

Defining the Future

It was a banner year for The Children's Hospital of Philadelphia and the Research Institute. We achieved a number of firsts, notably being named the top-ranked children's hospital by both *U.S. News & World Report* and *Parents* magazine. And the Research Institute leads other independent children's hospitals in NIH funding.

These achievements have helped cement our reputation as a leader in both the lab and the clinic. It's important, however, to view these accomplishments not just individually but in the tradition of our pioneering research. As bright as the promise is today of improving the health and well-being of children around the world, the future is even brighter.

We are leading the way in innovative therapies that save children's lives. The passion and expertise of our investigators contribute to the collective scientific knowledge and deliver promising therapies to patients. In addition, our investigators have assumed leadership positions that shape legislation and propel change broadly, and our commitment to training the next generation of scientists has never wavered.

In essence, we are not only leading pediatric research. We are defining its future.



DEFINING THE FUTURE

Taking Cancer Research to the Next Level

Bringing Expertise to Government Commission to Eliminate Child Abuse

Mining Electronic Medical Data to Advance Genetic Research

Celebrating the Birth of Our 1,000th Fetal Surgery Patient

Challenging the Conventional 'Wisdom' of Alternative Therapies

Setting the Stage for the Next Generation of Scientists

TAKING CANCER RESEARCH AND CARE TO THE NEXT LEVEL



Two Children's Hospital physicians are blazing new trails in childhood cancer research and giving renewed hope to families across the country.

The first pediatric Dream Team of researchers, led by John M. Maris, MD, director of CHOP's Center for Childhood Cancer Research (CCCCR), will build on pioneering results realized by CCCR's Director of Translational Research Stephan Grupp, MD, PhD, to treat childhood leukemia. These two researchers are actively involved in new classes of treatments to improve children's survival and quality of life in the 21st century.

Dr. Grupp recently achieved groundbreaking results using an innovative T cell therapy to treat a patient with an aggressive form of childhood leukemia called acute lymphoblastic leukemia (ALL). The most common form of childhood leukemia and the most common childhood cancer, ALL is highly treatable for approximately 85 percent of cases. But the remaining 15 percent of such cases resist standard therapy.

Dr. Grupp's work made all the difference for 7-year-old Emma Whitehead, whose prospects were bleak when her cancer relapsed after she received the conventional treatment for ALL. With few other viable options, Dr. Grupp turned to an experimental therapy using bioengineered T cells that were designed to multiply rapidly and destroy leukemia cells. In other words, Dr. Grupp reprogrammed Emma's own immune cells to attack the ALL cells.

As the workhorses of the immune system, T cells recognize and attack invading disease cells. However, cancer cells fly under the radar of immune surveillance, evading detection by T cells. In what's known as CTL019 therapy, CAR T cells (chimeric antigen receptor T cells) are engineered to specifically target B cells, which become cancerous in certain leukemias like ALL, as well as types of lymphoma, another cancer of the immune cells.

Amazingly, just three weeks after the treatment, Emma's doctors found no traces of cancer. A year later, Emma remains healthy and cancer-free.

Such dramatic results bode well for successfully treating resistant cases of childhood ALL and possibly other types of cancer as well. "These engineered T cells have proven to be active in B cell leukemia in adults," said Dr. Grupp. "We are excited to see that the CTL019 approach may be effective in untreatable cases of pediatric ALL as well. Our hope is that these results will lead to widely available treatments for high-risk B cell leukemia and lymphoma, and perhaps other cancers in the future."

Emma received the therapy as part of a research clinical trial conducted by investigators at CHOP and the Perelman School of Medicine at the University of Pennsylvania. Recently, Dr. Grupp and the CHOP/ Penn team have reported an 82 percent complete response rate in a study that has included 20 children — including Emma and one other pediatric patient — and 5 adults with ALL. A major update on this study will be presented at the upcoming American Society of Hematology annual meeting in December.

Emma was a guest of honor at the announcement of the first pediatric “Dream Team” of cancer researcher solely focused on creating new treatments for the most challenging childhood cancers. CHOP’s Dr. Maris was chosen to co-lead the Dream Team, which was announced at the American Association for Cancer Research annual meeting in Washington, D.C. Crystal L. Mackall, MD, chief of the Pediatric Oncology Branch of the National Cancer Institute, is the Dream Team’s other co-leader.

“The motivation for the creation of this collaborative research project is the realization that completely new strategies are needed if we are to have curative therapies for all childhood cancers,” said Dr. Maris. “Our team hopes to rapidly develop more precise and effective treatments based on the unique characteristics of each child’s tumor, here focusing on the genetic changes that make the cancer cells different from the rest of the child’s body.”

The Dream Team will receive \$14.5 million in funding over 4 years, provided by Stand Up to Cancer (SUC2) and St. Baldrick’s Foundation. The research project, called “Immunogenomics to Create New Therapies for High-Risk Childhood Cancers,” melds two disciplines that have historically functioned independently: immunotherapeutics and genomics. The goal of the project is to rapidly translate promising basic research into transformative, targeted treatments that will improve cure rates in children’s cancer.

Recent research in genomics has shown that pediatric cancers are fundamentally different from adult cancers, explained Dr. Maris. Children’s cancers are less likely to arise due to recurring mutations that can be countered with small molecule drugs. Instead, the Dream Team will exploit the unique feature of molecules on cell surfaces of childhood cancer cells that are not present on normal cells, and offer targets for treatments employing bioengineered agents working through the immune system.

“The success of the program will ultimately be judged by the number of lives saved through our efforts,” said Dr. Maris.

The Dream Team will take on the four most deadly pediatric cancers: malignant brain tumors, high-risk leukemias (such as the type of ALL that Emma had), neuroblastomas (which affect the peripheral nervous system), and sarcomas (other tumors of bone and other tissue). Dr. Grupp and Tom Curran, PhD, FRS, deputy director of the CHOP Research Institute, will lead the CHOP-based research efforts.

BRINGING EXPERTISE TO GOVERNMENT COMMISSION TO ELIMINATE CHILD ABUSE



Research Institute investigators are often more than just leaders in their fields. Seemingly tireless, many CHOP researchers regularly use their expertise to help improve public policies and legislation related to children's health, while also advancing pediatric medical research. By contributing to interdisciplinary programs and government panels, Children's Hospital researchers "lead from the front," advancing changes that will improve the health and welfare of children now and in the future.

In a recent significant example of this, co-director of The Children's Hospital of Philadelphia's PolicyLab [David Rubin, MD, MSCE](#), was recently appointed to a government commission tasked with working to end child abuse and neglect-related deaths. Dr. Rubin is one of twelve experts from a variety of fields to be named to the Commission to Eliminate Child Abuse and Neglect Fatalities, and one of just six appointed by President Obama. Notably, Dr. Rubin is the only health care provider appointed to the commission.

The commission was established as part of the [Protect Our Kids Act of 2012](#). By creating a commission of child welfare experts, pediatricians, and jurists, the Protect Our Kids Act seeks to "develop a national strategy and recommendations for reducing fatalities resulting from child abuse and neglect," according to the law's text. A rare example of bipartisan accord, the House of Representatives voted 330-77 in favor of the act before it quickly proceeded through the Senate. President Obama signed the act into law on January 14, 2013.

The Protect Our Kids Act was inspired in part by a [2011 Government Accountability Office \(GAO\) report](#) on child fatalities from abuse and neglect. According to the [National Child Abuse and Neglect Data System \(NCANDS\)](#) — a voluntary reporting system that collects data from all 50 states as well as the District of Columbia and Puerto Rico — in 2009 there were 1,770 child deaths due to abuse and neglect.

However, the true number of child deaths that year was likely higher, the GAO report states, both because the NCANDS is a voluntary data-collection system, and because "nearly half of states report to NCANDS data only on children who were already known to" child protective services (CPS). However, not all children who die from abuse or neglect are brought to the attention of CPS, the report states.

“As a society, we should be doing everything in our collective power to end child deaths and near deaths from maltreatment, and the collection and reporting of comprehensive data on these tragic situations is an important step toward that goal,” the GAO report concluded.

As a first step in preventing child deaths from mistreatment, the Protect Our Kids Act charges the Commission to Eliminate Child Abuse and Neglect Fatalities with conducting a survey of child welfare and protection services, in order to determine the effectiveness of existing policies and services. The commission, which will offer education opportunities to graduate students, will also examine barriers to improving child welfare, child abuse and neglect trends, and methods of improving data collection.

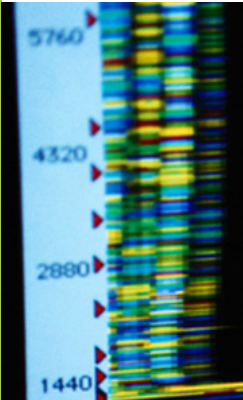
Based on its work, the commission will “develop recommendations to reduce fatalities from child abuse and neglect,” as well as developing data tracking guidelines. The commission is due to submit a report to the President and Congress on its work within two years.

Six members of the commission were appointed directly by President Obama, while three were appointed by the House of Representatives and three by the Senate. In addition to Dr. Rubin, commission members include [Theresa Martha Covington, MPH](#), director of the National Center for the Review and Prevention of Child Deaths, [Marilyn Bruguier Zimmerman, MSW](#), director of the National Native Children’s Trauma Center, and Susan Dreyfus, president and CEO of the [Alliance for Children and Families](#). The Commission will be chaired by [David Sanders, PhD](#), executive vice president of [Casey Family Programs](#).

Along with current co-director [Kathleen Noonan, JD](#), in 2008 Dr. Rubin founded PolicyLab, which works to develop evidence-based solutions for the most challenging health-related issues affecting children. In addition to his role at PolicyLab, Dr. Rubin is an associate professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania, a senior fellow at the [Leonard Davis Institute of Health Economics](#), and an associate program director of the Robert [Wood Johnson Clinical Scholars Program](#) at the University of Pennsylvania.

“As a pediatrician in Philadelphia, I see the toll that stress has on children and families,” Dr. Rubin said. “I am honored to have the opportunity to serve this commission and hope to bring my experiences serving children and families to think preventatively at the system level about what can be done to avoid unnecessary childhood injuries and fatalities.”

MINING ELECTRONIC MEDICAL DATA TO ADVANCE GENETIC RESEARCH



The CHOP Research Institute has joined a prominent network of hospitals and research bodies to translate genetic data into improved care that will benefit both current patients and future generations. The network is defining the future by using genetic information and electronic medical records to identify the genetic contributions to disease, with the overall goal of giving health care providers the tools to apply genomic knowledge to patient care.

CHOP's Center for Applied Genomics (CAG) was recently awarded approximately \$2.5 million over three years to mine electronic medical record data for future clinical use as part of the ongoing Electronic Medical Records and Genomics (eMERGE) Network. Hakon Hakonarson, MD, PhD, the director of CAG, serves as the principal investigator of the project and leads the network's pediatric-centered efforts.

Being a part of the eMERGE network will "elevate the important information that genomic information delivers," noted Dr. Hakonarson.

CAG's inclusion in eMERGE is especially significant because it currently has the largest pediatric biorepository — comprising more than 40,000 children — and genome-wide association study (GWAS) genotyping facility in the world. CHOP is one of only three pediatric sites selected to take part in eMERGE, now in its second phase, and one of only 10 sites included overall. So in addition to being selected to join eMERGE Phase II, CAG is taking on the role of pediatric leader in the network.

Further, CAG's participation will help advance the study of minority genetics because its biorepository includes a large minority population. This is an important contribution because only modest numbers of African-American patients have been included in GWAS to date. Approximately 38 percent of the subjects in CAG's biorepository are African American, 6 percent Hispanic, and 4 percent are Asian.

Dr. Hakonarson and his team plan to use patients' electronic medical records (EMRs) to mine "disease phenotypes and environmental exposure data in over 40 phenotypes" in order to establish a database for future clinical use. They will work to enable future sharing of genetic and genomic data with patients and establish guidelines for CAG's biorepository and databases. In doing so, Dr. Hakonarson hopes to generate informed consent procedures that will foster clinical use of genomic data in concert with other eMERGE members

CAG also plans to use this data to determine pharmacogenetic response profiles, working to determine biomarkers to inform clinical care. While the initial eMERGE funding will largely support disease susceptibility studies, Dr. Hakonarson also hopes to extend his group's pharmacogenetic research through additional grants.

Funded and organized by the National Human Genome Research Institute (NHGRI), the eMERGE initiative is a consortium of U.S. medical institutions brought together to “develop, disseminate, and apply approaches to research that combine DNA biorepositories with electronic medical record (EMR) systems, for large-scale, high-throughput genetic research,” according to NHGRI. In addition to including an expanded number of institutions, a key goal of eMERGE Phase II is to explore ways to best incorporate genetic information into EMR data so it can be used in a clinical setting.

CELEBRATING THE BIRTH OF OUR 1,000TH FETAL SURGERY PATIENT



Audrey Rose Oberio made history just by being born. Audrey, whose birth marked the Hospital's 1,000th fetal surgery patient, was born to Jackie and Gideon Oberio of Maryland.

CHOP's Center for Fetal Diagnosis and Treatment gave the Oberio family new hope and optimism for their baby's future. The Center's internationally renowned specialists treat the full range of fetal anomalies through highly complex surgical interventions to repair birth defects in the womb, changing outcomes for many children before they are even born.

The Center leads the way in fetal surgeries around the world. Approximately 4,000 fetal surgeries have been conducted worldwide, which means a quarter of them have been performed at CHOP, the largest number of any hospital in the world. The Center is firmly established at the forefront in providing and advancing fetal therapy, widely recognized as one of the most promising fields in pediatric medicine.

When Jackie Oberio was 19 weeks pregnant, the couple learned their unborn daughter had myelomeningocele, the most severe form of spina bifida, a condition in which part of the developing spine fails to close properly. With conventional postnatal surgery, myelomeningocele can still result in lifelong disabilities, including paralysis, bladder and bowel problems, and cognitive impairments.

After talking to local specialists and doing online research, the Oberios discovered that the Center for Fetal Diagnosis and Treatment pioneered a surgical procedure to repair spina bifida before birth. The Center's team of physicians found that addressing spina bifida by operating on the baby in the womb, months before birth, could reduce the need to divert fluid from the brain, improve neurologic function, and increase the likelihood that a child would be able to walk independently.

When she was born post-surgery, Audrey Rose weighed 5 pounds, 8 ounces, and had nothing more than a scar where her doctors had operated.

"Although birth defects remain the leading cause of infant mortality in the United States, we have been able to develop and share innovations that help advance treatment for these defects, relying on tools, techniques and experience not available 30 years ago," said N. Scott Adzick, MD, the Medical Director of the Center for Fetal Diagnosis and Treatment at CHOP, where he is also Surgeon-in-Chief.

Established by Dr. Adzick in 1995, the Center is now the largest and most comprehensive fetal program in the world, having welcomed nearly 15,000 expectant mothers from all 50 states and more than 50 countries. Each week at CHOP, highly sophisticated surgical teams repair spina bifida and other birth defects in the womb, place fetal shunts to treat life-threatening congenital conditions, or perform minimally invasive procedures in the mother's uterus to treat complications in fetal twins. The Center staff also manages pregnancies complicated by birth defects, in which newborns need immediate specialized medical care or surgery after delivery.

In 2011, Dr. Adzick and his team published the results of more than two decades of research in the *New England Journal of Medicine* that showed fetal surgery can significantly improve the outcomes for children diagnosed in utero with spina bifida. Their study demonstrated that two and a half years after fetal surgery children with spina bifida were better able to walk when compared to children who received surgery shortly after birth, and patients who received fetal surgery scored better on tests of motor function.

"It's very gratifying to take this idea forward over 30 years, starting with a concept and now offering hope — to families, mothers, and the children themselves," said Dr. Adzick.

CHALLENGING THE CONVENTIONAL 'WISDOM' OF ALTERNATIVE THERAPIES



Alternative medicine, including dietary supplements and acupuncture, has become increasingly popular with many people. However Paul Offit, MD, isn't one of them, and isn't afraid to say so.

Dr. Offit is a leader in the medical community's ongoing crusade against misinformation for his willingness to speak his mind, question popular (and at times ill-informed) wisdom, and defend science against its detractors. He is the chief of CHOP's Division of Infectious Diseases and directs CHOP's Vaccine Education Center. Dr. Offit is also a co-creator of the rotavirus vaccine Rotateq.

In a move sure to earn him some new critics, Dr. Offit recently published a new book, *Do You Believe in Magic?: The Sense and Nonsense of Alternative Medicine*. The book has received a great deal of attention from the media, including *NBC News* and *CBS This Morning*.

In his latest book, Dr. Offit examines the science and science fiction behind alternative therapies such as megavitamins and alternative treatments including coffee enemas and laetrile, a chemically modified form of amygdalin, a naturally-occurring substance found mainly in the pits of apricots and peaches, used to prevent and treat cancer.

Dr. Offit acknowledges in the book that people often turn to alternative treatments after becoming disillusioned with conventional medicine. However, while "conventional therapies can be disappointing, alternative therapies shouldn't be given a free pass," he says.

In fact, alternative medicine "can be quite harmful," Dr. Offit points out in the book. "Chiropractic manipulations have torn arteries, causing permanent paralysis; acupuncture needles have caused serious viral infections or ended up in lungs, livers, or hearts; dietary supplements have caused bleeding, psychosis, liver dysfunction, heart arrhythmias, seizures, and brain swelling; and some megavitamins have been found to actually *increase* the risk of cancer," he writes.

Conventional and alternative therapies should "be held to the same high standard of proof," he notes in *Do You Believe in Magic?* For example, because megavitamins and other supplements are not regulated by the U.S. Food and Drug Administration, "consumers don't know that taking megavitamins could increase their risk of cancer and heart disease and shorten their lives," Dr. Offit writes.

“The truth is, there’s no such thing as conventional or alternative or complementary or integrative or holistic medicine. There’s only medicine that works and medicine that doesn’t,” he says in the book.

No stranger to controversy, hate mail, and even death threats, Dr. Offit’s previous books include *Deadly Choices*, about the anti-vaccine movement, and *Autism’s False Prophets*, about the now-discredited connection between vaccines and autism.

SETTING THE STAGE FOR THE NEXT GENERATION OF SCIENTISTS



As one of the premier pediatric research institutions in the country, The Children's Hospital of Philadelphia Research Institute has long been committed to training the next generation of pediatric researchers and clinicians. The Institute offers education programs at all levels, from those geared to undergraduates to opportunities for physician fellows.

During fiscal 2013, the Research Institute received funding to support training programs in a wide variety of disciplines. Programs in pharmacology, hematology, genetics, cardiology, oncology, endocrinology, and neonatology offered trainees the chance to gain hands-on experience and exposure to advanced scientific training and research techniques.

For example, the Neurodevelopmental Disabilities Training Program (NDTP) was established as a joint initiative of Children's Hospital and the University of Pennsylvania in 1998, and is led by Children's Hospital neuroscientist Michael Robinson, PhD. During fiscal 2013, the NDTP received an additional five years of funding totaling more than \$1.7 million from the NIH's National Institute of Neurological Disorders and Stroke.

Neurodevelopmental "disorders have diverse genetic and environmental causes, but they share many co-morbidities," said Dr. Robinson. "Therefore the rationale was to bring together researchers from diverse training backgrounds and scientific expertise to both advance interdisciplinary training and encourage collaboration."

The NDTP pairs trainees with faculty mentors, who provide advanced research training designed to help the trainees achieve their career goals. In addition to working closely with a mentor, NDTP trainees attend lectures and seminars, participate in clinical practica, and develop skills like grant writing. Trainees who have taken part in the program come from a variety of disciplines, including neurology and neuroscience, physics, and clinical psychology. Of the 26 trainees who have completed training, 13 have taken faculty positions at prestigious academic institutions across the country.

"It is gratifying to support such a talented group of individuals. Like a parent, I'm proud of the accomplishments of these trainees." Dr. Robinson noted.

Several of the Research Institute's Centers of Emphasis also offer their own training programs. The Center for Childhood Cancer Research, for example, offers post-doctoral trainees opportunities to participate in fellowships and research training.

And the [Center for Injury Research and Prevention](#) (CIRP) has long been focused on training, with programs for both graduate and undergraduate researchers.

The Center offers programs in four [scientific disciplines](#): behavioral science, epidemiology and biostatistics, engineering, and outreach and advocacy. Aimed at undergraduates and graduate students, trainees who participate in CIRP's programs attend project and mentorship meetings, screen and enroll research project participants, submit protocols, and manage data.

CIRP also has several programs specifically for undergraduates studying behavioral science, education, engineering, injury prevention, or related fields. Supported by the [National Science Foundation](#), the [Research Experiences for Undergraduates](#) (REU) program offers student-scholars the chance to collaborate with CIRP mentors over the course of an intensive 10-week summer schedule. Living on the University of Pennsylvania campus, REU trainees work with their mentors while attending workshops, seminars, and field trips, while receiving training in research ethics and conducting studies.

"As fully integrated research team members, student trainees work alongside CIRP scientists helping to advance the science toward creating positive impact on the lives of children, adolescents, and young adults," said CIRP training manager [Carol Murray, MSS, MLSP](#). During fiscal 2013, 47 trainees took part in CIRP's programs, including 40 undergraduates, Murray said.

Speaking at the Research Institute's annual [Scientific Symposium](#), CHOP Research Chief Scientific Officer and Executive Vice President [Philip R. Johnson, MD](#), noted how CHOP Research's educational programs position the institution to meet the training challenges posed by decreased federal funding for research.

Another CHOP Research program, the [CHOP Research Institute Summer Scholars Program](#), which has a special emphasis on advancing translational pediatric research, "brings undergraduates into the Research Institute and shows them how great science is," Dr. Johnson said.

"These programs are the way we will build the future generation of scientists," Dr. Johnson said.

TRAILBLAZERS

New Gene Variants Linked to Neuroblastoma Risk

Antibiotic Usage Education, Interventions
Improve Prescription Practices

Lowering BMI Improves Insulin Sensitivity in Teens

Extending CPR Saves Lives, National Studies Find

Researchers Find New Cornelia deLange Syndrome Gene

Study Links BMI, Individuals of African Descent

CHOP Researchers Create Mitochondrial Disease Test

Genes Linked to Low Birth Weight, Diabetes Risk

Study Suggests Some Children Can 'Recover' From Autism

Study Suggests Fine-Tuning Drugs for Brain Tumors

Behavioral Interventions at Heart of New Study

New Award Looks at Antibiotic Use for Bacterial Infections

Autism Center Part of Landmark Grant

Grant May Lead to New Muscular Dystrophy Treatment



NEW GENE VARIANTS LINKED TO NEUROBLASTOMA RISK



Children's Hospital investigators discovered two gene variants that raise the risk of the pediatric cancer neuroblastoma. The study broadened the understanding of how gene changes can make a child susceptible to this early childhood cancer and how those changes can cause a tumor to progress.

Affecting the peripheral nervous system, neuroblastoma usually appears as a solid tumor in the chest or abdomen. It accounts for 7 percent of all childhood cancers, and 10 to 15 percent of all childhood cancer deaths.

The study team performed a genome-wide association study, comparing DNA from 2,800 neuroblastoma patients with that of nearly 7,500 healthy children. They found two common gene variants associated with neuroblastoma, both in the 6q16 region of chromosome 6. One variant is within the *HACE1* gene, the other in the *LIN28B* gene. They exert opposite effects: *HACE1* functions as a tumor suppressor gene, hindering cancer, while *LIN28B* is an oncogene, driving cancer development.

The current study showed that low expression of *HACE1* and high expression of *LIN28B* correlated with worse patient survival. To further investigate the gene's role, the researchers used genetic tools to decrease *LIN28B*'s activity, and showed that this inhibited the growth of neuroblastoma cells in culture.

"In addition to broadening our understanding of the heritable component of neuroblastoma susceptibility, we think this research may suggest new therapies," said first author Sharon J. Diskin, PhD.

ANTIBIOTIC USAGE EDUCATION, INTERVENTIONS IMPROVE PRESCRIPTION PRACTICES



As disease-causing microbes continue their worrisome trend of developing resistance to commonly used antibiotics, public health experts have called for more selective use of those medicines. A Children's Hospital study suggests that educating pediatricians in their offices, and auditing their prescription patterns, encourages them to choose more appropriate antibiotics for children with common respiratory infections.

"Although much research has focused on improving how hospitals use antibiotics, there have been few studies of interventions in outpatient settings, where the vast majority of antibiotic use occurs," said study leader and [infectious diseases](#) specialist [Jeffrey S. Gerber, MD, PhD](#). "We focused on increasing appropriate antibiotic prescribing in primary care practices."

Dr. Gerber and colleagues published their study of an "antimicrobial stewardship" program in [Journal of the American Medical Association](#). [Last year](#) Dr. Gerber and his team presented their research at the [IDWeek](#) conference, a joint meeting of the [Infectious Diseases Society of America](#), the [Society for Healthcare Epidemiology of America](#), [HIV Medicine Association](#), and the [Pediatric Infectious Diseases Society](#).

Antimicrobial stewardship, pointed out Dr. Gerber, usually involves prospective audits of prescription patterns — comparing the prescription for a given diagnosis to the current recommendations of professional organizations (in the current study, as issued by the [American Academy of Pediatrics](#)). For this study, stewardship also included personalized, private feedback reports to practitioners, advising them of whether their prescriptions followed current recommendations.

The study concentrated on whether the pediatricians prescribed narrow-spectrum antibiotics, as recommended, or broad-spectrum antibiotics for acute bacterial respiratory infections such as pneumonia, acute sinusitis, and streptococcal pharyngitis (or "strep throat"). All are common conditions for which children receive antibiotics.

The study team randomized 18 pediatricians' practices in CHOP's primary care network into two groups: one that received the intervention (an hour-long clinician-education session at the practice office, followed by audit and feedback of antibiotic prescribing), and a control group that did not receive the educational session, audit and feedback. The study encompassed nearly 1.3 million office visits by some 185,000 patients to 162 clinicians over a study period of 32 months, from 2008 to 2011.

Among the intervention practices, broad-spectrum antibiotic prescribing decreased from 26.8 percent to 14.3 percent, or nearly half, compared to a decrease from 28.4 percent to 22.6 percent in the control group. For children with pneumonia, the inappropriate broad-spectrum prescriptions declined by 75 percent among practices receiving the intervention.

LOWERING BMI IMPROVES INSULIN SENSITIVITY IN TEENS



Obesity has doubled in children and tripled in adolescents in the past 30 years, according to the CDC, raising the risk for developing health problems later in life, including diabetes.

A study involving Children's Hospital investigators found obese teenagers who reduced their body mass index (BMI) by 8 percent or more had improvements in insulin sensitivity, an important metabolic factor related to the later development of type 2 diabetes. The teens followed a family-based, lifestyle-modification weight loss program that offers the potential to become a broader model to reduce their BMI levels.

"This threshold effect that occurs at 8 percent suggests that obese adolescents don't need to lose enormous amounts of weight to achieve improvements," said pediatric endocrinologist [Lorraine Levitt Katz, MD](#), of [Children's Hospital's Diabetes Center for Children](#).

The findings were published in *The Journal of Pediatrics*. The article's first author is Pamela Abrams, MD, a member of the study team while at Children's Hospital. Children's Hospital psychiatrist [Robert I. Berkowitz, MD](#), who was the principal investigator of a clinical trial of weight loss treatments from which the researchers analyzed data for the current study, also contributed to the study.

The investigators looked at 113 primarily urban adolescents, aged 13 to 17, of whom 81 percent were female and 62 percent were African American. At the start of the study, their mean BMI was 37.1 — the severely obese range. Although none had type 2 diabetes, their obesity placed them at high risk for developing in the future.

An important goal of the study was to determine the threshold of weight loss that significantly impacted insulin sensitivity, glucose tolerance, and the presence of metabolic syndrome (MS). MS, as well as abnormal values in insulin sensitivity and glucose tolerance, is associated with the development of type 2 diabetes.

The research team found a significant improvement in all measures of insulin sensitivity. There was also a trend toward improvement in metabolic syndrome. And the threshold of 8 percent, the level at which a decreased BMI showed improved insulin sensitivity, was consistent with results found previously in adults.

EXTENDING CPR SAVES LIVES, NATIONAL STUDIES FIND



Children's Hospital researchers contributed to two studies showing that extending cardiopulmonary resuscitation (CPR) longer than previously thought useful saves lives in both children and adults. The teams analyzed the impact of duration of CPR in patients who suffered cardiac arrest while hospitalized.

"These findings about the duration of CPR are game-changing, and we hope these results will rapidly affect hospital practice," said [Robert A. Berg, MD](#), chief of [Critical Care Medicine](#) at Children's Hospital. Dr. Berg is also chair of the Scientific Advisory Board of the [American Heart Association's Get With Guidelines-Resuscitation](#) (GWTG-R), program a national registry that tracks and analyzes the resuscitation of patients after in-hospital cardiac arrests.

The investigators reported data from the GWTG-Resuscitation registry of CPR outcomes in thousands of North American hospital patients in two landmark studies, one of which was focused on children.

Dr. Berg was a co-author of the pediatric study, which was published in [Circulation](#). After analyzing the hospital records of 3,419 children in the U.S. and Canada from 2000 through 2009, the investigators found that among children who suffered in-hospital cardiac arrest, more children than expected survived after prolonged CPR. Of those children who survived prolonged CPR — which is defined as lasting longer than 35 minutes — over 60 percent had good neurologic outcomes.

The conventional thinking has been that CPR is futile after 20 minutes, but these results challenge that, said Dr. Berg.

The pediatric results parallel those found in the second GWTG-R investigation, which examined 64,000 adult patients with in-hospital cardiac arrests between 2000 and 2008. That study showed patients at hospitals in the top quartile of median CPR duration (25 minutes), had a 12 percent higher chance of surviving cardiac arrest, compared to patients at hospitals in the bottom quartile of median CPR duration (16 minutes). Survivors of prolonged CPR had similar neurological outcomes to those who survived after shorter CPR efforts.

The American Heart Association and American Stroke Association named the *Lancet* study as the top finding of the year in heart disease and stroke research in its annual list of major advances.

RESEARCHERS FIND NEW CORNELIA DELANGE SYNDROME GENE



Affecting an estimated 1 in 10,000 children, Cornelia deLange syndrome (CdLS) causes intellectual disability, limb deformations, and other disabilities resulting from impairments in early development. Researchers have identified a key gene that, when mutated, causes this rare multisystem disorder. By revealing how mutations in the *HDAC8* gene disrupt the biology of proteins that control gene expression and cell division, the research sheds light on this disease.

The CdLS research team, led by Matthew A. Deardorff, MD, PhD, focused on the cohesin complex, a group of proteins that form a bracelet-like structure that encircles pairs of chromosomes, called sister chromatids. Mutations that perturb normal cohesin function can interfere with normal human development, Dr. Deardorff noted. Such is the case in CdLS, which exemplifies a newly recognized class of diseases called cohesinopathies.

In the current study, the scientists investigated both acetylation — how an acetyl molecule is attached to part of the cohesion complex — and deacetylation, the removal of that molecule. Normally, deacetylation helps recycle cohesin to make it available during successive rounds of cell division. The study team found that mutations in the *HDAC8* gene threw off normal cellular recycling of cohesin.

Mutations in the gene cause loss of *HDAC8* protein activity, and consequently decrease the amount of “recharged” cohesin available to properly regulate gene transcription. This, in turn, the researchers suggest, impairs normal embryonic development and gives rise to CdLS.

The researchers showed in cell cultures that mutations in *HDAC8* lead to a decrease in cohesin binding to genes, similar to that seen for cells deficient in the NIPBL gene. They also identified *HDAC8* mutations in approximately 5 percent of patients with CdLS.

Because mothers of children with CdLS may carry mutations in the *HDAC8* gene, identifying these mutations will be very useful in accurately counseling families of their recurrence risk — the likelihood of having a subsequent child with CdLS. And by providing details of the underlying defect in CdLS, the current research suggests future approaches to treating the genetic disease.

STUDY LINKS BMI, INDIVIDUALS OF AFRICAN DESCENT



The United States has a weight problem: according to the CDC, more than one-third of American adults are obese. Moreover, as of 2010 one-third of children were either overweight or obese, with the rates of obesity doubling in children and tripling in adolescents in the past thirty years. And some groups are more inclined to be obese than others, with non-Hispanic blacks 51 percent more likely than whites to be obese, for example.

A recently published study may help researchers better understand why some populations are more susceptible to obesity than others. Struan Grant, PhD, associate director of the Hospital's Center for Applied Genomics, co-authored a study that discovered new *loci* associated with body mass index (BMI) in adults of African ancestry.

Previous genome-wide association studies had identified 36 BMI-associated *loci*. While those studies mainly investigated individuals of European descent, in the current study the researchers conducted a meta-analysis to determine whether more than 3.2 million single nucleotide polymorphisms were associated with BMI in men and women of African ancestry. In all, more than 70,000 men and women of African descent were studied.

In addition to Dr. Grant, Children's Hospital's Hakon Hakonarson, MD, PhD, director of CAG, Brendan Keating, PhD, CAG lead clinical data analyst and faculty member in UPenn Pediatrics and Surgery, and CAG bioinformatics specialist Jonathan Bradfield, also contributed and co-authored the study. More than 200 researchers representing over 50 institutions took part in the investigation, which was published online recently in Nature Genetics.

The research group discovered two new *loci* — 5q33 and 7p15 — associated with BMI in people of African ancestry, while a third, 6q16, was found to be suggestive of an association. "These findings provide strong support for shared BMI *loci* across populations, as well as for the utility of studying ancestrally diverse populations," the researchers say.

CHOP RESEARCHERS CREATE MITOCHONDRIAL DISEASE TEST



A team led by [Marni J. Falk, MD](#), has expanded next-generation gene sequencing tools designed to unlock the secrets hidden in nuclear DNA to analyze a separate source of DNA — that found within mitochondria. Mitochondria, which contain their own DNA, are key suppliers of the energy needed for the multiple functions of our cells, and play a pivotal role in human health and disease.

“A first step in developing treatments for a disease is to understand its precise cause,” said Dr. Falk, director of the Mitochondrial-Genetic Disease Clinic at Children’s Hospital. “We have developed a one-step, off-the-shelf tool that analyzes both nuclear and mitochondrial DNA to help evaluate the genetic cause of suspected mitochondrial disease.”

The investigators described their customized, comprehensive test — which they call the “1:1000 Mito-Plus Whole-Exome” kit — in [Discovery Medicine](#). To achieve their results, the study team adapted an existing whole-exome sequencing kit, expanding it to encompass the mitochondrial genome.

While individual mitochondrial diseases are rare, hundreds of causes of mitochondrial diseases are known. Some originate in mutations in DNA specific to the mitochondria, while many other mitochondrial diseases are based in nuclear DNA genes that affect mitochondrial function. The role of mitochondria in human disease has been recognized only since the 1980s, and is largely based on the pioneering research by CHOP’s [Douglas C. Wallace, PhD](#), a co-author of the current study. However, many mitochondrial diseases remain poorly understood.

One complicating factor is heteroplasmy — a mixture of mutated and normal mitochondrial genomes within the same cells or tissues. In contrast to conventional gene sequencing, which can detect only heteroplasmic mutations that reach levels of at least 30 to 50 percent, Dr. Falk’s kit has the sensitivity to detect mitochondrial genome mutations present at levels as low as 8 percent.

A second study led by Dr. Falk reviews progress made in diagnosing mitochondrial disease at a single center over a rapidly changing three-year period before whole-exome sequencing was generally available. The retrospective review, published in *Neurotherapeutics*, covers 152 child and adult patients evaluated at CHOP’s Mitochondrial-Genetics Diagnostic Clinic from 2008 to 2011.

GENES LINKED TO LOW BIRTH WEIGHT, DIABETES RISK



An international team of genetics researchers discovered four new gene regions that contribute to low birth weight. Three of those regions influence adult metabolism, and appear to affect longer-term outcomes such as adult height, risk of type 2 diabetes, and adult blood pressure.

“This large study adds to the evidence that genes have a strong influence on fetal growth,” said one of the co-authors, [Struan F.A. Grant, PhD](#), associate director of the [Center for Applied Genomics](#) at Children’s Hospital. “The cumulative effect of the genes is surprisingly strong; it’s equivalent to the effect of maternal smoking, which is already recognized as lowering a baby’s weight at birth. We already know that a low birth weight increases the risk of health problems in adult life.”

The article, published in *Nature Genetics*, was the second major study on birth weight by the [Early Growth Genetics \(EGG\) Consortium](#), composed of groups of scientists from multiple countries, including the United Kingdom, Finland, the Netherlands, and the United States.

The meta-analysis and follow-up study encompassed nearly 70,000 individuals, of European, Arab, Asian, and African American descent, from across 50 separate studies of pregnancy and birth. In addition to confirming that three previously discovered genetic regions increased the risk of low birth weight, the consortium discovered four new regions: genes *HMG2*, *LCORL*, *ADRB1*, and a locus on chromosome 5.

Two of the previously identified gene regions are connected to a risk of type 2 diabetes, while two of the newly found regions confer a risk of shorter adult stature. A third region, *ADRB1*, is associated with adult blood pressure — the first time that scientists have found a genetic link common to both birth weight and blood pressure.

STUDY SUGGESTS SOME CHILDREN CAN ‘RECOVER’ FROM AUTISM



A Children’s Hospital study verified the long-controversial belief that a few children, in exceptional cases, can “recover” from autism. The study, which included investigators from the Center for Autism Research, is the first solid science to confirm that, however rarely, with the help of behavioral therapy some children can make such great improvements that they no longer qualify as having autism.

The director of the Center for Autism Research Robert Schultz, PhD, served as one of the co-authors on the study published in the *Journal of Child Psychology and Psychiatry*.

The investigators sought to explore whether the autism-recovery phenomenon was the result of an initial misdiagnosis, or whether the children’s recovery was complete. For example, the investigators asked, could the recovered children have retained significant social impairments despite losing the technical diagnosis of autism?

To test and document children who were diagnosed with autism at a young age but who no longer were qualified as such, the research team compared three groups of patients. They examined a group with a history of autism and “optimal outcomes,” a second group who had high-functioning autism, and a group of children who were developing typically.

The study’s results “clearly demonstrate” that some children who had previously been diagnosed with autism later recovered, to the point that their communication and social skills were comparable to those of typically developing children.

The researchers caution, however, that they don’t yet understand why some children recover and others don’t, and have no way to predict which patients will do well.

According to Dr. Schultz, this study “provides an important scientific opportunity to study why and how these particular children did so well — what is it about their past interventions, their initial profile of strengths and weaknesses and their brain that we can learn from in order to try to generalize this result to the great majority of youth who don’t achieve this optimal outcome?”

STUDY SUGGESTS FINE-TUNING DRUGS FOR BRAIN TUMORS



While investigating the biology of brain tumors in children, pediatric researchers are finding that crucial differences in how the same gene is mutated may call for different treatments. A study offers glimpses into how scientists will be using the ongoing flood of gene-sequencing data to customize treatments based on very specific mutations in a child's tumor.

"By better understanding the basic biology of these tumors, such as how particular mutations in the same gene may respond differently to targeted drugs, we are moving closer to personalized medicine for children with cancer," said the study's first author, CHOP's [Angela J. Sievert, MD, MPH](#).

The study, of which Dr. Sievert was a co-first author with Children's Hospital's Shih-Shan Lang, MD, was published in the [*Proceedings of the National Academy of Sciences*](#).

The study focused on a kind of astrocytoma, the most common type of brain tumor in children. When surgeons can fully remove an astrocytoma (also called a low-grade glioma), a child can be cured. However, many astrocytomas are too widespread or in too delicate a site to be safely removed. So pediatric oncologists have been seeking better treatment options.

The study focused on mutations in the *BRAF* gene, one of the most commonly mutated genes in human cancers. Because the same gene is also mutated in certain adult cancers, the pediatric researchers were able to make use of recently developed drugs known as *BRAF* inhibitors that were already being tested in adults.

And by examining the molecular mechanisms behind drug resistance and working with the pharmaceutical industry, the investigators identified a new, experimental second-generation *BRAF* inhibitor.

This work result lays a foundation for multicenter clinical trials to test the mutation-specific targeting of tumors by this class of drugs in children with astrocytomas, said Dr. Sievert. As this effort progresses, it will benefit from CHOP's commitment to resources and collaborations that support data-intense research efforts.

BEHAVIORAL INTERVENTIONS AT HEART OF NEW STUDY



Failing to address the emotional and behavioral problems of school-age children can have serious, life-changing ramifications — poor grades, suspension and expulsion, and problems with the law later in life. Studies show, however, that only 1 in 5 children with emotional and behavioral disorders receive mental health services, with low-income and ethnically diverse children lagging far behind their middle class, Caucasian counterparts.

At the heart of this disparity is a shortage of specialized services in low-income communities, the high cost of these services, and the stigma attached to using them. Underscoring the problem is the fact that evidence-based interventions are not successfully deployed in urban schools. These interventions are all too often derailed by inadequate training and poor implementation by service providers in schools.

The [National Institute of Child Health and Human Development](#) awarded Children's Hospital a \$3.1 million grant to study the level of support school personnel needed to effectively implement an intervention program called School-Wide Positive Behavioral Interventions and Supports (SW-PBIS) for typically developing students as well as students with, or at risk for, externalizing or anxiety disorders.

SW-PBIS is a comprehensive service delivery strategy that, by combining universal and targeted interventions to address students' emotional and behavioral issues, can help improve overall school climate, perceived school safety, and student academic performance. The program focuses on preventing new cases of problem behaviors through school-wide discipline, classroom behavior management, and effective instructional practices.

The CHOP study, led by [Ricardo Eiraldi, PhD](#), examines whether school personnel can implement the components of a two-tier SW-PBIS program with the same level of fidelity, integrity, and effectiveness when they receive a relatively low level of support from coaches and supervisors as they can with a high level of support. Dr. Eiraldi and his team partnered with the School District of Philadelphia to select six schools in North Philadelphia for participation in the project.

NEW AWARD LOOKS AT ANTIBIOTIC USE FOR BACTERIAL INFECTIONS



Ron Keren, MD, MPH, director of the [Center for Pediatric Clinical Effectiveness](#), received nearly \$2 million from the [Patient-Centered Outcomes Research Institute](#) to lead a study of treatments for serious bacterial infections in children.

The three-year award supports a project examining whether children who have a serious bacterial infection that requires prolonged antibiotic therapy (greater than one week) do as well taking the antibiotics by mouth as they would if they received them via an intravenous (IV) catheter — specifically a peripherally inserted central catheter, or PICC, line.

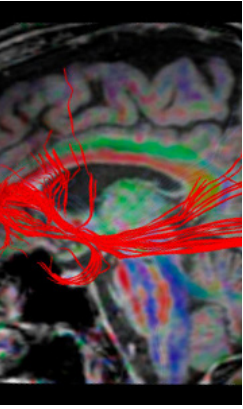
These two antibiotic treatment options have major implications for the overall experience of the child, families and caregivers, but there is a lack of real-world evidence on their benefits and drawbacks to help clinicians and patient families make an informed choice.

PICC lines also have some risks. They can clot, break, or become dislodged. And because they sit in large blood vessels directly above the heart, any bacteria that are inadvertently introduced into the catheter go directly to the heart and are pumped throughout the body, which can lead to a dangerous infection called [sepsis](#).

Oral antibiotics, on the other hand, are much easier for patients to take and caregivers to manage. However, because oral medications must pass through the digestive system, to have the same efficacy as IV medications oral antibiotics must have high “bioavailability” — the percentage of the drug that reaches the blood. Drugs administered via PICC lines have, by definition, 100 percent bioavailability.

“If we find that the prolonged IV option is no better than the oral route, we think that most families would prefer for their child to take oral antibiotics,” Dr. Keren noted. “However, if IV antibiotics are marginally better than oral antibiotics, then that benefit will need to be weighed against any reduction in quality of life and complications that we anticipate with the PICC lines.”

AUTISM CENTER PART OF LANDMARK GRANT



Autism is typically diagnosed around age two or three, and a growing body of research shows that early intervention yields better outcomes for individuals with autism. A new research grant will allow CHOP researchers to study children's brain development at even earlier ages, in the hope of finding an earlier starting point.

Supported by a grant through the National Institutes of Health's Autism Centers of Excellence program, the Children's Hospital of Philadelphia's Center for Autism Research will continue to work to identify early signs of autism spectrum disorders. Children's Hospital will share more than \$100 million in NIH funding for autism research, which is distributed across nine Autism Centers of Excellence (ACE) grants.

Under the five-year, \$2.2 million grant, CAR is part of a network of four research sites using advanced imaging techniques to study brain development in 200 infants beginning at three months of age. The researchers will follow infants every three months, through 24 months of age, to carefully chart brain development.

The research team plans to conduct follow-up behavioral and diagnostic testing of these children at 36 to 60 months, the age at which a diagnosis of autism is considered to be more stable. The study will also evaluate child and family-level characteristics to learn which are predictors for a later autism diagnosis.

The current grant is a continuation of an earlier ACE-funded brain imaging study conducted by CAR in collaboration with four other autism research centers throughout the country. This research network published a study earlier this year demonstrating significant differences in brain development as early as six months of age — well before the appearance of behavioral or “outward” symptoms of autism.

GRANT MAY LEAD TO NEW MUSCULAR DYSTROPHY TREATMENT



Muscular dystrophy is a group of genetic disorders that causes progressive loss of muscle structure and muscle contractility, strength, and function. The disease is characterized by chronic inflammation, muscle cell death, and increase and infiltration of fat and fibrous tissue. Current treatment options are limited to symptom management.

A new grant award is allowing a Children's Hospital investigator to study the effectiveness of certain drugs — retinoid agonists — in slowing or preventing muscle degeneration in those with muscular dystrophy. Findings from the study could lead to a new, groundbreaking treatment.

With a \$405,000, three-year grant from the [Muscular Dystrophy Association](#) (MDA), [Masahiro Iwamoto, PhD, DDS](#), a research scientist of the Translational Research Program in Pediatric Orthopaedics and research associate professor of Orthopedics at the [University of Pennsylvania School of Medicine](#), is testing his hypothesis that a retinoic acid receptor-gamma (RAR γ) agonist, a synthetic retinoid which selectively activates RAR γ , could be used to slow and even stop the disease progression of muscular dystrophy.

Retinoic acid, an active form of vitamin A, plays an important role in the functioning of numerous organs, including musculoskeletal systems. The clinical use of natural retinoids, however, is limited to the treatment of certain malignant tumors and skin conditions due to side effects. To improve drug effectiveness and reduce side effects, synthetic receptor-specific retinoid agonists have been developed.

Dr. Iwamoto and his team recently discovered that a class of selective RAR γ agonist block the formation of bone within muscle and prevents muscle degeneration. The findings were part of his research into heterotopic ossification (HO), the pathological formation of ectopic bone within soft tissue, primarily skeletal muscles.

With the MDA grant, Dr. Iwamoto builds upon his HO research to learn more about RAR γ properties and how the molecule contributes to the repair and maintenance of skeletal muscle. An RAR γ agonist known as R667 has already shown some promise in the lab and has been tested in humans for other conditions. Dr. Iwamoto is testing whether R667 has the potential for treating muscular dystrophy in mice without serious side effects.



TECHNOLOGY

Honing in on the Biological Markers of Autism

Treating the Chicken with the Egg

Collaboration Propels Innovation,
Novel Drug Development

Tech Transfer By the Numbers

HONING IN ON THE BIOLOGICAL MARKERS OF AUTISM



The prevalence of autism spectrum disorders, or ASD, is staggering — an estimated 1 out of 88 children have some form of ASD. As the word “spectrum” in the name suggests, ASD varies in its range and severity among those affected. The various forms of the disorder share some common characteristics, however, one of which centers on language and communication deficits.

A Children’s Hospital investigator is taking a unique approach to determine how those with autism process sounds, words, and images, and then use those findings to develop potential interventions. Rather than looking at autism from a behavioral or clinical perspective, Timothy Roberts, PhD, vice chair of the Department of Radiology, is using sophisticated imaging to hone in on the biological basis for autism.

Since 2007, Dr. Roberts, who also holds the Oberkircher Family Endowed Chair in Pediatric Radiology, has used magnetoencephalography (MEG) and advanced magnetic resonance imaging (MRI) to look at the “signatures” of brain functioning to reveal the biological nature of ASD. Dr. Roberts and his team observe not just where in the brain things are happening but also the differences in the timing, or frequency, of these signals. These split-second differences can lead to auditory processing delays seen in some children with ASD.

But knowing some of the autism signatures is not enough to move on to possible interventions. What’s needed, Dr. Roberts says, is “a little bit of biology” that can shed light on what’s giving rise to those signatures in the first place. Identifying and understanding potential biomarkers may then lead to more options for treating ASD.

With a multi-modal approach using MEG and MRI, Dr. Roberts and colleague James (Chris) Edgar, PhD, have found a biomarker in the white matter of the brain that may be the cause of delayed auditory processing. And he’s found a second one in a neurotransmitter called GABA. An inhibitory neuron, GABA must be in balance with another neurotransmitter — the excitatory glutamate.

“Those with ASD who have lower levels of GABA end up with a more ‘noisy brain,’” Dr. Roberts says. “This is a problem because it means these children are trying to encode their perceptual reality, their world — and they are trying to encode it with rhythms in a sea of noise.”

The tremendous variability, or heterogeneity, seen in children with ASD suggests that the problem for some may arise from abnormal white matter development and for others may stem from reduced levels of GABA.

Knowing the biological differences at play has led Dr. Roberts toward existing drugs that target GABA — the effectiveness of which he could measure using advanced imaging techniques — and toward developing a novel intervention for those whose ASD may arise from auditory processing difficulties.

“Five years ago we didn’t have signatures,” says Dr. Roberts. “Now we not only have signatures but we’ve transitioned into candidates for biomarkers. And we’ve filed a provisional patent application on the use of MEG as a biomarker for clinical trial design and, ultimately, therapeutic monitoring for those with ASD who have a GABA-glutamate imbalance.”

For those whose ASD stems from an abnormal structural connectivity in the language pathway of the brain, Dr. Roberts and his colleagues, including [David Embick, PhD](#), from the Department of Linguistics at the [University of Pennsylvania](#), are looking at ways to enhance what is called “repetition priming.” It works like this: saying the word “cat” likely conjures an image of a four-legged, green-eyed, furry animal with pointy ears and whiskers. The specifics of the cat’s characteristics — its color and so forth — vary among people, but the overall representation of a cat is the same for all of us.

For children with more severe forms of ASD whose problems arise from the brain’s language pathway, significant amounts of time and energy may be spent focusing on the details and differences in how people actually say the word “cat” — our individual intonations and so forth — and as a result they create separate representations each time they hear the same word.

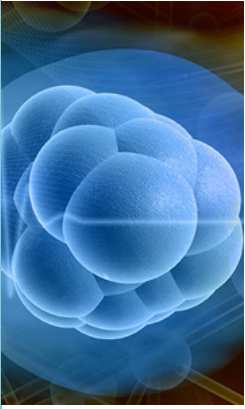
“These children may be working too hard on the details and are unable to form an object in their mind or categorize it,” Dr. Roberts says. “They may be unable to group things together or cluster them and therefore are treating them all as different. It just becomes a multi-sensory overload.”

Repetition priming speeds up our responses to things that are similar. If children with ASD aren’t able to grow a healthy language because they are doing too much work processing the myriad stimuli they receive, then helping them “cluster” these representations would help them make advance their language and communication.

Drs. Roberts and Embick are developing a device along the lines of a hearing aid (also with a provisional patent application filed) that would filter the incoming language, remove the subtle variations in how we all speak (therefore making everyone sounds the same) and produce one voice that would help children with ASD better form the representations that build their language and vocabulary. And by watching key parts of the brain through imaging, Dr. Roberts can measure whether it’s working.

“What’s great about this multi-modality approach is that we are harnessing cutting-edge imaging technology and using what we learn to forge a path that can make a real difference in the lives of children with autism spectrum disorders,” says Dr. Roberts. “It’s an exciting and promising time.”

TREATING THE CHICKEN WITH THE EGG



The term “stem cell,” *stammzellen*, was first used in 1868 by the German biologist Ernst Haeckel to describe the original, unicellular progenitor from which Dr. Haeckel supposed all multicellular plant and animal life might have descended. The question, Dr. Haeckel asked, was where that progenitor — the original stem cell — came from in the first place. The chicken or the egg?

Since then, just what defines a stem cell has undergone a few changes. The evolutionary sense of Dr. Haeckel’s term has been dropped, but the sense of stem cells being precursor cells, able to become specialized through the process known as differentiation, remains. Because of their ability to become many types of cells and to renew themselves, stem cells hold enormous promise in understanding and treating a variety of diseases.

What’s more, researchers have identified several different types of stem cells. These include what is perhaps the most popularly known type of stem cell, embryonic stem cells (ESCs), which as their name suggests are derived from embryos. Most often, these come from embryos that have been fertilized through *in vitro* fertilization and then donated for research purposes.

Another type of stem cell, somatic stem cells, are rare, undifferentiated cells found among other differentiated cells. Also called adult stem cells, there are several types of somatic stem cells — hematopoietic stem cells can differentiate into every type of blood cell, while mesenchymal stem cells can become fat, cartilage, and bone cells.

But in the past decade, researchers have detailed another type of stem cell: induced pluripotent stem cells, or iPSCs. Differentiated adult cells that have been “reprogrammed” and forced to express genes, these cells are capable of developing into many or even all cell types. During fiscal 2013, The Children’s Hospital of Philadelphia’s [Mitchell J. Weiss, MD, PhD](#), published two studies of using iPSCs to study the rare congenital blood disorder [Diamond Blackfan Anemia](#) and the childhood cancer [juvenile myelomonocytic leukemia](#).

[In the anemia study](#), Dr. Weiss and his colleagues — including investigators [Monica Bessler, MD, PhD](#), and [Philip J. Mason, PhD](#) — removed fibroblasts from Diamond Blackfan Anemia patients and reprogrammed the cells into iPSCs. As those iPSCs were stimulated to form blood tissues, like the patient’s original mutated cells they were deficient in producing red blood cells. However, when the researchers corrected the genetic defect that causes the disorder, the iPSCs developed into red blood cells in normal quantities.

“The technology for generating these cells has been moving very quickly,” said Dr. Weiss. “These investigations can allow us to better understand at a molecular level how blood cells go wrong in individual patients — and to test and generate innovative treatments for the patients’ diseases,” he added.

And in April of 2012, [Paul J. Gadue, PhD](#), published a study detailing a brand new type of stem cell, which the investigators call endodermal progenitor (EP) cells. Produced from ESCs and iPSCs, EP cells have two advantages over these other stem cell types: they do not form tumors when transplanted into animals, and they can form functional pancreatic beta cells in the laboratory. Both ESCs and iPSCs in the undifferentiated state will form a type of tumor called a teratoma when transplanted in animal studies, so it has been critical that any cell generated from ESCs or iPSCs and used for transplantation is purified to exclude undifferentiated cells with tumor-forming potential, Dr. Gadue pointed out.

In addition to producing beta cells, the researchers also directed EP cells to develop into liver cells and intestinal cells — both of which normally develop from the endoderm tissue layer early in human development. The challenge, Dr. Gadue said, has been to differentiate stem cells into one particular cell type in culture, as ESCs and iPSCs can form any cell type in the body. EP cells seem to be limited to cells of the endodermal lineage such as liver, pancreas, and intestine, making it easier to generate pure populations of cells from these organs.

“Our cell line offers a powerful new tool for modeling how many human diseases develop,” said Dr. Gadue, who along with Deborah L. French, PhD, is the co-director of CHOP’s [human embryonic stem cell/induced pluripotent Stem Cell \(hESC/iPSC\) core facility](#). “Additionally, pancreatic beta cells generated from EP cells display better functional ability in the laboratory than beta cells derived from other stem cell populations.”

In a follow-up review published in fiscal 2013 in *Current Opinion in Cell Biology*, Dr. Gadue and colleagues discussed the generation of endodermal cells from pluripotent stem cells, including EP cells. Stem cells such as EP cells “can be expanded robustly in culture” and “provide a powerful system to study and model human diseases in vitro, as well as generating a source of cells for transplantation.”

Indeed, there is a big push to use stem cells to perform disease modeling with human cells as opposed to mice, as well as to use stem cells to perform drug and toxicity screenings, Dr. Gadue pointed out, noting that while mouse models offer an incredibly valuable resource they are not perfect and using human cells when possible is important. And once they are created, EP cells can be expanded almost without limit — to the point that Dr. Gadue estimates his laboratory has grown “trillions” of cells — which offers researchers a wealth of research resources.

Going forward, Dr. Gadue, has been working with a number of colleagues, including endocrinologist [Diva D. De León-Crutchlow, MD](#), to better understand and hopefully develop treatments for diabetes.

COLLABORATION PROPELS INNOVATION, NOVEL DRUG DEVELOPMENT



Numerous research teams at Children's Hospital work tirelessly year in and year out to uncover the inner workings of biological systems and the causes behind diseases. Armed with their discoveries, the next step may involve using that knowledge to develop new therapeutics to bring to a patient's bedside.

It sounds like a simple and straightforward approach but, in reality, it isn't.

Navigating the complex landscape of drug development to treat diseases is a long and detailed process that brings no guarantee of success. Resources to fund the development needed to bridge the gap between the discovery phase and clinical trials are often not readily available. Close collaborations with the pharmaceutical industry are helping to speed the pace of innovation and drug development.

As an example, Children's Hospital and [Pfizer, Inc.](#) joined forces in FY13 to translate biomedical discoveries into novel treatments. The Hospital joined the [Centers for Therapeutic Innovation](#) (CTI) network, a novel collaboration model built by Pfizer that brings academic researchers together with Pfizer scientists to expedite the pace of innovation.

"We are excited to have this opportunity to accelerate the process of moving scientific insights toward therapies that healthcare providers can offer in the clinic," said [Philip R. Johnson, MD](#), chief scientific officer and executive vice president at Children's Hospital. Dr. Johnson is one of CHOP's representatives on a joint steering committee with Pfizer representatives that will direct CTI's activities in Philadelphia.

This expedited timetable that is part of the CTI network is much faster than the typical schedule for federally sponsored research. Many partnerships between private industry and academia that focus on one highly defined end-product; however, CTI is designed to identify cutting-edge areas of research in areas of high unmet need that hold strong potential for therapeutic interventions. The goal is to advance a project into a Phase 1 clinical trial.

Children's Hospital is only the second pediatric center to participate in the CTI network, which has established partnerships with 21 academic medical centers throughout the United States.

"Working with leading academic researchers is a key part of the CTI model," said Anthony Coyle, PhD, CTI's Chief Scientific Officer. "CHOP's world-class reputation as a leading research hospital means it is an ideal partner for CTI as we continue our determined efforts to translate exciting science into effective medicines for patients."

TECH TRANSFER BY THE NUMBERS

STATS

50

Disclosures
Received

22

US Patent Applications Filed
(Utility & Nationalized PCT)

26

US Patent Applications
Filed (Provisional)

7

U.S. Patents
Issued to CHOP

4

International
Patents Issued

93

International Patent Applications
Filed (PCT & Foreign)

LIST OF PATENTS

U.S. Patent No. 8,236,764

Rodney Camire, PhD, and Valder Arruda, MD, PhD

This patent describes methods for creating stable activated coagulation Factor V for treatment of hemophilia A or B. CHOP researchers have devised several potential treatments for hemophilia and this patent covers one such potential treatment.

U.S. Patent No. 8,252,281

Richard Levy, MD, and
Clifford Deutschman, MD, MS, FCCM

Drs. Levy and Deutschman have devised a method for treatment of cardiac dysfunction caused by sepsis and associated conditions such as Sepsis-associated Inflammatory Syndrome (SIRS) and Multiple Organ Dysfunction Syndrome (MODS). The treatment entails administration of cytochrome C, a mitochondrial protein involved in cellular respiration, either alone or in combination with ascorbate. This method can also be a potential treatment for cardiac dysfunction associated with trauma, ischemia, inborn errors of metabolism, cardiomyopathies, et cetera.

U.S. Patent No. 8,334,275

Terry Finkel, MD, PhD, and Jiyi Yin

This patent expands previously obtained protection for a method of inducing apoptosis, otherwise known as programmed cell death, in cells infected with HIV as a potential treatment for the disorder.

U.S. Patent No. 8,329,168

Sriram Krishnaswamy, PhD, Elsa Bianchini, PhD, and Steven Orcutt

Proteins of the coagulation pathway are inefficiently converted to the active forms and often require co-factors to do so. This invention related to modification of a variant form of the thrombin zymogen/protease complex to facilitate production of the active polypeptide as a potential treatment for hemophilia.

U.S. Patent No. 8,383,386

Rodney Camire, PhD

This represents another treatment for hemophilia as well as an antidote for over-administration of anti-coagulants. The inventors have created a novel variant of Factor Xa, a component of the coagulation pathway. This invention is licensed and a phase I clinical trial may begin in during FY14.

U.S. Patent No. 8,263,127

Ivan Alferiev, PhD, Ilia Fishbein, MD, PhD,
Michael Chorny, PhD, Robert Levy, MD,
Benjamin Yellen, PhD, and Darryl Williams, PhD

There is an urgent need for better interfaces between implantable medical devices and tissues. A common cause of implantable device failure relates to inflammation of the surrounding tissues. This patent describes a photo-activatable bio-polymer that could be used to coat the devices and reduce the likelihood of failure.

U.S. Patent No. 8,461,125

Michael Grunstein, MD, PhD

Alternatives to use of corticosteroid treatment of asthma are badly needed. These treatments can have serious side effects and are not always efficacious. This patent describes novel siRNA duplexes directed against CD-23 that will inhibit IgE binding to airway smooth muscle, thereby ameliorating the airway's response to inhaled allergens.



INVESTMENT

New Affinity Group Bolsters Understanding
of DNA-Protein Interaction

Exploring the Genetic Landscape of
Children's Brain Tumors

Spreading Knowledge: CHOP Research Hosts
Major Genomic, Cancer Conferences

NEW AFFINITY GROUP BOLSTERS UNDERSTANDING OF DNA-PROTEIN INTERACTION



Research at Children's Hospital is organized not only by clinical departments but also by scientific discipline. Extending beyond the traditional academic structure — for example, cardiology or immunology, among many others — the Institute's Centers of Emphasis and Research Affinity Groups are structured to foster collaboration and innovation.

The affinity groups at the CHOP Research Institute reflect the increasingly interdisciplinary and multidisciplinary nature of many key research questions. This approach aligns with the emerging national consensus that multidisciplinary centers are essential to advancing the nation's research agenda. One of the most critical areas benefiting from this forward-thinking approach to research is with respect to genomics.

Since the completion of the Human Genome Project, there has been a natural surge in biomedical research aimed at gene discovery. Using genome-wide association studies (GWAS), bioinformatics, and other approaches, this process has focused largely on determining what genes are implicated in specific diseases.

While this process may shed light on *what* genes are involved in diseases, it has done little to help investigators understand *why* a gene or genomic region may be involved in a disease or a disease risk.

A new Research Affinity Group at CHOP Research is taking the findings from various types of studies, including GWAS, a step further in order to understand entire networks underpinning disease susceptibility.

At the heart of the DNA-Protein Interaction Research Affinity Group is the analysis of data derived from chromatin immunoprecipitation coupled with high-throughput sequencing. More commonly referred to as ChIP-seq, the technique is used to look at how proteins like transcription factors interact with DNA, and to find the regions of the genome these transcription factors occupy to control gene expression.

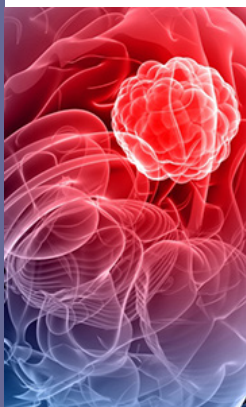
The DNA-Protein Interaction research affinity group, co-led by Struan Grant, PhD, of the Department of Pediatrics and Genetics, and Andrew Wells, PhD, of the Department of Pathology, deals with the processing and analyses of ChIP-seq and related data to gain insight into disease networks, identify vulnerabilities in given networks, and look for points amenable to therapeutic intervention.

“The new affinity group is a forum for investigators with diverse backgrounds and expertise to learn the downstream effect of transcription factors and related DNA binding proteins,” says Dr. Grant. “We can now work to analyze and translate the numerous findings made from GWAS and elsewhere — a natural step in discovering not only what causes disease but why.”

Also relevant to the goal of the affinity group is leveraging the data from the public research consortium ENCODE — the **Enc**yclopedia **Of** **DNA** **E**lements — to better understand and integrate genome-wide data sets generated by investigators at CHOP. Launched by the National Human Genome Research Institute nearly a decade ago, the ENCODE project aims to ultimately identify all functional elements in the human genome sequence.

“The sequencing of genomic information is not the bottleneck — it’s the analysis,” says Dr. Wells. “The DNA-Protein Interaction affinity group creates a community that can benefit from what we can learn about disease networks through ChIP-seq and related techniques, and then develop a pipeline to find novel ways to understand and target those diseases.

EXPLORING THE GENETIC LANDSCAPE OF CHILDREN'S BRAIN TUMORS



Though enormous advances have been made against childhood cancers in recent years, pediatric brain tumors remain devastating: childhood brain tumors are the second leading cause of cancer-related death in children. There are many different types of pediatric brain tumors, and their location — in the brainstem, cerebellum, cerebrum, or spinal cord — often means that children with brain tumors face extremely challenging treatment regimens.

For example, the treatment for medulloblastoma, the most common form of malignant brain tumor in children, can be onerous. Typically, children with medulloblastoma must first undergo surgery, which is then followed by chemotherapy and radiation. And cancer treatments can cause a range of debilitating side effects, including heart and lung abnormalities, reproductive issues, cognitive and developmental challenges, and in some cases secondary tumors.

Despite these sorts of challenges, only a fraction of the National Cancer Institute's (NCI) budget is devoted to supporting childhood cancer research and pediatric brain tumor research. For example, in 2011 the NCI devoted \$195.5 million to pediatric cancer research, out of a total budget of more than \$5.058 billion — slightly less than 4 percent. Clearly then, in an era of decreased federal funding for scientific research, other approaches are needed to improve the health of children with brain tumors. One such approach is the Childhood Brain Tumor Tissue Consortium (CBTTC).

The CBTTC is multi-institutional, collaborative research organization dedicated to the collection, annotation, and analysis of children's brain tumors, with the ultimate goal of improving outcomes for children with brain tumors. The CBTTC is comprised of The Children's Hospital of Philadelphia, the Children's Hospital of Pittsburgh of UPMC, Seattle Children's Hospital, and Ann & Robert H. Lurie Children's Hospital of Chicago. The consortium's operations center is housed at Children's Hospital.

Tom Curran, PhD, FRS, deputy science director of the Children's Hospital of Philadelphia Research Institute, Peter C. Phillips, MD, director of CHOP's Pediatric Neuro-Oncology Program, Phillip (Jay) Storm, MD, incoming CHOP Neurosurgery Division Head, and Adam Resnick, PhD, Assistant Professor of Neurosurgery, lead Children's Hospital's involvement in the CBTTC. The consortium was initially set up with the support of the Childhood Brain Tumor Foundation (CBTF), who then partnered with the International Licensing Industry Merchandiser's Association (LIMA) to further develop the consortium's infrastructure. Both the CBTF and LIMA continue to lend key support to the CBTTC's efforts.

“Children with brain tumors deserve the very best that science has to offer,” Dr. Curran said, but unfortunately “many groups struggle to obtain enough specimens for their studies. Therefore, we decided several years ago that the best way to make progress was to share all materials, all data and, especially, all ideas in pursuit of better treatments.”

Consortium member institutions are currently engaged in several research projects. Three projects are investigations of specific types of brain tumors — craniopharyngiomas, diffuse fibrillary astrocytomas, and gangliogliomas — while a fourth project is focused on better understanding pediatric and adult gliomas. Much of the consortium’s work is reliant on genomic sequencing, which is performed at Children’s Hospital.

In addition to collaborating on research projects, consortium members freely share biospecimens, data, and ideas on how to apply the latest technologies to pediatric brain tumor research. Notably, in the fall of 2013 the CBTTC biorepository was launched. The biorepository has the ability to receive specimens for member institutions, and can bank cerebral spinal fluid, DNA, RNA, and tissue samples. And in fiscal 2013, the [CBTTC Data Specimen and Inventory portal](#) — an online system built on a platform designed by Children’s Hospital’s [Center for Biomedical Informatics](#) — was made available. The new data platform allows researchers around the world free access to brain tumor data 24 hours a day.

CBTTC-associated researchers have also been working outside the laboratory to raise awareness of childhood brain tumors. Recently, Children’s Hospital investigators traveled to Capitol Hill to report on the important brain tumor research being done at CHOP as part of the CBTTC. [Dr. Resnick](#), along with Kristen and Rich Gillette of the [Kortney Rose Foundation](#), met with staffers from the offices of New Jersey Sens. [Bob Menendez](#) and Jeff Chiesa, as well as [Rep. Frank Pallone](#).

With the ongoing support of the CBTF and LIMA, the CBTTC has made great strides toward its goal of increasing worldwide brain tumor-related research collaboration. Through the integration of a state-of-the-art biorepository of tissue samples, informatics advancements, and by bringing together experts from around the world, the consortium is positioned for long-term growth and sustainability. By laying the foundation for new treatments, the CBTTC is working to inform therapeutic decisions and improve outcomes for children with brain tumors.

To learn more about the Childhood Brain Tumor Tissue Consortium, visit the consortium’s [website](#).

SPREADING KNOWLEDGE: CHOP RESEARCH HOSTS MAJOR GENOMIC, CANCER CONFERENCES



Making discoveries, publishing results, and striving to translate research findings to clinical care are major aspects of the research endeavor at Children's Hospital. But the efforts don't stop there.

Sharing scientific knowledge and spurring meaningful conversations with colleagues both inside and outside of the CHOP Research community about trends in research, future needs, and new approaches, all contribute to the collective scientific knowledge and help advance research.

In another sign of its leadership in biomedical research and care, in FY13 CHOP Research hosted two meetings that brought together world-class gatherings of researchers and clinicians.

Both the genomics-focused [ICG Americas 2012](#) conference and the Center for Childhood Cancer Research's inaugural pediatric cancer symposium featured pioneering investigators from both inside and outside the Research Institute, discussing the groundbreaking work of today that will lead to the cures of tomorrow.

Held last September, the ICG Americas 2012 conference was the first international meeting on genomics to be held in the United States, and was hosted jointly by [international genomics institute BGI](#) and Children's Hospital. More than 350 genomics researchers, industry executives, and policymakers attended.

"I think that everybody knows that we're truly on the dawn of a revolution in genomics, in medicine, and in healthcare," said Steven M. Altschuler, MD, CHOP chief executive officer, in his welcoming remarks. Genomic technology and research "has the potential to radically change the way that we think about the delivery of healthcare," Dr. Altschuler said.

Among the more than 50 speakers at the ICG Americas 2012 conference were CHOP's own [Hakon Hakonarson, MD, PhD](#), director of the Center for Applied Genomics, and [Douglas Wallace, PhD](#), director of the [Center of Mitochondrial and Epigenomic Medicine](#). [Eric Green, MD, PhD](#), director the [National Human Genome Research Institute](#), and Huanming Wang, PhD, chairman of BGI, also presented.

"No doubt it's a revolution ... no doubt it's an opportunity," Dr. Wang said of the promise offered by genomic medicine, after noting that 2013 marks the tenth anniversary of the mapping of the human genome and the 60th anniversary of the publication of DNA's double helix structure.

Dr. Hakonarson's talk highlighted his work with a fasoracetam, a drug that was originally developed to treat Alzheimer's disease but, after being put through clinical trials, was shelved for efficacy reasons. Dr. Hakonarson and his team are now investigating whether the drug can be used to treat attention deficit hyperactivity disorder, a project he called a "representation of what genomics is offering." Using genomics to determine new indications for available products can help speed therapies to market, Dr. Hakonarson noted.

Genomic medicine allows researchers "to identify a subset of patients who have mutations in certain gene pathways and networks that disturb the networks and, when you are lucky and a drug already exists that has already been proven safe, the ability to take a shortcut and fast-track a clinical trial and subsequently get a drug out is obviously significantly enriched," Dr. Hakonarson noted.

A few weeks later the Center for Childhood Cancer Research (CCCR) held its inaugural symposium on pediatric cancer research. The meeting focused on translational research, or "how the work is going to impact patients in real time," said John Maris, MD, director of the CCCR.

The day included presentations from pioneering cancer researchers and innovators, including Columbia University's Adolfo Ferrando, MD, PhD; Kevin Shannon, MD, from the University of California San Francisco; and the Broad Institute and Harvard Medical School's Matthew Meyerson, MD, PhD. The symposium was made possible with support from Alex's Lemonade Stand Foundation.

In his opening remarks, Philip R. Johnson, MD, chief scientific officer of the CHOP Research Institute and executive vice president, noted that while he has at times struggled to translate what constitutes translational research into "understandable stories," the work done by the oncology group always made his job easier. People "get it immediately, they understand that the science impacts the care and the care impacts the science," Dr. Johnson said.

A number of the day's presentations focused on using the highly specific targeting offered by genomics to treat cancer, with the CCCR's Yael Mossé, MD, giving a talk on her work treating neuroblastoma in patients who express the anaplastic lymphoma kinase (ALK) gene. Dr. Mossé's investigation of crizotinib, a drug originally developed to treat lung cancer in adult patients who express ALK, sparked a frenzy of media attention in the spring after Dr. Mossé and her team found complete responses in a number of patients involved in a phase 1 trial.

Though the "inhibition of mutated ALK is complex and remains a therapeutic challenge," it is her patients who "really inspire me every day," Dr. Mossé said.

LEADING THE WAY

Tom Curran, PhD, FRS: Named to First Class of AACR Academy Fellows

Claudio Giraudo, PhD: Among the Latest Pew Scholars

Paul Offit, MD: Vaccine Expert Twice Honored

Kathy High, MD, HHMI: Honored for Gene Therapy Blindness Trial

Robert Doms, MD: New Chief of Pathology

Beverly Lange, MD: Celebrating 40 Distinguished Years

Barbara Medoff-Cooper, PhD, RN, FAAN:
Receives Prestigious Nurse Scientist Award

Garrett Brodeur, MD: Award Highlights Lifetime Cancer Research

Donna McDonald-McGinn, MS, CGC: Chromosome Deletion Work Honored

Jeffrey Silber, MD, PhD: Recipient of New Endowed Chair in Health Services

TOM CURRAN, PHD, FRS: NAMED TO FIRST CLASS OF AACR ACADEMY FELLOWS



World-renowned cancer investigator Tom Curran, PhD, FRS, was honored by the American Association for Cancer Research as it inaugurated the first class of the fellows of the AACR Academy.

Dr. Curran, who is also the deputy scientific director of the CHOP Research Institute, was formally inducted into the Academy on April 5 in Washington, D.C. He was one of 106 fellows from across the country to receive the honor of induction into the AACR Academy.

The Academy was created to recognize and honor distinguished scientists whose major scientific contributions have propelled significant innovation and progress against cancer. The fellows were selected through a rigorous peer review process that evaluates individuals on the basis of their stellar scientific achievements in cancer research.

Dr. Curran, a past president of the AACR, studies brain development and pediatric brain tumors, with an eye toward identifying molecular changes and potential drug targets. He also investigates the mechanism of action of anticancer drugs in tumor cells and cancer models.

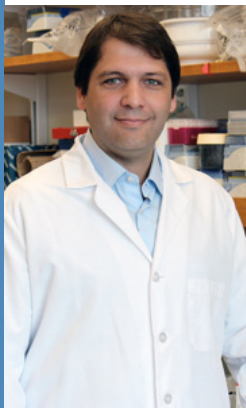
Specifically, Dr. Curran discovered the Fos oncogene and its binding partner from another oncogene called *Jun*. He later showed that these two oncogenes regulate gene expression associated with cell proliferation and differentiation, cell death and neuronal activation. This work illuminated the pathways that go awry in cancer cells, and initiated the use of Fos as a marker for activity-dependent changes in the nervous system.

Dr. Curran recently united his interests in cancer and neurobiology to study children's brain tumors. He developed a high-incidence model of pediatric medulloblastoma that he used to demonstrate how orally bioavailable, small molecule inhibitors of Hedgehog signaling rapidly eliminate even large tumors in mice. This work led to clinical development of inhibitors of Smoothened for the treatment of basal cell carcinoma and medulloblastoma.

Additionally, Dr. Curran considers among his greatest achievements his contribution to the development of a drug that is now in pediatric trials — Erivedge, which in 2012 was approved by the FDA to treat cancer in adults.

In addition to serving as the Deputy Scientific Director at CHOP Research, Dr. Curran is a Professor of Pathology and Laboratory Medicine and Professor of Cell and Developmental Biology at University of Pennsylvania's Perelman School of Medicine. He is also the associate director of Translational Genomics at the Penn Genome Frontiers Institute in Philadelphia.

CLAUDIO GIRAUDO, PHD: AMONG THE LATEST PEW SCHOLARS



Children's Hospital investigator Claudio Giraudo, PhD, of the Department of Pathology and Laboratory Medicine, joined the prestigious community of Pew Scholars in 2013. Previous Pew Scholars have included Nobel laureates, MacArthur fellows, and many others who were awarded Pew grants to help launch their careers.

Dr. Giraudo was one of just 22 investigators to be selected out of 134 nominated for the Pew Scholars Program in the Biomedical Sciences. The Pew Scholars were each awarded \$240,000 over four years to conduct their research.

The Pew Scholars Program “identifies and invests in talented researchers in medicine or biomedical sciences,” enabling “promising scientists to take calculated risks and follow unanticipated leads to advance human health,” according to the Pew website. Since 1985, Pew has awarded more than 500 investigators over \$130 million in research funding.

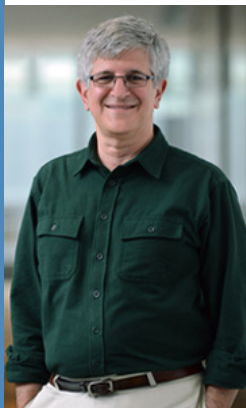
Dr. Giraudo's research interests center on intracellular membrane trafficking and calcium-regulated exocytosis in eukaryotic cells, particularly how immune cells secrete granules that destroy infected cells.

With the support of the Pew Scholar grant, Dr. Giraudo said he hopes “to identify the protein machinery cytotoxic T lymphocytes (CTLs) use to secrete granules that break down cells.” A type of white blood cell, CTLs target and kill other cells, including cancer cells and cells that have been infected with viruses.

“This award will give me the chance to study what happens at the cell membrane during the body's immune response, which could be therapeutically targeted to improve prognosis and quality of life of patients,” Dr. Giraudo said.

In addition to better understanding cell-mediated killing, the Pew-supported research project could also shed light on how similar processes lead to disease, such as in diabetes and brain disorders, he added.

PAUL OFFIT, MD: VACCINE EXPERT TWICE HONORED



Paul A. Offit, MD, was lauded for his more than three decades of vaccine research and advocacy with back-to-back honors. The blog Vaccine Nation named him one of the 50 most influential people in vaccines, and he was also awarded the 2013 Maxwell Finland Award for Scientific Achievement, given annually by the National Foundation for Infectious Diseases (NFID).

Along with late Children's Hospital researcher Fred C. Clark, DVM, PhD, and University of Pennsylvania Emeritus Professor Stanley A. Plotkin, MD, Dr. Offit is a co-creator of the rotavirus vaccine, Rotateq. Prior to the invention of Rotateq, thousands of children in the U.S. were hospitalized with rotavirus each year, and the drug is credited with saving hundreds of thousands of lives a year around the world.

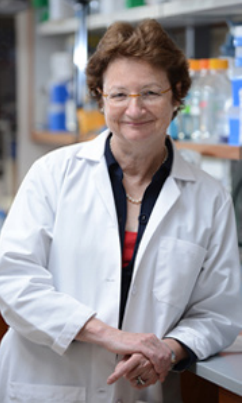
Dr. Offit, director of CHOP's Vaccine Education Center and chief of the Division of Infectious Diseases, is also an ardent champion of the safety and necessity of vaccinations, and his willingness to speak his mind has earned him many vocal critics over the years.

Vaccine Nation conducted a survey of its subscribers, Linkedin group members, and contacts to compile its list of the top 50 people in vaccines. Dr. Offit, who was named the sixth most influential person, is joined on the list by Dr. Plotkin, as well as the philanthropists Bill and Melinda Gates.

The NFID award recognized Dr. Offit and other "who have made outstanding contributions to the understanding of infectious diseases or public health." Past winners of the award include Dr. Plotkin and former U.S. Surgeon General C. Everett Koop, MD.

Calling Dr. Offit "an impassioned advocate for immunizations," the NFID award citation noted that he "has rallied the scientific counteroffensive against those who would denigrate the power and worth of vaccines."

KATHY HIGH, MD, HHMI: HONORED FOR GENE THERAPY BLINDNESS TRIAL



A groundbreaking clinical trial of gene therapy for a form of congenital blindness conducted by Children's Hospital and the University of Pennsylvania was recognized with the Distinguished Clinical Research Achievement Award from the Clinical Research Forum, an organization of clinical research centers, industry, and volunteer groups.

That award is the second highest in the CRF's annual Top 10 Clinical Research Achievement Awards. Recognizing studies published in 2012, the CRF focused on a Feb. 2012 article in Science Translational Medicine, co-authored by researchers from CHOP and the Perelman School of Medicine at the University of Pennsylvania. The authors reported on the most recent phase of a clinical trial for Leber's congenital amaurosis (LCA), a rare retinal disease that progresses to total blindness by adulthood.

The study team reported on further improvements in vision in three adult patients previously treated in one eye who then received the same innovative gene therapy in the second eye.

This LCA research is an ongoing collaboration among Jean Bennett, MD, PhD, F.M. Kirby professor of Ophthalmology at the University of Pennsylvania School of Medicine; CHOP'S Katherine A. High, MD, HHMI, director of the Center for Cellular and Molecular Therapeutics (CCMT); and Albert M. Maguire, MD, of Penn Medicine and CHOP.

Dr. High, a pioneer of gene therapy, directs the CCMT, which sponsors the clinical trial in LCA and manufactured the genetically engineered virus used to carry the therapeutic gene. Dr. Maguire, a retina specialist, injected the corrective gene into the eyes of adult and pediatric study subjects at Children's Hospital.

As widely reported in October 2009, this clinical trial of gene therapy achieved dramatic results in children with LCA. Building on their previous work, the research team is now conducting the first Phase 3 gene therapy study for genetic disease in the U.S. This is also the world's first Phase 3 gene therapy study for a non-lethal disorder. If successful, it could lead to the first approved gene therapy product in the United States.

ROBERT DOMS, MD: NEW CHIEF OF PATHOLOGY



Renown AIDS researcher [Robert W. Doms, MD, PhD](#), joined Children's Hospital in September 2012 as pathologist-in-chief and chair of Pathology and Laboratory Medicine.

Much of Dr. Dom's work as an investigator has focused on AIDS pathogenesis and how viruses enter cells, but more recently his lab has also studied West Nile Virus and other emerging pathogens. He has won a number of awards for his work, including the Elizabeth Glaser Scientist Award from the [Pediatric AIDS Foundation](#).

In his role as the new Chief of Pathology, Dr. Doms plans to work to integrate next generation sequencing (NGS) techniques into the Department of Pathology's work, a project he calls a "big challenge." By reducing sequencing time and costs, NGS can help researchers and clinicians to efficiently identify the genetic variants underlying diseases through whole-exome or whole-genome sequencing.

"I am very pleased that Dr. Doms has agreed to join us at CHOP, and we look forward to his contribution to an exceptional Pathology and Laboratory Medicine program," said Children's Hospital Chief Executive Officer Steven M. Altschuler, MD. "Bob is internationally known and recognized for his discoveries in HIV/AIDS research, and his reputation for excellence will certainly enhance our efforts at CHOP."

Before joining Children's Hospital, Dr. Doms spent more than two decades at the [University of Pennsylvania](#), where he retains a dual appointment.

BEVERLY LANGE, MD: CELEBRATING 40 DISTINGUISHED YEARS



During her decades-spanning career, Beverly J. Lange, MD, played a number of important roles both at Children's Hospital and in the scientific community at large. After four decades of leadership at Children's Hospital — more than 35 of which she spent working on childhood cancers — Dr. Lange retired in FY13.

As part of a celebration of her career, in March Dr. Lange presented a talk called, "Survival on the Yellow Brick Road," in which she highlighted some of her many accomplishments while touching on her recent work helping to better understand and alleviate the myriad side effects of cancer treatment.

Dr. Lange worked on many aspects of pediatric oncology over her career, including groundbreaking work on acute myelogenous leukemia (AML). While AML is the second most common form of leukemia in adults, the disease is relatively rare in children, with only 500 to 600 children diagnosed each year.

AML survival rates have greatly increased over the last several decades, with the 5-year survival rate now around 85 percent.

Dr. Lange's research interests also focused on how cancer therapy impacts pediatric patients' cognitive function. Cancer-related cognitive dysfunction (CRCDD), also known as "chemo brain," can lead to learning and memory deficits as well as problems later in life. CRCDD is therefore particularly worrisome in young children who are still developing,

Dr. Lange has advocated for improved CRCDD assessments as well as more feasible trials to better understand the effects of CRCDD, and encouraged clinicians and investigators to make CRCDD a priority for families.

In addition, Dr. Lange had an interest in the mitigation and prevention of other effects of cancer treatment. For example, she and her colleagues recently completed a trial aimed at preventing hearing loss associated with treatment with cisplatin, a drug used to treat a variety of cancers and which can cause a number of side effects in addition to irreversible hearing loss.

In honor of her work and many accomplishments in pediatric cancer, Dr. Lange was honored in July 2012 with the "Pitcher of Hope" award during an Alex's Lemonade Stand Foundation (ALSF) fundraising event held. The "Pitcher of Hope" award is presented annually to a Children's Hospital professional who shows extraordinary commitment to caring for children with cancer.

In addition to her role at Children's Hospital, Dr. Lange held a number of prestigious appointments outside CHOP over the years, including leadership roles in the American Society of Pediatric Hematology and Oncology and membership in the Children's Oncology Group. She has also received a host of awards and honors, including a 2006 Temple University Alumni Achievement Award, as well as a lifetime achievement award from the Children's Oncology Group in 2008.

Dr. Lange, who now splits her time between Philadelphia and Venice, Italy, called her work with cancer and leukemia "the love of my life."

BARBARA MEDOFF-COOPER, PHD, RN, FAAN: RECEIVES PRESTIGIOUS NURSE-SCIENTIST AWARD



Three decades of innovative research led the Council for the Advancement of Nursing Science to honor nurse-scientist Barbara Medoff-Cooper, PhD, RN, FAAN, with its Outstanding Nursing Scientist Award.

The Council is the country's leading scientific organization for nurse-scientists. The award acknowledges Council members whose research studies have had significant impact on nursing and healthcare knowledge and practice.

Dr. Medoff-Cooper is a nationally and internationally known expert on developmental outcomes, feeding behaviors and infant temperament in high-risk infants. She has received six grant awards from the National Institutes of Health to support her research, including her latest study that uses state-of-the art telehealth technology for in-home monitoring of infants who underwent neonatal cardiac surgery.

"This ongoing study has the potential to change the paradigm of home monitoring care for extremely vulnerable populations," said Dr. Medoff-Cooper, who has published more than 70 journal articles and is the co-inventor of Neonur, a feeding device allowing researchers and clinicians to objectively measure feeding behaviors in neonate and young infants.

Her work extends outside of patient care and includes participation in many NIH review groups and serving as the chair of a national task force to develop protocols for the care of preterm infants.

Dr. Medoff-Cooper holds the Ruth M. Colket Endowed Chair in Pediatric Nursing at CHOP, the first endowed chair for nursing in a children's hospital. She also serves as a professor at the University of Pennsylvania School of Nursing and previously served as the director for the Center for Nursing Research at Penn.

GARRETT BRODEUR, MD: AWARD HIGHLIGHTS LIFETIME CANCER RESEARCH



A pediatric oncologist with the Hospital's Cancer Center received a national award highlighting his lifetime research on neuroblastoma, the most common solid tumor of childhood. The American Society of Clinical Oncology conferred one of its highest awards on Garrett M. Brodeur, MD, who received the Pediatric Oncology Award and delivered the Pediatric Oncology Lecture.

The Award and Lecture, held during the ASCO annual meeting in Chicago, recognizes “outstanding scientific work of major importance to the field of pediatric oncology” during the course of a career.

A cancer of the peripheral nervous system that typically appears as a tumor in a child's abdomen or chest, neuroblastoma varies greatly in severity, ranging from forms that spontaneously disappear to high-risk subtypes that are difficult to cure. Because of this variability, researchers have sought ways to predict the course of disease in order to select the most appropriate treatment for each patient. The underlying assumption of this approach is that better understanding of the biology of this form of cancer will allow pediatric oncologists to avoid undertreating or overtreating a child.

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

His research first demonstrated in the 1980s that when neuroblastoma cells developed multiple copies of the *MYCN* gene — a process called amplification — a high risk subtype of neuroblastoma occurs, requiring more aggressive treatment. This discovery ushered in the current era of genomic analysis of tumors, both in adult and pediatric oncology. Profiling specific molecular alterations in a given patient's tumor helps oncologists to predict that patient's outcome and select the most appropriate treatment.

Dr. Brodeur and his colleagues also identified deletions of important genes on chromosomes 1 and 11 as markers of high-risk neuroblastoma. He has collaborated with other CHOP investigators who identified the *ALK* gene as the gene responsible for most cases of hereditary neuroblastoma.

Another major focus of his research has concerned receptor tyrosine kinases, a family of signaling proteins that control the clinical behavior of neuroblastomas.

His preclinical work led to a clinical trial with a novel drug that selectively blocks TRK signaling. He is now working on second-generation TRK inhibitors, as well as on nanoparticle delivery systems to treat patients more effectively, and with less toxicity.

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

DONNA MCDONALD-MCGINN, MS, CGC: CHROMOSOME DELETION WORK HONORED



Chromosome 22q.11.2 deletion syndrome is a congenital disorder that occurs when a portion of the DNA on chromosome 22 is missing. The loss of genetic material has multiple effects, which may include abnormalities in the immune system, the heart, the endocrine system, facial features, and cognitive abilities.

Over the years, researchers have found that deletions on this section of chromosome 22 are an underlying cause of various clinical diagnoses, known by such names as DiGeorge syndrome, velocardiofacial syndrome, and conotruncal anomaly face syndrome.

In recognition of her years of work on chromosome 22 deletions, Donna McDonald-McGinn, MS, CGC, received the Angelo DiGeorge Medal of Honor.

The Angelo DiGeorge Medal recognizes outstanding contributions to understanding and/or treatment of chromosome 22q.11.2 deletion syndrome, a relatively common multisystem genetic disorder. The International 22q11.2 Deletion Syndrome Consortium established the award in 2010 to commemorate the life and work of the late Dr. DiGeorge, a pediatrician who described aspects of the syndrome nearly 50 years ago.

Ms. McDonald-McGinn, associate director of Clinical Genetics and program director of the Hospital's "22q and You" Center, is only the second person to receive this highly esteemed honor.

In addition to publishing more than 80 articles on this deletion syndrome, she has served as a tireless advocate for children and families, and has spent countless hours working on support and educational events related to this condition.

While presenting the award, Dr. Peter Scambler of Great Ormond Street Hospital for Children in London praised her "singular breadth of achievement and dedication." In particular, he singled out her recent work co-authoring an important scientific article that presents best practice recommendations for patients with this syndrome.

JEFFREY SILBER, MD, PHD: RECIPIENT OF NEW ENDOWED CHAIR IN HEALTH SERVICES



Since its inception in 1988, the Hospital's Endowed Chair program has supported pioneering investigators working to understand and treat childhood diseases. Named for an honoree, endowed chairs provide crucial, assured funding to more than 100 CHOP investigators.

Center for Outcomes Research director Jeffrey Silber, MD, PhD, was named the first Nancy Abramson Wolfson Endowed Chair in Health Services in FY13. A pediatric oncologist, cancer survivorship researcher, and health care economist, Dr. Silber is the first researcher to hold this endowed chair.

The new Endowed Chair is named for longtime Children's Hospital Board of Trustees member Nancy Abramson Wolfson, who has served as the chair of the Hospital's annual fundraising Daisy Day Luncheon for the past 15 years. Since its inception, the luncheon has raised more than \$14 million to support care and research at CHOP, and the 2013 Daisy Day Luncheon raised more than \$1.5 million to support Children's Hospital's Pain Management Program.

The Endowed Chair was created to honor Nancy Abramson Wolfson's contributions, and to ensure that the Hospital will be able to continue to recruit and support top researchers and pediatricians like Dr. Silber.

An authority on outcomes measurement, Dr. Silber created the Failure-to-Rescue quality of care measures, which were subsequently adopted by the National Quality Forum, a nonprofit organization that works to improve healthcare.

Dr. Silber also leads the Hospital's Center for Outcomes Research, which aims to improve healthcare by using healthcare outcomes research and by teaching and mentoring clinicians. The Center has been instrument in looking at the impact of restricting residents' work hours on errors and quality of care, obesity and surgical outcomes, and the effect obstetric unit closures have had on pregnancies.

More recently, Dr. Silber has contributed to studies of race and obesity in operative procedure length, and to an investigation of the association between acute kidney injury and obesity.



FACTS & FIGURES

Financials

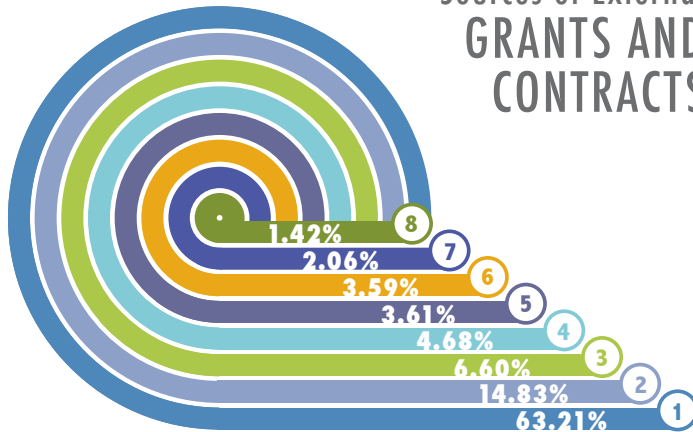
Who's Who

Credits

Links of Interest

FINANCIALS

Sources of External GRANTS AND CONTRACTS



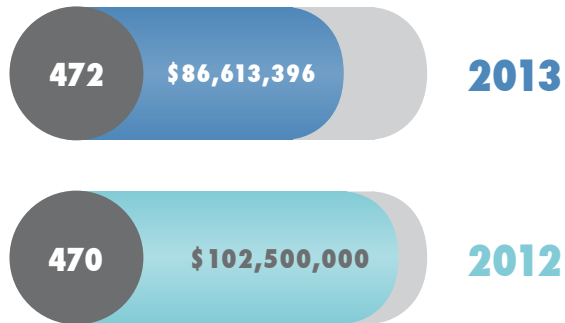
- ① Federal
- ② Children's Oncology Group Federal
- ③ Foundation
- ④ Industrial
- ⑤ Children's Oncology Group Foundation/Industry
- ⑥ Other
- ⑦ State/Local
- ⑧ Federal - Stimulus

NUMBER OF GRANTS Stimulus/Non Stimulus

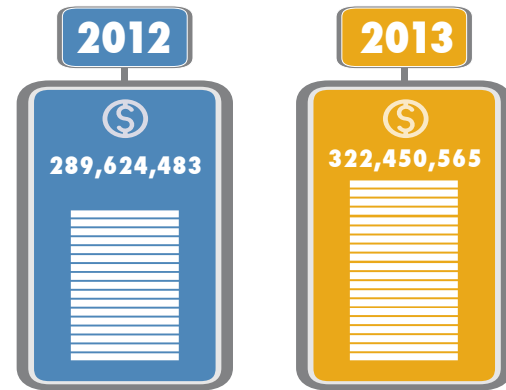


NEW AWARDS

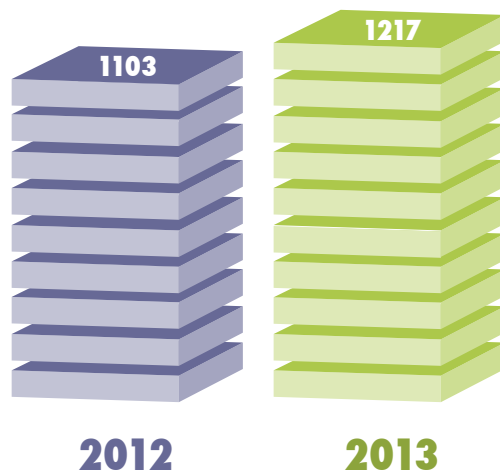
Grants/Contracts



Total Research OPERATING EXPENSES

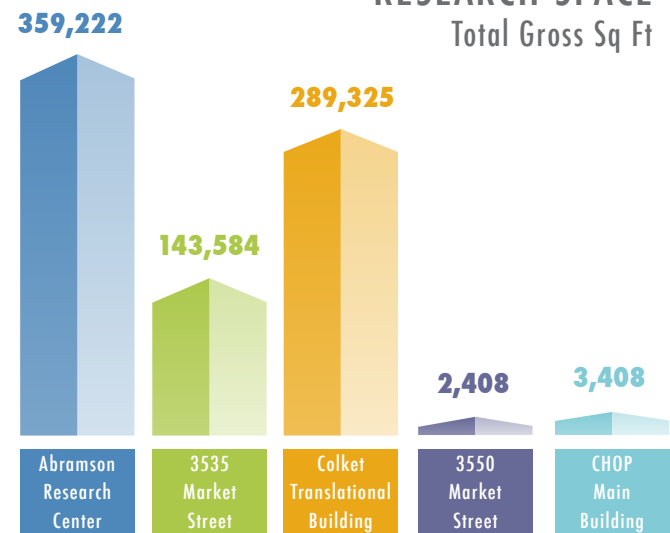


PUBLICATIONS



RESEARCH SPACE

Total Gross Sq Ft



Who's Who

CHOP Research Institute Leadership

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

Tom Curran, PhD, FRS
Deputy Scientific Director

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

Mary Tomlinson
Deputy Administrative Director
Senior Vice President for Research

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Frederick Bertley, PhD
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Denise M. Melvin
Paul Offit, MD
Mortimer Poncz, MD
Sue Souder
Matthew N. VanKouwenberg
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Timothy Roberts, PhD
Michael Levine, MD
Struan Grant, PhD
Stewart Anderson, PhD
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Gelvina Stevenson

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Diana Stanescu, MD
Natalie Steinel
David Taylor, PhD
Mary Anne Timmins
Rita Valentino, PhD
David Weber, MD
Mitch Weiss, MD, PhD
Susan Weiss, PhD

Centers of Emphasis

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Center for Autism Research

Director: [Robert Schultz, PhD](#)

Center for Biomedical Informatics

Director: [Peter White, PhD](#)

Center for Cellular and Molecular Therapeutics

Director: [Katherine High, MD, HHMI](#)

Center for Childhood Cancer Research

Director: John Maris, MD

Center for Injury Research and Prevention

Directors: Flaura Winston, MD, PhD, and
Dennis Durbin, MD, MSCE

Center for Mitochondrial and Epigenomic Medicine

Director: Douglas Wallace, PhD

Center for Pediatric Clinical Effectiveness

Director: Ron Keren, MD, MPH

PolicyLab

Director: David Rubin, MD, MSCE

Research Affinity Groups

DNA-Protein Interaction

Group Leaders: Struan Grant, PhD, and
Andrew Wells, PhD

Fetal Biology and Therapy

Group Leader: Alan Flake, MD

Genes, Genomes, and Pediatric Disease

Group Leaders: John Maris, MD, and
Nancy Spinner, PhD

Health and Behavior

Group Leaders: Stephen Leff, PhD, and
Joel Fein, MD, MPH

Metabolism, Nutrition, and Physical Development

Group Leader: Babette Zemel, PhD

Mitochondria

Group Leaders: Marni Falk, MD

Neuroscience

Group Leader: Michael Robinson, PhD

Normal and Malignant Hematopoiesis

Group Leader: Carolyn Felix, MD

Proteins

Group Leader: Yair Argon, PhD

Vaccine and Immunotherapies

Group Leaders: Paul Offit, MD, and
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Leonard and Madlyn Abramson Endowed
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Michael Bennett, PhD

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

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

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Mitch Weiss, MD

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Werner and Gertrude Henle Endowed Chair
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Monte Mills, MD

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Ritu Verma, MD, ChB

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Pending Appointment

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Pending Appointment

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Pending Appointment

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Louis Starr Endowed Chair in Pediatrics
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J. William Gaynor, MD

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Pending Appointment

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Clinical and Translational Research

Mary Leonard, MD, Director

Clinical Trials Financial Management

Mitch Appleson, Director

Core Facilities Administration

Lisa MacDowell, Administrative Director

Faculty Development

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Postdoctoral Affairs

Wendy Williams, PhD, Director

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Marsha Wallace, Assistant Director

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Bethann Kurek, Assistant Director

Research Human Resources

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Research Information Systems

Peter Witzleb, Director

Robert Del Campo, Assistant Director

Research Resources

Howard Eck, Director

Research Safety

Raymond Colliton, Director

Denise Melvin, Assistant Director

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Brigid Czyszczin, Assistant Director
Robert Denight, Assistant Director

Supply Chain

Kimberly Gossin, Manager

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Greg Baker, PhD, Associate Director
Debbie Schmidt, Associate Director

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Chief Executive Officer

Madeline Bell
President

Philip R. Johnson, MD
Chief Scientific Officer
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Translational Medicine and Science
Director, CHOP Research Institute

Mary Tomlinson
Deputy Administrative Director
Senior Vice President for Research

Jennifer Long
Director, Research Communications

Kevin O'Rourke
Medical/Science Writer

Angela Knott
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Melissa LaVigne
Graphic Designer

Juliet Kilcoyne
Production and Creative Services Coordinator

Robert Neroni
Photographer

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[The Children's Hospital of Philadelphia Research Institute Website](#)

[The Children's Hospital of Philadelphia Website](#)

[Cornerstone, CHOP Research's blog](#)

[The CHOP Research Institute Press Releases](#)

[Bench to Bedside, CHOP Research's Monthly News Publication](#)

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