do not know if a 13-year-old whose PH stems from a genetic mutation and starts medicines earlier than a 35-year-old with the exact same genetic mutation will have a longer, better life, noted Brian Hanna, MDCM, PhD, the director of CHOP's pulmonary hypertension program.

"We still have more questions than answers," said <u>Rachel Hopper, MD</u>, an attending cardiologist in pulmonary hypertension at the <u>CHOP Cardiac Center</u> and assistant professor of Pediatrics at the <u>Perelman School of Medicine at the University of Pennsylvania</u>. "Who gets pulmonary hypertension? Why do they get pulmonary hypertension? Why do some children with hypertension improve over time, while others will end up needing a lung transplant? We need to collaborate as practitioners to pool enough data to answer those questions."

On its own, an individual pediatric PH center would not be able to gather information for a large enough number of children with PH. But the PPHNet registry will provide a shared infrastructure and standardized data collection in a single resource so that investigators can evaluate specific outcomes for a group of patients who share the same condition. For example, the PPHNet registry could help researchers determine the response of children with PH to certain therapies.

The grant project will also address concerns that registries tend to be expensive to run because they require diligent maintenance to ensure that the data is precisely collected and valid for research. The PPHNet project will explore if it is possible to obtain the same type of data using computer software to scour electronic health records. Researchers will compare the value of both the software and traditional methods and determine whether the data generated produces the same results.

As they figure out the most efficient and accurate way to collect and store registry information about children with PH, researchers also hope to gain important insights into the causes, clinical course, and diagnostic approaches to the diverse conditions associated with PH that will lead to better treatment.

"The concept of pooling and precisely phenotyping children is going to make a huge difference," said Dr. Hanna, who is also a clinical professor of Pediatrics at the <u>Perelman School of Medicine at the University</u> <u>of Pennsylvania</u>. "A key thing is that we eventually will be able to make diagnoses and conduct research protocols all the same way. We'll be able to advance the science faster and understand it better, so that we'll be to answer questions about pediatric pulmonary hypertension."

CHOP, Temple Research to Destroy HIV in Brain Cells

Why has the human immunodeficiency virus (HIV) that causes AIDS been so difficult to eradicate?

Researchers from <u>The Children's Hospital of Philadelphia</u> and <u>Temple University</u> want to help solve that puzzle by exploring potential methods to boost the immune system's ability to attack HIV infection. Specifically, they are focusing on new ways to destroy HIV that lingers in brain cells despite conventional antiviral treatment.

CHOP and Temple received a \$4.3 million, four-year NeuroAIDS grant from the National Institute of Mental Health (NIMH) in October 2014 to explore different biological pathways that make HIV so tenacious. The two institutions are collaborating with the Penn Mental Health AIDS Research Center at Penn Medicine and CHOP, and Temple's Comprehensive NeuroAIDS Center — two centers focused on mental health and HIV that are supported by the National Institutes of Health.

The co-principal investigators of the grant are <u>Steven D. Douglas, MD</u>, chief of the Section of Immunology at CHOP and a professor of Pediatrics at the University of Pennsylvania, and Jay Rappaport, PhD, professor of Neuroscience and Neurovirology at the Temple University School of Medicine. They are overseeing three separate research projects focusing on HIV that remains in brain cells after antiviral treatments.

The first project, led by Dr. Rappaport, focuses on the metabolism of ATP, which is the chemical that serves as energy currency in cells. Because HIV infection stimulates enzymes that break down ATP and weaken the body's immune responses, Dr. Rappaport's research team is studying drugs that may inhibit those enzymes.

The second project, led by Tracy Fischer-Smith, PhD, assistant professor of Neuroscience and Neurovirology at Temple, is studying immune polarization, in which cells called macrophages stop playing a protective role and start immunity-suppressing activities. The research team is concentrating on the "signaling proteins" that drive immune polarization, with the goal of counteracting those proteins' disruptive signals in order to restore infection-fighting functions to immune cells.

The third project, led by Dr. Douglas, looks at "substance P," a neuropeptide that plays a key role in stimulating inflammation during HIV infection. Dr. Douglas' team hopes to prevent the virus from entering cell reservoirs by manipulating a cell receptor known as NK-1R that binds to substance P, thereby blocking the viral replication that causes HIV's devastating effects.

The teams will spend the first two years of the grant determining which pre-clinical approaches are most likely to be successful when they begin studies using animal models in the third and fourth years. The goal of the animal studies is to demonstrate proof-of-concept for strategies that may lead to human trials of new HIV treatments.

CHOP Joins Project to Crack Mystery of Preterm Birth

Preterm birth, the leading cause of newborn death in the U.S., poses one of the most perplexing riddles in medical science. One in nine babies is born prematurely in the U.S., according to the <u>March of Dimes</u>, a rate that has remained frustratingly steady despite years of investigation.

<u>The Children's Hospital of Philadelphia</u> has joined a new effort to change the future of premature birth by analyzing the causes to learn more about how to prevent it. CHOP is part of a transdisciplinary team established by the new <u>March of Dimes Prematurity Research Center</u> at the <u>Perelman School of</u> <u>Medicine at the University of Pennsylvania</u>. In a collaboration announced in February 2015, the research team is applying sophisticated technology and methodology in molecular biology and genomics to better understand preterm birth.

Babies born before 37 weeks are considered to be premature and, because their bodies and organ systems have not matured completely, they often need help for everything from breathing, eating, and fighting infection to simply staying warm. Preterm babies can have long-term health problems, including cerebral palsy, cognitive impairments, and sensory disorders.

The March of Dimes is investing \$10 million over the next five years to create the Prematurity Research Center. More than 40 investigators are focusing on three key research themes to uncover important new findings about the causes of preterm birth: bioenergetics and genetics, cervical remodeling, and placental dysfunction. The research center at the Perelman School of Medicine is one of four created by the March of Dimes around the country. The other three centers are located at the Stanford University School of Medicine in California; a partnership of Ohio research centers in Cincinnati, Columbus, and Cleveland; and Washington University in St. Louis.

"This kind of cooperation and collaboration is on a different scale than has ever been developed for preterm birth," said <u>Rebecca A. Simmons, MD</u>, the project leader for the bioenergetics and genetics theme and an attending neonatologist at CHOP and the Hospital of the University of Pennsylvania. "It's not only collaborative across our campus and many different departments within the Penn/CHOP system, but we also collaborate between centers, which is a very unique structure."

Deborah A. Driscoll, MD, the Luigi Mastroianni Jr. Professor and Chair of the Department of Obstetrics and Gynecology at the Perelman School of Medicine, is the director of the Prematurity Research Center. Dr. Simmons, the Hallam Hurt Professor of Pediatrics, and Samuel Parry, MD, associate professor of Obstetrics and Gynecology and chief of the Division of Maternal-Fetal Medicine at the University of Pennsylvania, serve as the research project's principal investigators. For the first research theme of bioenergetics and genetics, the March of Dimes is tapping CHOP researchers' expertise in mitochondrial biology and biochemistry. Mitochondria are organelles often described as the body's cellular power plants because they extract energy from nutrient molecules in order to perform cells' most basic and critical functions. Dr. Simmons, along with <u>Marni Falk, MD</u>, director of the <u>Mitochondrial-Genetic Disease Clinic</u> at CHOP, and Neal Sondheimer, MD, PhD, an attending physician at CHOP, will investigate how impaired cellular metabolism could result in power shortages in the reproductive tract that contribute to preterm labor.

Researchers will look at reproductive tissues from mice and humans to identify any patterns of mitochondrial dysfunction. They will then see whether these disturbances interfere with the tissues' ability to maintain bioenergetics and metabolic stability during pregnancy.

The center's second theme ties into this hypothesis by exploring how the microbiome, a community of bacteria that normally inhabit the vagina and cervix, may influence cervical remodeling. A dynamic process during delivery, cervical remodeling transforms the cervix from a rigid structure into a pliable passageway for the baby.

Preliminary studies suggest that the microbiome is different in women who experience preterm birth. Accordingly, the researchers will explore whether the abnormal bacteria cause mitochondrial distress and inflammation that prematurely accelerates cervical remodeling. The cervical remodeling research will be led by Michal Elovitz, MD, associate professor of Obstetrics and Gynecology and director of the <u>Maternal</u> <u>and Child Health Research Program</u> at the University of Pennsylvania.

"If we do find changes in the microbiome, those are targets for therapeutics that can be developed," Dr. Simmons, who is also a professor of Pediatrics at the Perelman School of Medicine. "We'll look for strategies to either change the composition of the microbiome or change how the microbiome is functioning."

The third research theme, led by Dr. Parry, focuses on placental dysfunction. Researchers will investigate mitochondrial deficiencies and an unhealthy microbiome as possible factors that disrupt metabolic processes in the placenta and lead to early labor.

Further, the researchers recognize that some of the answers to the medical mystery of preterm birth also may lie within complex gene-environment interactions. Therefore, the research teams plan to explore the evolving field of epigenetics, which is the study of mechanisms that change how genes are expressed without altering the underlying DNA sequence.

The teams hope to gain insights into the multiple pregnancy-related risk factors — biological, behavioral, social, physical, and environmental — that could cause epigenetic modifications. For example, Dr. Simmons will explore how any abnormalities in the genes and biochemical pathways that regulate mitochondrial metabolic function could have a role in preterm birth. "We think that if we can identify novel metabolic pathways, we can certainly design future interventions," Dr. Simmons said.

As the Prematurity Research Center moves from the discovery phase to targeting and developing therapeutics, the researchers hope that their findings along the way will spark additional preterm birth studies. The center is offering a series of pilot grants to investigators to encourage them to tackle this important health challenge.



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LEADERSHIP >

Steven Douglas, MD, Recognized for Advancing HIV Research

<u>Steven D. Douglas, MD</u>, chief of the Section of Immunology at <u>The Children's Hospital of Philadelphia</u>, hopes to see an AIDS-free generation in his lifetime. A pioneer in the field, he has established core laboratories at CHOP and the University of Pennsylvania that are vital to human immunodeficiency virus (HIV) research across the lifespan and mentored investigators pursuing clinical and translational science.

In particular, Dr. Douglas has spent his prolific career studying the biology of immune cells, with emphasis on the relevance of monocyte-derived macrophages to potential treatment for human HIV infection. The <u>International Society for NeuroVirology</u> (ISNV) honored Dr. Douglas for his seminal work by presenting him the society's 2015 Paradigm Builder Lectureship Award.

"Dr. Douglas has been in the forefront of research in immunology where he has been continuously funded for over 40 years," according to a statement from the ISNV about the award, noting that his work intersects the disciplines of psychiatry, immunology, neurology, and AIDS.

In addition to identifying the mechanisms of HIV infection, Dr. Douglas has led numerous clinical trials focused on pediatric, adolescent, and adult populations living with the disease. He currently serves as a member of the Scientific Oversight Leadership Committee for the International Maternal Pediatric Adolescent AIDS Clinical Trials, belongs to many professional and scientific societies, and holds positions on several national scientific committees. In these leadership roles, he helps to set the agenda for HIV research domestically and globally.

Dr. Douglas has had his finger on the pulse of the AIDS epidemic since it became a crisis in the 1980s. While AIDS now can be managed as a chronic condition, Dr. Douglas stressed that it remains a huge public health issue. He is passionate about the discovery of <u>cutting-edge</u> strategies aimed at HIV prevention, treatment, cure, vaccines, and co-morbidities.

"My major motivation is the challenge to do something good to help people," said Dr. Douglas, who for the past 35 years has been at CHOP and at the University of Pennsylvania, where he is a professor of Pediatrics in the <u>Perelman School of Medicine at the University of Pennsylvania</u>.

Starting in the late 1970s, Dr. Douglas established laboratory methods for investigating two types of immune cells: monocytes and macrophages. Those cell culture methods have enabled laboratory research throughout the world.

Dr. Douglas was among the first scientists to discover that HIV-1 infects macrophages derived from monocytes. He first showed that an important chemical, substance P, exists on these cells, and that it plays a crucial role in neurological manifestations of AIDS. He then identified a pathway shared by substance P and a particular cell receptor as a potential target for treating HIV infection.

Currently, he is collaborating with co-investigators from Temple University in a joint \$4.3 million <u>NeuroAIDS</u> grant from the <u>National Institute of Mental Health</u>. This grant funds research on new methods to eradicate HIV that lurks in brain cells despite conventional antiviral treatments.

CHOP scientists are ideally positioned to accomplish such innovative research, Dr. Douglas said, because they have access to valuable repositories of biological specimens, a marvelous support staff and infrastructure at the Research Institute, and a uniquely engaged patient population who receive state-of-the-art medicine provided by expert clinicians.

"It is very important to recognize the commitment of the children and their families," Dr. Douglas said. "Participating in a clinical trial can be a big commitment, and CHOP is very nurturing and understanding. The care is wonderful here. You're not a number on a piece of paper."

Dr. Douglas is the seventh scientist to receive the Paradigm Lectureship Award, established in 2006.

Robert Campbell, MD, Receives Patient Impact Award

A device created by a CHOP expert is changing the lives of children with a debilitating rare disease, offering hope of drastically improved outcomes.

<u>Robert M. Campbell, MD</u>, a professor of Orthopaedic Surgery at the <u>Perelman School of Medicine at</u> the <u>University of Pennsylvania</u>, invented the vertical expandable prosthetic titanium rib (VEPTR), the first device <u>approved by the FDA</u> to treat <u>thoracic insufficiency syndrome</u> (TIS), a rare condition affecting children in which the thorax cannot support regular growth or breathing.

His pioneering work led <u>Pennsylvania Bio</u> to honor him with the Patient Impact Award at the organization's annual dinner in March.

"I am deeply honored by the <u>Pennsylvania Bio's Patient Impact Award</u> for our work with the VEPTR device," Dr. Campbell said. "Our future work will involve integrating quantitative dynamic lung MRI analysis into our treatment strategies."

Pennsylvania Bio's Patient Impact Award "recognizes a company or organization that has made a significant contribution to the quality of healthcare or length of life of patients in 2014." Last year, the University of Pennsylvania and CHOP were jointly given the award for their groundbreaking <u>immune therapy research</u>.

Dr. Campbell led a recent <u>Journal of Pediatric Orthopaedics</u> study that showed VEPTR treatment improved survival to nearly 70 percent, compared to a 20 to 30 percent survival rate without treatment, in patients with Jeune syndrome, a severe form of TIS.

Left untreated, TIS can be devastating. As children with TIS grow, the condition causes the chest to become deformed, and children with TIS are often born with scoliosis, or curvature of the spine. TIS can lead to death due to respiratory insufficiency. However, since Dr. Campbell implanted the first VEPTR in 1989, the device — which as its name implies can be expanded as the child grows — has proven to be a lifesaver.

The founder and Director of CHOP's <u>Center for Thoracic Insufficiency Syndrome</u> and a highly accomplished pediatric orthopaedic surgeon, Dr. Campbell has been working to improve outcomes for TIS patients for more than 25 years.

Watch a short video highlighting Dr. Campbell and the VEPTR implant.

International Society Gives Award to Thrombosis Expert

<u>Sriram Krishnaswamy, PhD</u>, a CHOP investigator and associate professor of Pediatrics at the University of Pennsylvania, received a <u>Biennial Awards for Contributions to Hemostasis</u> (BACH) Investigator Recognition Award for his work advancing our understanding of coagulation. The <u>International Society on</u> <u>Thrombosis and Haemostasis</u> (ISTH) honored Dr. Krishnaswamy, at its annual meeting in Toronto during the <u>ISTH's 2015 Congress</u> in June.

The BACH awards are given to investigators who "have made significant contributions to research and education in blood coagulation," according to the ISTH site. Previous CHOP awardees include <u>Katherine</u> <u>A. High, MD</u>, who is now at <u>Spark Therapeutics</u>.

A thrombosis and hemostasis researcher, Dr. Krishnaswamy investigates the biochemical underpinnings of coagulation. He has led or contributed to numerous papers on the mechanics of coagulation and related topics. Last year he contributed to a *Blood* study led by <u>Rodney M. Camire, PhD</u>, a CHOP investigator and associate professor of Pediatrics at the University of Pennsylvania, that examined the development of prothrombinase, the enzyme complex responsible for thrombin formation. By shedding light on the location of prothrombinase formation, the study lays the groundwork for future research.

More recently, his lab has been investigating specific blood coagulation factors, aiming to better understanding the factors' structure and how they contribute to prothrombinase assembly. In one line of research, Dr. Krishnaswamy and colleagues are studying the venom of the <u>eastern brown snake</u>, *Pseudonaja textilis*. One of the most venomous snakes in the world, the eastern brown snake is found in Australia and New Guinea.

Following <u>previous work published in *Blood*</u>, Dr. Krishnaswamy and his colleagues — including CHOP's <u>Shekhar Kumar, PhD</u>, and the University of Cambridge's James Huntington, PhD — solved the X-ray structure of a protein in the venom of the eastern brown snake, which is very much like the human coagulation factor Va. Despite having similar structures, the mammalian and reptile factors have radically different functions, acting as hemostatic agents and toxins, respectively. Overall, the researchers' work is leading to a greater understanding of how coagulation factors operate.

Dr. Krishnaswamy's work is supported, in part, by grants from the <u>National Heart, Lung, and Blood</u> <u>Institute</u> to study the mechanisms of blood coagulation.

Kristy Arbogast, PhD, Takes on New Leadership Role

<u>Kristy Arbogast, PhD</u>, was recently promoted to co-scientific director of the <u>Center for Injury Research</u> <u>Prevention</u> (CIRP) and will continue to serve as this Center of Excellence's director of engineering.

In her new role, Dr. Arbogast helps lead a group of behavioral scientists, clinicians, engineers, and other professionals who are focused on injury prevention, violence prevention, physical and emotional recovery following injury, and digital health, among other topics.

Dr. Arbogast has been with CIRP since its inception nearly 20 years ago, when she joined <u>Flaura K.</u> <u>Winston, MD, PhD</u>, and <u>Dennis Durbin, MD, MSCE</u>, as a co-investigator on the seminal <u>Partners for Child</u> <u>Passenger Safety</u> project, a 10-year-long national study that led to significant policy and safety design advances for child motor vehicle occupants.

"This is a natural transition for CIRP," Dr. Winston said. "As Kristy's career has matured and flourished, so has CIRP. She has helped to grow our Center's international reputation as a thought leader in child injury prevention and pediatric biomechanics."

Her work has greatly expanded the quality and quantity of biomechanical and human factors engineering tools that will help industry to engineer better restraint systems to protect child occupants in motor vehicles. More recently, Dr. Arbogast has been studying concussions, not only from motor vehicle crashes, but also from sports. She served on the Institute of Medicine Committee on Sports Concussion in Youth and is a member of the National Council on Youth Sports Safety.

And since 2011, Dr. Arbogast has helped lead a multidisciplinary team from across CHOP called Minds Matter: Improving Pediatric Concussion Management. The program has streamlined and standardized concussion diagnosis, treatment, and follow-up care across the CHOP network, and is now working to develop a concussion registry that can capture critical data from more than 12,000 concussion visits seen at CHOP each year. These data will help guide the field toward developing objective tools for diagnosing concussion and monitoring recovery.

Dr. Arbogast continues to serve as the co-director of the <u>National Science Foundation</u>-sponsored <u>Center for Child Injury Prevention Studies</u> at CHOP, the <u>University of Pennsylvania</u>, and The Ohio State University. Dr. Arbogast is also research associate professor of Pediatrics at the University of Pennsylvania.

"I have benefitted from the interdisciplinary structure of CIRP," Dr. Arbogast said. "Working with colleagues from diverse academic backgrounds and research interests has expanded my own understanding of child injury prevention. We are all dedicated to translating our research into action to reduce preventable child injuries and deaths."

Alarm Fatigue Research Grabs Attention and Awards

The constant blips, chirps, and buzzes generated by hospital monitors can warn clinicians of trouble, from dangerous heart rhythms and blocked IV lines to disconnected ventilators and low oxygen levels. The problem is that these alarms are so sensitive that they go off all the time, and most of the time they are false. Research shows that <u>85 percent to 99 percent</u> of alarms do not require clinical intervention.

This creates a problem akin to the story of the boy who cried wolf. Staff become desensitized to alarms, and they begin responding more slowly when they go off. They even ignore some alarms completely. But on the rare occasion the alarm truly represents a medical emergency, an immediate response is what is needed. The <u>ECRI Institute</u>, an independent nonprofit that researches the best approaches to improving patient care, named clinical alarms the No. 1 health technology hazard for 2014.

"Physiologic monitors and other medical devices have tremendous potential to save lives," said <u>Christopher Bonafide, MD, MSCE</u>, an attending physician and patient safety researcher at <u>The Children's</u> <u>Hospital of Philadelphia</u>. "Unfortunately, due in part to their design and in part to how hospitals use them, they generate so many false alarms that clinicians lose trust in them."

Dr. Bonafide and his research team are focused on studying this problem and coming up with creative solutions to improve medical device alarms and prevent alarm fatigue. They created a video research lab that uses small GoPro cameras temporarily mounted in patients' rooms, with families' and nurses' permission. Every time an alarm goes off, the research team can see simultaneous views of the patient room, a close-up view of the patient, a full view of monitor screens and ventilator displays, and views of the caregivers responding to the alarms. The researchers used delays in caregivers' response times as a proxy for alarm fatigue.

"No one has actually quantified alarm fatigue in the hospital before," said Dr. Bonafide, who also is an assistant professor of Pediatrics at the <u>Perelman School of Medicine at the University of Pennsylvania</u>. "We want to evaluate the relationship between the number of false alarms that nurses are exposed to and their response time to critical alarms. In doing this, we hope to learn more about the science behind alarm fatigue and discover new ways to combat it."

They synchronized the video with monitor data to allow for objective review by experts to determine the validity of alarms and measure response time. The team described the video methods, how they managed the large data files, and how they generated a time-stamped list of alarms that occurred during the video session to use as "bookmarks" during the review process, in an article recognized as <u>best research paper</u> in 2015 by The Association for the Advancement of Medical Instrumentation's (AAMI) journal *Biomedical Instrumentation and Technology*.

ECRI Institute also recognized the innovative work being done by the patient safety researchers to measure alarm fatigue by selecting the project as a finalist for its <u>9th Annual Health Devices Achievement</u> <u>Award</u>. The award recognizes an outstanding initiative undertaken by an ECRI Institute member healthcare institution that improves patient safety, reduces costs, or otherwise facilitates better strategic management of health technology.

The award-winning entries discussed how the study team performed 40 video sessions and then analyzed the data generated by 4,962 alarms. They determined that caregiver response times increased as the number of false, or nonactionable, alarms increased. In the intensive care unit, 87 percent of alarms in heart and lung failure patients were characterized as false. In the general wards, 99 percent of alarms were false.

Dr. Bonafide also received a <u>2015 Young Investigator Award</u> from the Academic Pediatric Association for his team's latest project aimed at reducing unnecessary alarms.

"Now that we are convinced that alarm fatigue is real, we need to begin the hard work of reducing alarm fatigue," said Dr. Bonafide, who received a <u>five-year career development award</u> from the <u>The National</u> <u>Heart, Lung, and Blood Institute</u> to continue his patient safety research. "To do this, we need to work within our own institutions and across institutions to develop and test new interventions to improve the ways we manage alarms. It is also critical that we work with leaders in the medical device industry to actively participate in designing the next generation of monitors with smarter alarms."

Prestigious Award Goes to Sleep Medicine Investigator

<u>Carole Marcus, MBBCh</u>, has spent most of her career studying the physiology of pediatric <u>obstructive</u> <u>sleep apnea</u> (OSA) and trying to understand the factors leading to airway collapse in sleep.

Her efforts were honored in June, when she received the 2015 William C. Dement Academic Achievement Award at the <u>Annual Meeting of the Associated Professional Sleep Societies</u>. The award recognizes members of the sleep field who have displayed exceptional initiative and progress in the areas of academic research.

During OSA, a child stops breathing, usually attributed to a blockage from enlarged tonsils or adenoids. A brief arousal from sleep increases muscle tone, opens the airway, and allows the child to resume breathing.

Through her research, Dr. Marcus has identified that most children have very active upper airway neuromotor reflexes that allow them to compensate when their airways become narrowed during sleep. Children who experience OSA, however, do not appear to have these reflexes. It remains unclear whether they lost them over time or never developed them in the first place.

Dr. Marcus is excited about a new study, called <u>Steroids for Pediatric Research in Kids</u> (SPARK) that she is leading at CHOP to look at the effects of nasal steroids on treating OSA as an alternative to surgery.

"Sleep is just so fascinating," Dr. Marcus said. "We're in an era where we have the gene for so many diseases, and yet we don't fully understand why people sleep. Sleep remains one of the big enigmas in medicine. So little research has been done in pediatric sleep, and there is so much to find out."

Nightly episodes of sleep disruptions caused by OSA have been associated with adverse behavioral, cognitive, quality of life, and health outcomes in children. Dr. Marcus was the first author of a large, multicenter study published in the *New England Journal of Medicine* in 2013 called the <u>Childhood</u> <u>Adenotonsillectomy Study for Children With OSAS</u> (CHAT). Participants who had surgery to remove their adenoids and tonsils had notable improvements in behavior, quality of life, and supportive care, but the researchers did not find any improvements in cognition.

Dr. Marcus continues to find practicing sleep medicine extremely gratifying because she often sees how diagnosing sleep problems and then recommending appropriate therapies can make a huge difference in patients' and families' lives. She directs a <u>sleep laboratory</u> at the <u>The Children's Hospital of Philadelphia</u> main campus and two satellite sites in suburban Philadelphia and New Jersey, with a total of 14 beds.

"I am extremely honored," said Dr. Marcus, who since 2003 has directed the <u>Sleep Center</u> at CHOP. "Dr. Dement is the father of sleep medicine and someone I really admire. He has taught me to be open to new ideas. A lot of research is not believing what you see and following the path that your research takes, even if it's an unexpected turn."

Pediatric Neuropathologist Retires After 50 Years at CHOP

Lucy B. Rorke-Adams, MD, donated samples of Albert Einstein's brain to the <u>Mutter Museum</u> in Philadelphia in 2012, an event noted by the BBC, in the *New Yorker*, and in news stories around the world. During her tenure at the city's famed public Philadelphia General Hospital (PGH) from 1957 to 1977, Dr. Rorke-Adams had received one of five sets of the famed scientist's brain tissue that were distributed to various pathologists by the medical examiner who autopsied Einstein.

For some people, possessing samples of Einstein's brain might be a life's high point. For Dr. Rorke-Adams, it was one episode in a long and varied medical career. A worldwide leader in pediatric neuropathology, Dr. Rorke-Adams, 86, retired June 19 after 50 years at <u>The Children's Hospital of Philadelphia</u>.

Dr. Rorke-Adams began working at CHOP part-time in 1965, overlapping with her time at PGH. There, she had been the first and only female president of the medical staff in that hospital's 188-year history. She joined CHOP full-time upon its closure. She went on to become acting chair of Pathology at CHOP, president of the <u>American Association of Neuropathology</u>, a professor at the <u>University of Pennsylvania</u> <u>Perelman School of Medicine</u>, an international expert on pediatric brain tumors and shaken baby syndrome, and an invited speaker at medical schools and professional societies throughout the world. She also served as president of the medical staff at CHOP, and unexpectedly helped run the Hospital for 18 months starting in 1986 during an extended search for a chief executive officer. On top of this, she had longtime associations with the Philadelphia Medical Examiner's Office, the Wistar Institute, and Wyeth Research Laboratories.

This remarkable professional pedigree marks some of the highest peaks reached in a bold life's journey that has spanned the scenic terrain of revolutions in medicine, a story relayed by Dr. Rorke-Adams herself in an <u>autobiography in the *Journal of Child Neurology*</u>.

Dr. Rorke-Adams' parents, like Einstein, immigrated to America from turmoil in Europe. Her mother survived the Armenian genocide in Turkey in 1915, and in 1921 made her way to Minneapolis, with tickets from an Armenian émigré who would become her husband. The youngest of their five girls, the future Dr. Rorke-Adams, was born Lucy Balian and spoke Armenian before she spoke English.

As commonly happens, contingencies caused detours in her life path. As a teenager, she wanted to be an opera singer — until her out-of-town audition with a Metropolitan Opera mezzo-soprano was cancelled when the professional singer took sick. She started as a clinical psychologist and worked evenings in a psychology clinic while earning her medical degree from the University of Minnesota. She moved to Philadelphia to begin her internship at PGH in 1957. She considered specializing in psychiatry or surgery, but facing the prospect of more sleep deprivation, she chose pathology.

Of her long career in pathology, Dr. Rorke-Adams is proudest of her work on pediatric brain tumors. Based on her expertise, she proposed reclassifications of embryonal pediatric brain tumors in a 1981 presidential address to the American Association of Neuropathologists. This was a direct challenge to a professor in attendance, then a world authority in the field, but in her words, she "threw down the gauntlet." Subsequent research by other scientists supported her position, and led to improved treatment and outcomes for patients.

In the 1990s, she presented another hypothesis, controversial at the time, on the origin of brain malformations arising in early human development, in so-called migration disorders. Using animal studies and gene analyses, she proposed that disordered genetic control allows neurons to migrate to abnormal, disease-causing locations.

Later studies strengthened that hypothesis. One of Dr. Rorke-Adams' trainees, Jeffrey Golden, MD, chose to focus on migration disorders, and eventually became CHOP's pathologist-in-chief, a position held by Dr. Rorke-Adams years before. In addition, before taking a position at Brigham and Women's Hospital and Harvard Medical School, he became the first holder of a CHOP endowed chair in Pediatric Neuropathology named after Dr. Rorke-Adams.

Despite encountering resistance early in her career from some physicians hostile to women in their profession, and being one of a tiny minority of women in medical school and residency, Dr. Rorke-Adams said, "I never felt any kind of prejudice as a woman." Or perhaps when it existed, she persisted anyhow.



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COMMITMENT >



President Obama appointed <u>Peter C. Adamson, MD</u>, an oncologist at <u>The Children's Hospital of</u> <u>Philadelphia</u> and an internationally recognized leader in pediatric cancer drug development, to the <u>National Cancer Advisory Board</u> (NCAB).

The appointment follows the President's announcement during a recent State of the Union address of a <u>Precision Medicine Initiative</u> that will harness research and technology toward developing individualized treatments for many diseases.

Dr. Adamson is the only pediatric oncologist to currently serve on the NCAB, and he works to ensure decision makers in the federal government hear the voices of the pediatric cancer community.

In his new role Dr. Adamson is advising the <u>U.S. Secretary of Health and Human Services</u>, the director of the <u>National Cancer Institute</u> (NCI), and the President on a wide range of issues relating to the national cancer program, including NCI operations.

Notably, the NCAB and the <u>President's Cancer Panel</u> are the only advisory bodies at either the <u>National</u> <u>Institutes of Health</u> or the <u>Department of Health and Human Services</u> whose members are appointed by the President.

A renowned investigator and leader in cancer drug development for children, Dr. Adamson has served as <u>chair of the Children's Oncology Group</u> (COG), the world's largest organization devoted exclusively to childhood and adolescent cancer research, since 2011. Through COG, he works with leading pediatric cancer researchers at CHOP and across the country who are hard at work on the most promising new therapies. Dr. Adamson is also a professor of <u>Pediatrics and Pharmacology at the Perelman School of Medicine at the University of Pennsylvania</u>.

From 1999 to 2014, Dr. Adamson was chief of the <u>Division of Clinical Pharmacology and Therapeutics at</u> <u>CHOP</u>, and he also served as director of the Office of Clinical and Translational Research from 2005 to 2011. Prior to joining CHOP in 1999, he was a member of the Pediatric Oncology Branch of the NCI.

"We are extremely proud of Dr. Adamson on his appointment by President Obama to this distinguished advisory board," said <u>Joseph St. Geme, MD</u>, physician-in-chief and chair of the <u>Department of Pediatrics</u>. "This recognition is a testament to his dedication and leadership within the medical community in furthering research to advance treatment for childhood cancer."

Cancer Research Leader Hungers for a Cure

In a fight to eradicate all childhood cancers, it helps to have a strong general leading the charge. <u>The Children's Hospital of Philadelphia</u> welcomed a new leader in pediatric oncology in November 2014.

<u>Stephen P. Hunger, MD</u>, a nationally prominent specialist in children's cancer, became the new director of the <u>Center for Childhood Cancer Research</u> (CCCR) and chief of the <u>Division of Oncology</u>. He joined CHOP from <u>Children's Hospital Colorado</u>.

"I am tremendously excited by this opportunity to join one of the premier pediatric cancer programs in the world and to help CHOP develop more and better therapies toward our eventual goal of curing all pediatric cancers," Dr. Hunger said.

He is a fitting leader for CHOP's comprehensive program, staffed by internationally recognized experts in pediatric cancer who rely on the most current advances in research and treatment. In *U.S. News & World Report's* most recent rankings of pediatric care specialties, CHOP's cancer care ranked second in the nation.

Dr. Hunger has a particular research interest in acute lymphoblastic leukemia (ALL), the most common childhood cancer. His recent papers include a <u>Nature Communications</u> paper <u>detailing the evolution</u> <u>of genetic changes in ALL</u> from diagnosis through remission and relapse, a <u>New England Journal of</u> <u>Medicine report</u> on the largest study of ALL genetics that identified new potential therapies for a newly described high risk subset, the <u>first invited review on childhood ALL published in the New England Journal</u> <u>of Medicine</u> in 10 years, a <u>Journal of Clinical Oncology</u> pharmacokinetic study in ALL patients, and an <u>Annals of the New York Academy of Sciences</u> paper on the development of asparaginase as an ALL treatment.

A leading member of the <u>Children's Oncology Group</u> (COG), the national cooperative organization of pediatric cancer centers, Dr. Hunger has sat on numerous COG study committees, and served as chair of the organization's acute lymphoblastic leukemia committee from 2008 to 2015. He was recently appointed the next Scientific Committee Chair of the International Society of Pediatric Oncology, and also has served on NIH study sections and committees of the <u>National Cancer Institute</u>, the <u>American Society of Clinical Oncology</u>, and numerous other foundations and groups.

"We are delighted to welcome this internationally renowned pediatric oncologist to CHOP to lead our pediatric cancer program, advancing the treatment of children, adolescents, and young adults with cancer and overseeing pediatric oncology research," said <u>Joseph St. Geme, MD</u>, CHOP's physician-in-chief and chair of the Department of Pediatrics. "Dr. Hunger has an impressive background as a clinician, investigator, teacher, and leader in pediatric oncology and will undoubtedly have a major impact at CHOP."

Extending Reach to Participants in Clinical Studies

The key to the success of a clinical research investigation is the contribution of time, energy, and effort of patients willing to participate. Without them, the hard work of clinical research teams to find better treatments and cures could never get done.

<u>The Children's Hospital of Philadelphia Research Institute</u> established a new centralized resource this year focused on helping busy investigators with the often-challenging effort in finding and recruiting study participants.

The Recruitment Enhancement Core (REC) led by Chris Gantz offers assistance with recruitment plans, creating marketing and promotional materials, and giving investigators access to a registry of potential recruits. The REC falls under CHOP Research Institute's <u>Clinical Research Support Office</u>.

Much of the REC's work draws on Gantz's decade of clinical research experience and marketing background. For example, the REC team works with investigators to create recruitment letter content and appearance — even the envelopes — all with the goal of making sure letters are actually opened once they are sent out. Likewise, Gantz is setting up a centralized, accessible space in the Hospital to display recruitment flyers. Another REC goal is to create a version of CHOP Research Institute's <u>Clinical Research Finder</u> tool for the <u>Hospital's website</u>.

The REC team also is building a robust registry of people interested in being involved in research, in part by encouraging investigators to start the dialogue with their patients. Indeed, according to <u>a study</u> by the <u>Center for Information & Study on Clinical Research Participation</u>, 95 percent of study volunteers would consider participating in another clinical research study in the future.

"The problem is that we haven't always been asking," Gantz said.

The REC team works with the <u>University of Pennsylvania</u> to identify opportunities for collaboration to enhance recruitment across both institutions, as well as participating in community engagement activities to raise awareness of CHOP and clinical research participation opportunities.

With the REC's help making the match between participants and studies, CHOP study teams can recruit participants for clinical research more efficiently and effectively than ever before — and investigators and participants can move together swiftly toward better treatments and better outcomes from childhood disease.

New Program Working Ahead to Protect Newborns' Brains

More than 30 years ago, <u>The Children's Hospital of Philadelphia</u> pioneered life-saving early surgeries for children with complex heart defects. Today, researchers are investigating ways to intervene even sooner — before birth — to protect these infants' brain development and prevent brain injury.

The <u>Fetal Neuroprotection and Neuroplasticity Program</u> at CHOP launched in June builds upon growing evidence of the interaction of heart disease and brain development in the fetus. This research, much of it developed at CHOP, shows that in utero brain development is abnormal in fetuses with <u>congenital heart</u> <u>disease</u> (CHD), leading to delayed maturation, poor growth, and white matter injury.

Neurodevelopmental disability is now recognized as the most common complication of critical CHD — those patients requiring cardiac surgery in infancy — and has the most negative impact on quality of life, academic performance, and opportunity for independence as an adult.

"The Fetal Neuroprotection and Neuroplasticity Program is another innovative initiative in a long series of identifying opportunities to ensure that children with CHD not only survive, but truly thrive, as they grow into adulthood," said <u>J. William Gaynor, MD</u>, cardiac surgeon and director of the Fetal Neuroprotection and Neuroplasticity Program, and an assistant professor of Surgery at the <u>Perelman Medical Center at the University of Pennsylvania</u>. "This program allows us to enhance our continuum of care from conception through adulthood."

The focus of the new program is to investigate the factors that cause abnormal brain development in the fetus with CHD and, for the first time, to conduct clinical trials of fetal interventions to determine whether novel prenatal treatments can reduce brain injury and improve neurodevelopmental outcomes in newborns with CHD who subsequently undergo cardiac surgery. One such study aims to evaluate whether the hormone progesterone, administered prenatally to the mother, has a neuroprotective effect on brain development.

The program is a joint project of the Hospital's <u>Cardiac Center</u>, the <u>Fetal Heart Program</u>, the <u>Center for</u> <u>Fetal Diagnosis and Treatment</u>, and the <u>Division of Neurology</u>.

"We now have an opportunity to not only offer the best diagnostic care to the fetus with heart disease, but to also begin to explore ways in which we can optimize long-term outcomes from the neurocognitive perspective," said <u>N. Scott Adzick, MD</u>, surgeon-in-chief at CHOP, and a professor of Pediatrics, Obstetrics and Gynecology at the Perelman School of Medicine. In the U.S., approximately one in every 120 newborns is diagnosed with CHD, making it the most common birth defect. As recently as the 1960s, only 20 percent of newborns with critical CHD survived to adulthood. Thanks to better prenatal diagnosis, advances in surgery, and improved postoperative care, early survival is over 90 percent.

While the Fetal Neuroprotection and Neuroplasticity Program initially focuses on the fetus with CHD, it will expand in the future to include fetuses with other birth defects, such as <u>congenital diaphragmatic hernia</u> and <u>pulmonary hypoplasia</u>.

Pediatric MATCH Pairs Drugs With Tumors' Genetic Makeup

Children with advanced cancers often do not have a known curative pathway because their tumors may acquire different genetic alterations that resist current treatments. A new research opportunity supported by the <u>National Cancer Institute</u> (NCI) called <u>Pediatric MATCH</u> (Molecular Analysis for Therapy Choice), which will be conducted by the <u>Children's Oncology Group</u> (COG), aims to use the power of <u>precision</u> <u>medicine</u> to potentially provide investigational therapies for these stubborn cases.

"Pediatric MATCH will try to match genomic changes in certain children's cancers with drugs that are either approved for adult cancers or with drugs that are still under investigation and not yet approved," said <u>Peter Adamson, MD</u>, chair of the Children's Oncology Group and a pediatric oncologist at CHOP. "Based on what we currently know about the genomics of childhood cancer, we estimate that perhaps 15 percent of children with relapsed cancer may have a finding for which there is an investigational drug that could be studied to determine its effectiveness."

When a child participating in Pediatric MATCH undergoes a tumor biopsy at relapse, some of the tissue will be sent to a centralized center for specific genomic testing. Once investigators define the tumor's genomic profile, they will sort through a group of approximately 10 or more targeted drugs to see if there is a drug that specifically targets the pathways identified by the genomic profile. Those children with matches may then receive the investigational new drug as part of this phase 2 trial.

The Pediatric MATCH trial is a combined effort of the NCI the COG, and a range of pharmaceutical companies that already have committed to providing drugs to be tested in the adult NCI MATCH Trial that began in July 2015. Dr. Adamson anticipates that many of this counterpart trial's pharmaceutical agreements will carry over to Pediatric MATCH.

"That is of great importance to this project because all childhood cancers are rare and ultra-rare diseases. Pharmaceutical companies generally do not have an economic incentive to study childhood cancers, and thus partnership with the NCI and pharmaceutical companies is essential for success of this project," said Dr. Adamson, who also is a professor of Pediatrics and Pharmacology at the <u>Perelman School of Medicine at the University of Pennsylvania</u>.

The Pediatric MATCH study team will share tumor analysis results with the child's cancer specialists to help them guide the family's treatment choices. In addition, the tissue samples will be highly valuable to future researchers as they try to explain the basis of cancer treatment failure and relapse.

Pediatric MATCH is a high priority for the COG, the world's largest organization devoted exclusively to childhood and adolescent cancer research. Five working groups are focused on launching the trial in 2016, Dr. Adamson said.

Pediatric Health Disparities at Heart of New CHOP Center

A new center at <u>The Children's Hospital of Philadelphia Research Institute</u> seeks to support vulnerable patients by conducting research to better understand the root of disparities — be they racial, gender-based, or caused by geography.

Though clinicians are tasked with doing their best to extend the same level of care to all patients, the fact remains disparities exist in care and health outcomes, especially in pediatric patients.

Led by <u>Scott Lorch, MD, MSCE</u>, the Harriet and Ronald Lassin Endowed Chair in Pediatric Neonatology, the <u>Center for Perinatal and Pediatric Health Disparities Research</u> (CPHD) will work to "identify, describe, and understand disparities in care and care practices among perinatal and pediatric patients."

"Research in adult patients has shown that there are extensive disparities in the care received by minority patients, particularly Hispanic and African-American patients," Dr. Lorch said. "CPHD, through multidisciplinary academic and clinical research, aims to understand how these same disparities apply to the perinatal population, where the mother-fetal interaction is of primary importance, and the pediatric population, where family/mother-child interaction is of primary importance."

Dr. Lorch is an ideal choice to lead the new Center, because his work — focused on health disparities, the economics and geography of healthcare, and perinatal epidemiology — dovetails nicely with the Center's mission.

Dr. Lorch is also director of the Neonatal-Perinatal Medicine Fellowship Program in the Division of Neonatology and deputy director of the <u>Center for Outcomes Research</u> at CHOP, as well as an associate professor of Pediatrics in the <u>Perelman School of Medicine at the University of Pennsylvania</u>.

Other faculty associated with the new Center include Nadia Dowshen, MD; Kristen Feemster, MD, MPH, MSHP; Chén Kenyon, MD, MSHP; and Saba Khan, MD. The Center's associate director is Ashley E. Martin, MPH, while Molly Passarella, MS, will perform statistical programming for the CPHD.

And though it was only recently established, the CPHD has already announced its first round of pilot project funding for junior investigators associated with CHOP. Designed to support pediatric and perinatal health disparities projects, the CPHD <u>Pilot Grant Program</u> "aims to engage fellows and junior faculty in HD research and to assist established faculty in developing new lines of research in this area," Martin said.

Recent recipients of the pilot grant program include Whitney V. Cabey, MD, Dr. Feemster, Megan S. Ryerson, PhD, and <u>Douglas Wiebe, PhD</u>, who are exploring transportation access as a barrier to on-time immunization; and Stephanie Doupnik, MD, <u>Chris Feudtner, MD, PhD, MPH</u>, and <u>Alexander Scharko, MD</u>, who are investigating the prevalence of mood and anxiety disorders among hospitalized school-age children and adolescents.

The CPHD has also partnered with a number of community organizations and other partners to advance its goals of identifying and addressing pediatric and perinatal disparities. They range from the governmental like the <u>Philadelphia Department of Behavioral Health and Intellectual disAbility Services</u> (DBHIDS), to those in higher education such as the University of Pennsylvania's Netter Center for Community Partnerships, and nonprofit organizations like <u>Public Citizens for Children and Youth</u>.

All of the CPHD's research seeks to better understand and confront disparities. Ultimately, Dr. Lorch said, with its work the Center hopes to inspire the next generation of pediatric medical researchers to conduct health disparities research, and to start a dialogue about pediatric and perinatal health disparities, with the ultimate goal of improving outcomes for patients.

Center of Excellence Focuses on Leukodystrophy

Children living with degenerative inherited white matter diseases, known as <u>leukodystrophies</u>, now have access to state-of-the-art diagnostics and integrated multidisciplinary care at <u>The Children's Hospital of</u> <u>Philadelphia's</u> new <u>Leukodystrophy Center of Excellence</u>.

Leukodystrophies affect the white matter in the brain and spinal cord resulting in developmental regression and premature death. Although these debilitating diseases do not currently have cures, if detected in the newborn period, a stem cell transplant may be a therapeutic option for some patients. Early detection also allows for preventative care strategies to improve quality of life for children and their families.

CHOP's Leukodystrophy Center of Excellence is a diagnostic, clinical care, and research initiative launched in response to legislation in Pennsylvania and New Jersey that has added leukodystrophies to the newborn screening panel. This is expected to result in an increase of patients requiring specialized care to address their complex needs.

"This type of comprehensive approach is a critical component in the treatment of children living with inherited white matter diseases," said <u>Amy Waldman, MD</u>, a CHOP pediatric neurologist and medical director of the Leukodystrophy Center of Excellence.

CHOP will offer a clinic specifically for infants identified by expanded newborn screening programs. They will have access to state-of-the-art diagnostic imaging studies and top specialists across CHOP, including experts from neurology, metabolics, rehabilitative medicine, physical therapy, occupational therapy, and complex care pediatrics.

The Hospital announced the launch of the Leukodystrophy Center of Excellence May 15 at the <u>Calliope</u> <u>Joy Foundation's</u> "An Evening with Jim and Jill Kelly" gala at the Rittenhouse Hotel in Philadelphia. Hall of Fame quarterback Jim Kelly and his wife, bestselling author Jill Kelly, established Hunter's Hope in memory of their son who died from Krabbe disease, a type of leukodystrophy. For the past decade, the Kelly's have been staunch advocates for newborn screening for Krabbe disease and have been instrumental in creating Leukodystrophy Care Centers across the nation.

Funds raised at the gala will support clinical programs, design treatment plans, create imaging and laboratory diagnostics, establish the newborn screening evaluation clinic, and form a pilot research program.

"This is a game changing moment for the care and treatment of leukodystrophies, and we are so pleased the doctors and researchers at CHOP believe they can give hope to the children and families that was unimaginable not long ago," said Maria Kefalas, co-founder of Calliope Joy Foundation, a nonprofit organization that raises funds to help children living with leukodystrophy through improved care, research, and family support.



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INSPIRATION >

Brain Injury Specialist Pursues Dietary Therapy Research

The National Institutes of Health (NIH) gave <u>The Children's Hospital of Philadelphia's</u> Akiva S. Cohen, PhD, a prestigious award in July 2014, signaling its confidence in his research into using an amino acid-based dietary therapy to mitigate the long-term effects of traumatic brain injuries (TBIs).

The R37, or Method to Extend Research in Time (MERIT), award is designed "to provide long-term grant support to investigators whose research competence and productivity are distinctly superior and who are highly likely to continue to perform in an outstanding manner," according to the NIH. Researchers do not apply for the award. Instead, MERIT awardees are chosen by NIH staff and a review board, who make their recommendations based on researchers' past successes and productivity.

A concussion and TBI expert, Dr. Cohen's work focuses on the cellular and molecular mechanisms underlying pathologies caused by head injuries. He is studying the use of a "cocktail" of cellular nutrients to address brain damage associated with TBIs.

Approximately 2 million TBIs occur each year in the U.S, with more than 500,000 TBIs suffered by children age 14 years and younger, according to the Centers for Disease Control and Prevention. While many TBIs are milder forms such as concussions, even "mild" brain injuries can lead to long-term health challenges, such as cognitive and emotional issues.

"I am honored and humbled to be nominated and receive a MERIT award," Dr. Cohen said. "And I am driven even more to determine the alterations in brain function that contribute to cognitive impairment caused by brain injury."

In late 2014, Dr. Cohen led a study published in *Science Translational Medicine* that found dietary therapy improved sleep disturbances caused by brain injuries in mice. He theorized that dietary therapy could have broader applications. As he said at the time, "If this type of dietary treatment is proved to help patients recover function after traumatic brain injury, it could become an important public health benefit."

In addition to the MERIT award, the NIH recently invited Dr. Cohen to serve a two-year appointment as a member of its Center for Scientific Review's Brain Injury and Neurovascular Pathologies (BINP) Study Section. Along with other experts on the panel, Dr. Cohen will review grant applications submitted to the NIH that are aimed at "understanding mechanisms of neural injury, related vascular abnormalities, and alterations in the blood brain barrier in stroke," among other topics.

Dr. Cohen joins a very small, exclusive group of CHOP investigators who have received MERIT awards (including the National Institute of Neurological Disorders and Stroke's R37, the Javits Neuroscience Investigator Award). Currently, only two other CHOP researchers have active MERIT awards — hematologist Gerd A. Blobel, PhD, and hyperinsulinism expert Charles Stanley, MD. Several other investigators, including Tom Curran, PhD, FRS, and Douglas A. Coulter, PhD, received MERIT/Javits support in the past.

Neuroscientist Receives Career Award for Epilepsy Research

<u>Ethan Goldberg, MD, PhD</u>, is the first researcher at <u>The Children's Hospital of Philadelphia</u> to receive a <u>Career Awards for Medical Scientists</u> (CAMS) grant from the <u>Burroughs Wellcome Fund</u> (BWF).

The award provides \$700,000 over five years for Dr. Goldberg's research into neuronal circuit-related epilepsy research, with an eye toward developing new epilepsy therapies. It was one of 12 CAMS awarded in July 2014.

A private grant-making organization based in Research Triangle Park, N.C., BWF is "dedicated to advancing the biomedical sciences by supporting research and other scientific and educational activities," according to its website. "[The CAMS] funding supports individual scientists poised to become leaders in their fields," said BWF President John Burris, PhD. "These awards are highly competitive, and we look forward to seeing great things happen."

An attending physician and neuroscientist, Dr. Goldberg studies cellular neurophysiology, large-scale imaging of neuronal network function, and epilepsy mechanisms in experimental models. He is also an assistant professor of Neurology at the Perelman School of Medicine at the University of Pennsylvania.

"I am thankful to the Burroughs Wellcome Fund for this generous grant," Dr. Goldberg said. "Gaining a greater understanding of how neuronal circuits function will yield insight into how circuit function goes awry in epilepsy. My work focuses on developing novel treatments for epilepsy in preclinical experimental models by targeting dysfunctional elements of epileptic circuits."

Epilepsy, a brain disorder marked by seizures of varying intensity and type, affects approximately 2 million Americans. While there is no cure for epilepsy, about 70 percent of those who have the disease can control their seizures with medication, according to the <u>National Institute of Neurological Disorders and</u> <u>Stroke</u>.

CHOP has a robust epilepsy treatment and research program. Part of CHOP's <u>Division of Neurology</u>, the <u>Pediatric Regional Epilepsy Program's</u> (PREP) team of clinicians, nurse practitioners, and researchers works with families to design personalized treatment plans that best control epilepsy with as few side effects possible.

With the support of the CAMS grant, Dr. Goldberg will continue his work studying basic mechanisms of inhibition in the hippocampal dentate gyrus, a sub-region of the brain that is critical for normal cognitive operations and is dysfunctional in epilepsy.

His next step will be to attempt to correct epileptic circuit dysfunction by manipulating the activity of a subset of neurons called inhibitory interneurons. One aim of the grant involves collaborating with <u>Stewart</u> <u>Anderson, MD</u>, by using inhibitory interneurons derived from embryonic stem cells generated in Dr. Anderson's laboratory to treat epilepsy in model systems.

The BWF CAMS award follows the publication of a manuscript by Dr. Goldberg and <u>Douglas A. Coulter</u>, <u>PhD</u>, in *Nature Reviews Neuroscience* examining recent advances in the field of epileptogenesis that could have an impact on epilepsy treatment. In their paper, Drs. Goldberg and Coulter suggest that "a greater mechanistic understanding of circuit function and circuit-level dysfunction in epilepsy will lead to the development of successful and broadly applicable interventions in epileptogenic processes, which remain a primary unmet need in epilepsy therapy."

Grant Supports Research to Improve Hemophilia Therapy

<u>The Children's Hospital of Philadelphia's Lacramioara Ivanciu, PhD</u>, has received funding to explore a potential alternative strategy for treating hemophilia, an inherited bleeding disorder that occurs in approximately 400 babies a year in the U.S.

The <u>BHAP Early Career Investigator grant</u> was awarded in August 2014 through the <u>Bayer Hemophilia</u> <u>Awards Program</u> (BHAP), which is administered by <u>Bayer HealthCare</u>, a subsidiary of the German pharmaceutical giant Bayer AG. BHAP is a "unique initiative dedicated to supporting innovative research and educational initiatives that benefit people with hemophilia," according to the program.

A researcher in CHOP's <u>Division of Hematology</u>, Dr. Ivanciu is focusing on designing new bypass agents for the treatment of hemophilia. Her research deals with the blood coagulation response, and in particular the coagulation factor IX (FIX). An important part of the coagulation system, deficiency in FIX results in hemophilia B, which is most often treated by replacement FIX therapy.

However, FIX replacement therapy is currently not ideal for patients. Because FIX has a short half-life, FIX replacement therapy requires multiple injections and high doses. Dr. Ivanciu hopes her research on bioengineering FIX will result in an improved therapy for hemophilia B.

"The novel FIX variants are expected to have prolonged half-life and efficacy and thus, be more efficient at lower doses," Dr. Ivanciu said. "This could greatly benefit the patients with hemophilia by reducing the therapeutic dose, an important goal in the replacement therapy."

Saying she was "very pleased" to receive the award, Dr. Ivanciu noted that its support will allow her "to advance the understanding of bleeding disorders by developing and applying new systems models and therapeutics to these problems."

Dr. Ivanciu's findings have appeared in peer-reviewed journals. She recently published two first author papers in *Blood* that focused on coagulation factors, factor Xa and factor Va. Additionally, she co-authored a paper published in the same journal examining recombinant activated human Factor VII.

Groundbreaking Study Targets Resilience to Stress

Who is not stressed out at one time or another these days? But chronic stress, whether it is from illness, interpersonal relationships, or other social stressors, can have a major impact on the brain and body.

And yet, only some people develop illnesses such as anxiety, depression, and post-traumatic stress disorder (PTSD) in response to chronic stress. <u>Seema Bhatnagar, PhD</u>, an associate professor in the CHOP Research Institute's <u>Division of Stress Neurobiology</u> is trying to figure out why.

In a new research project funded in August 2014 by the <u>National Institute of Mental Health</u>, Dr. Bhatnagar and colleagues are studying peptides called orexins and their possible link to a person's resilience or vulnerability to the effects of stress.

"If we could understand better the brain mechanisms that lead to vulnerability to stress, then we could either prevent the effects of stress from happening or help treat individuals who are sick and even try to identify them before they get sick," Dr. Bhatnagar pointed out.

While other neurochemicals are being studied for their potential role in controlling an individual's response to stress, Dr. Bhatnagar's research project is the first to center on orexins. First described by scientists about 17 years ago, orexins are important neurochemicals related to arousal, sleep, vigilance, and feeding. Orexins are made in the hypothalamus, and increasing evidence indicates that orexins play a role in people's ability to be alert and respond to stressful stimulus.

Dr. Bhatnagar's research team is studying the potential link between orexin levels and the different coping strategies used by young adult male rats exposed to repeated social defeat. When exposed for a week to a larger, more aggressive and territorial rat, some rats that show anxiety and depressive-type behaviors will give up quickly and assume a defeat posture. Other rats are more active in resisting the larger rat and appear more resilient. Based on preliminary data, it appears that the resilient rats exhibit lower orexin levels.

"If we're correct that orexins are important in vulnerability and resilience, you could imagine developing drugs that inhibit orexin release could be used in a situation of chronic stress or trauma to decrease arousal and maybe prevent the effects of stress from happening," Dr. Bhatnagar said.

The research team will use an emerging technology called DREADDs (designer receptors exclusively activated or inhibited by designer drugs) to modulate orexin release in the rats. These viral vectors, which have mutated receptors that are either stimulatory or inhibitory, are injected into the brain where they enter the orexin cells. Researchers can then target the viral vectors through a drug administered peripherally to stimulate or inhibit the orexin cells.

Researchers will observe whether this manipulation of the orexin cells affects the rats' behavior during periods of stress and whether it is possible for vulnerable animals to become more resilient, and vice versa.

Initial data the researchers gathered on orexins came from a study supported by the <u>Defense Advanced</u> <u>Research Projects Agency</u>. That early research examined neural substrates of arousal and, in collaborations with the <u>Philadelphia VA Medical Center</u>, focused on clinical studies of military service members with PTSD.

Dr. Bhatnagar also is a co-primary investigator of a <u>National Institutes of Health</u>-funded study on adolescent stress that eventually could provide insights into the specific involvement of orexins.

"There's very clear literature that stress in early life has long-lasting impact for producing depression and anxiety," Dr. Bhatnagar said. "We don't know if the orexin system is important in mediating resilience or vulnerability to early life stress as it develops across the lifespan. We hope to gather enough data to expand our research to look at the pediatric and adolescent periods."

Turning Off Allergic Reactions by Turning On Enzymes

Allergies are an uncomfortable fact of life for many children and adults around the world. In a new study funded by the <u>National Institute of Allergy and Infectious Diseases</u> (NIAID), researchers at <u>The Children's</u> <u>Hospital of Philadelphia</u> are hoping to figure out how to activate certain enzymes in the cell to prevent or treat allergic disease.

Chronic allergic disorders affect millions of individuals worldwide, and their frequency is increasing, especially in children and adults living in the U.S. Too often, multiple allergic diseases, such as asthma, food allergies, atopic dermatitis, and some gastrointestinal disorders can occur in a single patient.

Researchers are studying the underlying biological features that could be common from one allergic disease to another. They are particularly interested in how two small adapter proteins, known as Ndfip1 and Ndfip2, activate enzymes called E3 ubiquitin ligases. The solution to this cellular puzzle could play an important role in preventing chronic allergies.

"A small protein, ubiquitin, is the basis for the garbage disposal system of the cell," explained <u>Paula M.</u> <u>Oliver, PhD</u>, who is part of the Cell Pathology Division at CHOP and an associate professor of Pathology and Laboratory Medicine at the <u>Perelman School of Medicine at the University of Pennsylvania</u>. "When ubiquitin is tagged to a protein, one of the outcomes can be degradation of that protein. So it is the cell's way of removing unneeded proteins. When you don't get rid of those proteins, you can get allergic disease."

Dr. Oliver's research team is using genetically engineered mice to study E3 ubiquitin ligase function. The researchers previously found that mice in which a particular ligase — aptly named ITCH — cannot function develop an allergic dermatitis-like phenotype that causes them to scratch. The mice also develop an inflammation of the lungs reminiscent of asthma and gastrointestinal disorders that have features similar to food allergies.

Dr. Oliver's current project, which received NIAID funding in July 2014, builds on previous findings. The research team already has figured out how E3 ubiquitin ligases remain inactive in a closed, "off" position until Ndfip1 and Ndfip2 seem to open them up and turn them "on."

"We took the next step in thinking that maybe there are some ways of forcing that to happen and that we might design therapeutic strategies to turn on these enzymatic pathways in cells to prevent or treat allergic disease," Dr. Oliver said.

The ability to turn on cells' enzymatic pathways would be an exciting alternative to current treatments for allergic disease that globally shut down immune function, Dr. Oliver noted. This potential alternative would disarm only the component of the immune system that drives allergic responses, without affecting its ability to respond to viruses or pathogenic bacterial infections, she explained.

Dr. Oliver's research team will work to develop therapeutic methods to regulate the activation of E3 ubiquitin ligases. Specifically, the researchers will design small penetrating peptides aimed at catalyzing the transfer of ubiquitin to a substrate protein in the cell. They also will partner with a local company on a second possible approach, creating small molecule activators of the ligases.

"We are quite sure that there are other mechanisms that might control these things as well, so we're continuing to understand exactly how this happens," Dr. Oliver said. "We're also trying to understand what the substrates are that need to be gotten rid of, because that might tell us more about how allergic diseases start or which proteins are important in driving allergic diseases."

In addition to the NIAID funding, Dr. Oliver's work is supported by the American Asthma Foundation.



Many parents would love to find a better treatment for childhood obstructive sleep apnea syndrome (OSAS) than surgically removing their child's tonsils and adenoids. While an adenotonsillectomy, currently the primary therapy for OSAS, is relatively safe, about 3 percent of children have significant post-operative hemorrhaging, and other complications can also occur.

<u>Carole L. Marcus, MBBCh</u>, director of the <u>Sleep Center</u> at The Children's Hospital of Philadelphia, might be able to help.

Researchers from the Sleep Center launched the "Steroids for Pediatric Research in Kids (SPARK)" trial in September 2014 to investigate the use of nasal corticosteroids as a possible treatment for OSAS. According to Dr. Marcus, OSAS is seen in 2 to 4 percent of children, but is greatly underdiagnosed.

Usually, a blockage from enlarged tonsils or adenoids obstructs the child's breathing and disrupts his or her sleep in what is known as apneas and hypopneas. If OSAS is left untreated, it can result in significant complications, ranging from behavioral problems and sleepiness in mild-to-moderate cases, and cognitive abnormalities, high blood pressure, and growth disturbances in more severe cases.

Dr. Marcus said she learned from being a co-investigator on a previous childhood OSAS study that families want better treatments and more therapeutic choices. "Most families were hoping to hold off on surgery because they were scared," she pointed out. The earlier study, the Childhood Adenotonsillectomy Study for Children With OSAS (CHAT Study), specifically compared the effectiveness of surgery vs. watchful waiting for OSAS.

Nasal steroids may prove to be a viable alternative treatment for pediatric OSAS. Over the past few years, several small, short-term studies reported nasal steroids offered overall benefits for mild OSAS cases. But the studies did not include more severe cases of OSAS, and the results varied tremendously among individuals.

Further, the <u>American Academy of Pediatrics</u> clinical practice <u>guidelines</u> for the diagnosis and management of OSAS, which were issued in 2012 and chaired by Dr. Marcus, included nasal steroids as a treatment option. However, there was not enough evidence about the nasal steroids' effectiveness for the academy to provide a strong recommendation.

With funding from the <u>National Heart, Lung, and Blood Institute</u>, Dr. Marcus and colleagues launched the SPARK study to increase knowledge about the effect of nasal steroids and to identify which subgroups of patients with OSAS are most likely to benefit. For example, the research team will determine if children with asthma and/or atopy respond better to nasal steroids. Another subgroup they will focus on is African-American children because strong data from the CHAT Study and others found they have more severe OSAS and do not respond as well to surgery.

Sophisticated genetic tests used in the SPARK study will help researchers further characterize responders vs. non-responders. The double-blind, randomized control trial also will assess nasal steroids' duration of action and possible side effects, which for a small number of children can include growth problems, ocular abnormalities, and adrenal suppression.

Other concerns will also be addressed. "Does the disease recur if you stop nasal steroids?" Dr. Marcus asked. "Is it cured forever? Do you keep doing sleep studies? If kids are on the steroids long-term, are you likely to see complications?"

In order to answer those questions, children will be randomly chosen to receive either nasal steroids or a placebo for three months. After three months, those receiving the nasal steroid will be re-randomized to receive either ongoing steroids or a placebo for another nine months.

The multidisciplinary study team will include investigators from general pediatrics and several specialty areas including sleep medicine, endocrinology, ophthalmology, allergy, and otolaryngology. The team's goal is to randomize 156 participants from these diverse practice settings.

"I'm hoping we'll find a nonsurgical alternative for some children but that it also will lead to more personalized medicine," Dr. Marcus, who is also a professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania. "One treatment does not fit all."



Discovery Unites Three Families with Rare Syndrome

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Discovery Unites Three Families with Rare Syndrome

When they met as a group for the first time, Leta, Liam, and Nadira seemed to bond instantly. All three are under 4 feet tall, have similar mannerisms, wide-set eyes, and bubbly personalities. They live with chronic respiratory problems and other medical challenges, in addition to cognitive and physical developmental delays.

"They look more like siblings than their actual blood siblings," said Melissa Ashton-Grant, mother of Nadira. "To see how they interacted with each other, it felt right."

The children's similarity was no coincidence — and confirming and understanding their connection was no small matter. The three families gathered in March to celebrate because researchers at <u>The Children's</u> <u>Hospital of Philadelphia</u> had discovered the rare genetic mutation their children share, and had given their cryptic constellation of symptoms a name: <u>CHOPS Syndrome</u>. CHOPS is an acronym that stands for Cognitive impairment and coarse facial features, Heart defects, Obesity, Pulmonary involvement, Short stature and skeletal dysplasia (abnormal bone development).

A team led by <u>Ian D. Krantz, MD</u>, co-director of the <u>Individualized Medical Genetics Center</u> at CHOP and an associate professor at the Perelman School of Medicine at the University of Pennsylvania with colleagues from the University of Tokyo, reported in <u>Nature Genetics</u> that a mutation in the gene AFF4 causes CHOPS Syndrome. The mutated AFF4 gene produces mutated proteins, which then accumulate and cause a cascade of abnormalities in other genes controlled by AFF4, leading to harmful effects in multiple organs and biological systems.

It is a finding the team could not have made without Nadira, age 11; Leta, 17; Liam, 15; and their families.

A DANGLING THREAD

For many years, Nadira Grant's medical odyssey felt like a dangling thread. The little girl's case was a question no doctor could answer. From her first respiratory crisis as a young infant, through her slowed physical and cognitive development, doctors could not identify the reason behind her symptoms. As far as they could tell, she was one of a kind.

"For so many years, I felt that I was alone going through this," recalled her mother, Melissa, of Brooklyn. "I didn't have anyone I could relate to."

INSPIRATION

Along with her husband and a supportive extended family, Melissa persevered, raising her warm, loving daughter and seeing her through the unexplained medical and developmental challenges, never knowing what lay ahead. She also worried during subsequent pregnancies: Would Nadira's two little sisters be at risk of developing the same mysterious disorder?

"Not knowing what the future has in store, the uncertainty made it much harder as a family," she said.

FINDING CHOPS

Melissa now has answers to some of these questions since Nadira's diagnosis of CHOPS Syndrome.

Dr. Krantz had first suspected the three children were connected when his evaluation of all of them revealed their similar clinical features and characteristics. Kosuke Izumi, MD, PhD, then a resident in pediatrics and genetics in Dr. Krantz' lab, spearheaded research to confirm that suspicion. The research team used relatively new technology to scan the children's whole exome — the 20,000 expressed genes in the body — and identified their unique common difference in one of those genes – *AFF4*.

Dr. Krantz is excited by the discovery's potential to help caregivers like Melissa better manage the disorder in their loved ones, and to better understand the underlying biology of a key developmental pathway.

"We can more effectively counsel families about recurrence risk for themselves and family members," Dr. Krantz added.

They now know CHOPS Syndrome is a *de novo* condition — being caused by a new mutation arising in a single egg or sperm that went on to form the affected child, but not present in the patient's parents. This reassured the CHOPS Syndrome families that any of their other children would not carry the change and that future children are extremely unlikely to be affected.

THREADS INTERWOVEN

Finally having an explanation and finding each other also means that the families' medical odyssey is no longer a lonely one.

Leta's mother, Lainey Moseley, of Philadelphia, said, "We share a medical bond and now have a support group to compare notes about our kids, like what medicines are the doctors prescribing for their lung disease? What kind of communication devices do we each use? Does your child have the same hyperactive personality as mine?"

In an <u>interview with *People* magazine</u>, Liam's mother, Kathleen Hilferty, of West Chester, Pa., agreed: "I finally have someone to talk to who knows exactly what I'm dealing with."

INSPIRATION

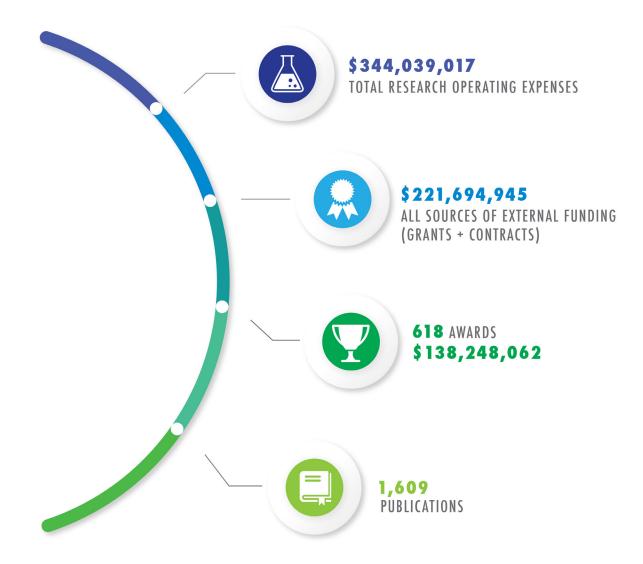
While the three families are finding strength in their newly interwoven lives, there is also the possibility that their community will grow. As has happened with a number of rare disorders that are being identified thanks to genetic sequencing, more families are beginning to come forward for evaluation and three more children have been identified from as far away as Australia and France. Perhaps other families' struggles for a diagnosis will tie into the CHOPS tapestry soon.

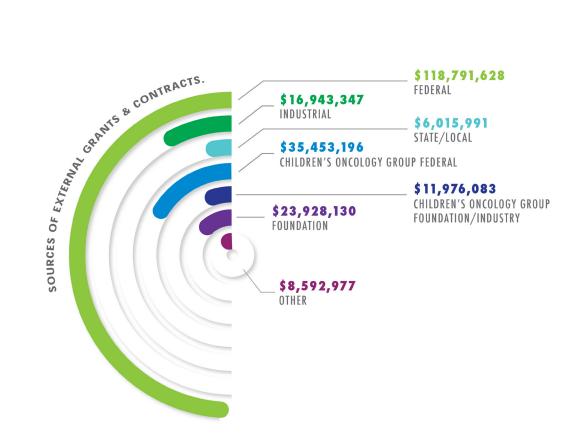
"If they find an answer, they will share that sense of relief we've all felt," Melissa said.

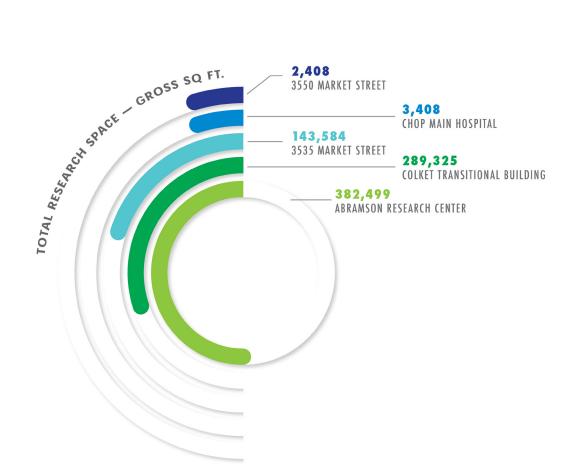


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Who's Who

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Dennis Durbin, MD, MSCE Director, Office of Clinical and Translational Research

Mary Tomlinson Deputy Administrative Director Senior Vice President, Research Administration

Centers of Emphasis

<u>Center for Applied Genomics</u> Director: <u>Hakon Hakonarson, MD, PhD</u>

Center for Autism Research Director: Robert Schultz, PhD

Raymond G. Perelman Center for Cellular and Molecular Therapeutics Director: <u>Beverly Davidson, PhD</u>

<u>Center for Childhood Cancer Research</u> Director: <u>Stephen P. Hunger, MD</u>

Center for Clinical Pharmacology Director: <u>Athena F. Zuppa, MD, MSCE</u>

<u>Center for Injury Research and Prevention</u> Directors: <u>Flaura Winston, MD, PhD</u>, and <u>Kristy Arbogast, PhD</u>

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

<u>Center for Pediatric Clinical Effectiveness</u> Director: <u>Theokolis Zaoutis, MD, MSCE</u>

PolicyLab Director: David Rubin, MD, MSCE

Research Affinity Groups

Developmental Biology Group Leaders: <u>Judy Grinspan, PhD</u>, and <u>Stewart Anderson, MD</u>

DNA-Protein Interaction Group Leaders: <u>Struan Grant, PhD</u>, and <u>Andrew Wells, PhD</u> Fetal Biology and Therapy Group Leader: <u>Alan Flake, MD</u>

Genes, Genomes, and Pediatric Disease Group Leaders: <u>John Maris, MD</u>, and <u>Nancy Spinner, PhD</u>

Health and Behavior Group Leaders: <u>Stephen Leff, PhD</u>, and <u>Joel Fein, MD, MPH</u>

Metabolism, Nutrition, and Physical Development Group Leader: <u>Babette Zemel, PhD</u>

Mitochondria Group Leader: <u>Marni Falk, MD</u>

Neuroscience Group Leader: <u>Michael Robinson, PhD</u>

Normal and Malignant Hematopoiesis Group Leader: <u>Carolyn Felix, MD</u>

Proteins Group Leader: <u>Yair Argon, PhD</u>

Protective Immunity and Immunopathology Group Leaders: <u>Edward Behrens, MD</u>, and <u>Paula Oliver, PhD</u>

Stem Cells and Benign Hematopoiesis Group Leader: Mortimer Poncz, MD

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

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Distinguished Chair in the Department of Pediatrics Gail Slap, MD

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

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Kwame Ohene-Frempong Endowed Chair in Pediatric Hematology Pending Appointment

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

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Jane Fishman Grinberg Endowed Chair in Stem Cell Research Mortimer Poncz, MD

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

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

Werner and Gertrude Henle Endowed Chair Phyllis Dennery, MD

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

Joseph Lee Hollander Endowed Chair in Pediatric Rheumatology, University/CHOP Chair Pending Appointment

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

Edmond F. Notebaert Endowed Chair in Pediatric Research Pending Appointment

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

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

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

Regional Autism Center Endowed Chair Robert T. Schultz, PhD

Mildred L. Roeckle Endowed Chair at The Children's Hospital of Philadelphia Andrei Thomas-Tikhonenko, PhD

Lucy Balian Rorke-Adams Endowed Chair in Neuropathology Pending Appointment

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

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Thomas Frederick McNair Scott Endowed Chair in Pediatrics Theoklis Zaoutis, MD, MSCE

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

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

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Wawa Endowed Chair in International Adoption Susan Friedman, MD

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Mai and Harry F. West Endowed Chair in Pediatric Research Pending Appointment

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

Nancy Abramson Wolfson Endowed Chair in Health Services Research Jeffrey H. Silber, MD, PhD

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

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Cornerstone, CHOP Research's blog

The CHOP Research Institute Press Releases

Bench to Bedside, CHOP Research's Monthly News Publication

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