A Banner Year for Research Discoveries; Foundation Laid for Future Successes

Tribute to Audrey Evans, M.D.

Distinguished Cancer Researcher Retires After a 60-Year Career

Dr. Evans joined Children's Hospital in 1969 as the first director and chief of the Division of Oncology.

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Clinical HIV Investigator
Richard Rutstein, M.D.

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Center for Pediatric Nursing Research

» Read More, Section C, pg. 15

Bridging Research and the Marketplace

» Read More, Section E, pg. 20

Colket Translational Research Building

Building Upon Our Solid Foundation of Cutting-Edge Research

The Colket Translational Research Building, the first of several buildings slated for the Hospital's new South Campus, opened the doors to its new state-of-the-art, environmentally responsible research facility.

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HIV’s resultant disease, acquired immune deficiency syndrome (AIDS), has claimed the lives of tens of millions of people, and 33 million people are living with HIV or AIDS today. People continue to become infected with HIV at an alarming rate, with five new infections every second.

Investigators at Children’s Hospital take a multifaceted approach to unraveling the inner workings of HIV in the hope of dismantling the virus’ complex and elusive defense mechanisms. These endeavors focus on preventing infection through a novel vaccine strategy, understanding what happens both inside and outside cells when the virus invades, and the best approach to treating infection in children and adolescents.

Together, these approaches may one day lead to more effective treatments, a cure or a vaccine for one of the greatest and costliest epidemics.

The widespread infection rate underscores the need for novel approaches and a better grasp of HIV and its inner workings.

For more than 20 years, scientists across the globe have attempted to better understand and eradicate human immunodeficiency virus (HIV), which infects nearly 3 million people worldwide annually despite extensive research and prevention programs.
Over the past century, physicians and scientists have understood the importance of vaccines in preventing diseases and, by extension, providing a cost-effective way of protecting public health. Vaccines deliver immunity in a less risky way than naturally acquired immunity, which involves contracting a disease and allowing the body to defend itself—sometimes with severe symptoms and deadly complications.

For more than two decades, investigators around the world have been attempting to develop a vaccine for HIV, for which the vast majority of people are unable to mount a sufficient immune response.

But HIV is unique, making vaccine development more difficult than for other viruses. HIV possesses an unusual ability to hide within host cells, evade detection, and destroy certain cells that are critical to the body’s immune response. The virus has also proven exceptionally proficient in mutating and evolving when needed for its survival.

Traditional approaches to an HIV vaccine that attempt to stimulate the natural immune system have failed, so Philip Johnson, M.D., who maintains a vibrant research program while serving as director of The Children’s Hospital of Philadelphia Research Institute and holding the Edmond F. Notebaert Endowed Chair in Pediatric Research, pursued a novel gene transfer approach that may have broken the vaccine impasse by leapfrogging over the body’s natural immune system response.

Working with simian immunodeficiency virus (SIV), which is similar to HIV but occurs in nonhuman primates, Dr. Johnson and his research team and collaborators developed proteins that act like antibodies. These proteins, called immunoadhesins, were specifically designed to bind to SIV and prevent the virus from infecting cells.

Dr. Johnson and his team then engineered DNA for these SIV-specific immunoadhesins and delivered them directly to the nonhuman primates through an adeno-associated virus. One month later the nonhuman primates were injected with live SIV.

This gene transfer approach used by the investigators produced molecules that blocked SIV infection, completely protecting the nonhuman primates from the otherwise deadly virus.

The novel technique, featured in the prestigious journal Nature Medicine, may offer promise in preventing HIV infection in the future, but additional research is needed to see if the technique used in the animal studies generates similar successes in the development of an HIV vaccine.

“In addition to further research, the next big decision point for the HIV vaccine approach rests with the FDA to pave the way for human trials,” says Dr. Johnson, who adds that any vaccine may be years from realization and better molecules that work against HIV are needed.

However, in the meantime, the novel technique holds the promise of preventing one of the deadliest chronic human diseases and its use may be applicable in preventing other infectious diseases.

“Dr. Johnson’s groundbreaking research represents one of the biggest, most significant findings in the history of research at Children’s Hospital,” says Steven Douglas, M.D., chief of the Section of Immunology. “This approach represents a paradigm shift in HIV research.”

Visit the Philip Johnson Research Laboratory Web site at:
http://www.research.chop.edu/programs/johnsonlab/
How T Cells Are Triggered

Terri Finkel, M.D., Ph.D.

Sometimes the most powerful weapons in maintaining health are the ones you cannot see with naked eyes. In immunology, T cells often wield the greatest power in fighting infection, allowing the body to recover from foreign invaders.

The severity of HIV is often measured in the number of a patient’s T cells, white-blood cells with a crucial role in how the body’s immune system functions. HIV has proven proficient in killing T cells, rendering those with low T-cell counts susceptible to developing AIDS. Although existing therapies may help patients with HIV maintain a T-cell load that optimizes their immune function as much as possible, the treatment regimen for infected people is rigorous and adherence is difficult.

A key to fighting the virus once it has infected cells is therefore to understand what triggers, or activates, T cells in the first place so that they will amass their defenses to fight infection and call upon other cells that are needed to mount an effective immune response.

Building upon her years of success in HIV research, Terri Finkel, M.D., Ph.D., chief of the Division of Rheumatology and Joseph Lee Hollander Endowed Chair in Pediatric Rheumatology, continues her pursuit by investigating T-cell activation and other biological functions that are key to understanding and battling HIV. She is currently investigating what starts the chain of events leading to T-cell activation, working closely with Zhengyu Ma, M.D., Ph.D., a new research assistant professor at the CHOP Research Institute.

A T cell is activated after one of its receptors binds to a peptide complex on another cell — in the case of HIV infection, on an infected cell. The T-cell receptor and the peptide-loaded major histocompatibility complex, or pMHC, form a lock-and-key mechanism.

However, Dr. Finkel and her colleagues have found that it isn’t the “locking” of the infected cell’s pMHC that triggers T-cell activation to fight infection and engage other cells needed in an immune response. Rather, T cells appear to be activated when these cells pull apart.

Dr. Finkel has turned her attention to a phenomenon between the cells called “rupture force,” created by the T cell “essentially pulling back from the surface of a cell as it bounces along looking for the appropriate receptor. But the elusive nature of HIV and its ability to mutate in infected cells has compromised the critical rupture force needed for T-cell activation. In HIV, the correct lock-and-key mechanism occurs between the T cell and peptide complex but the virus is clever enough to change its peptide antigen, its lock. The T cell no longer recognizes the antigen as the one needed to achieve rupture force and fight an infection. T cells will try to mount a force to deal with the new antigen but then HIV changes again.

Dr. Finkel is therefore exploring what specific part of the T-cell receptor is critical so it may one day be added back in through a gene therapy approach. Her colleague, Dr. Ma, is the first to use a process called atomic force microscopy to apply rupture force to T-cell receptors to eventually develop better T cells and receptors.

“What we are using to test this are receptors that have been put into T cells and have been shown to eliminate virus, at least in the test tube,” says Dr. Finkel. “Interestingly, they eliminate all strains of HIV. We are working with a company to design a super T-cell receptor that can recognize and kill cells that express a whole range of viruses. So even if the virus tries to escape, that lock-and-key mechanism is strong enough that the virus can’t get away.”

Dr. Finkel is looking to expand her HIV research program to use atomic force microscopy to further learn how T cells and other immune cells function, how infections evade the immune system, and how that system responds to foreign invaders.

She and her colleagues are also continuing their investigation of HIV latency, and have identified a new function for a viral protein, called Vif, which may be involved in HIV’s emergence from latency and allows the virus levels to soar within the body.

Future research may lead to the development of new drugs that target Vif and its cellular partners, or may bring infected cells out of latency so they can be treated with antiretroviral drugs.

Visit The Vaccines and Immunotherapies Research Affinity Group Web site at:
http://www.research.chop.edu/research/affinity_groups/vaccines_immunotherapies/
In an effort to prevent HIV from developing into AIDS, infected patients must adhere to a drug regimen that over the years has proven difficult to follow. The therapy, called highly active anti-retroviral therapy, or HAART, is not effective for all patients and sometimes fails to control some of the neuropsychiatric problems experienced by nearly half of all patients with AIDS.

Although the existing regimen has improved the quality of life and longevity of those with HIV and AIDS, the therapy includes medicines that do not sufficiently cross from the blood and into the brain, where reservoirs of HIV exist. These virus pools often cause problems like dementia and a variety of cognitive problems.

Steven D. Douglas, M.D., chief of the Section of Immunology and director of the Hospital’s Clinical Immunology Laboratories, continues to build upon his groundbreaking research to develop a novel HIV drug that targets the neurokinin-1 receptor (NK1R) in human immune cells to treat these HIV-related cognitive impairments, called NeuroAIDS.

More than a decade ago, Dr. Douglas and his colleagues found that immune cells in the human body have NK1R cell receptors and also produce a neurotransmitter called substance P that binds to the receptor. Later, Dr. Douglas found that an NK1R antagonist prevented HIV from entering these immune cells with the NK1R receptor. The antagonist inhibited HIV by impeding the activity of a major HIV co-receptor on cell surfaces called CCR5.

These seminal findings have paved the way for a potential new class of drugs used to treat the often severe psychological and neurological effects in NeuroAIDS. Dr. Douglas now leads a new $6 million cooperative program grant from the National Institute of Mental Health to find the most effective ways to use NK1R antagonists to block HIV replication.

“Our latest endeavor will look at the most effective ways to use NK1R antagonists to keep HIV from replicating,” says Dr. Douglas. “We will investigate not only the drug’s antiviral activity and its ability to relieve the symptoms associated with NeuroAIDS, but also whether it improves the body’s built-in, innate immunity.”

Aprepitant, a drug frequently used to prevent nausea, is one NK1R antagonist that Dr. Douglas and his colleagues are evaluating. The aprepitant study builds upon their recently completed laboratory and clinical investigations.

The new investigation involves cell studies, translational work to apply basic knowledge to treatments, and a clinical trial. Dr. Douglas and his team will look at how NK1R drugs function in both immune and brain cells, and they will investigate whether depression makes immune cells more vulnerable to HIV infection. The team will also evaluate whether aprepitant may prevent HIV from entering the cells while restoring the immune function of natural killer cells, a type of white blood cell that plays a critical role in immunity.

Dr. Douglas hopes the results of the new study will lead to a novel treatment for HIV and NeuroAIDS that he can bring to the clinical side of HIV care, in which he leads two worldwide therapeutic trials for pediatric and adult HIV/AIDS — the Philadelphia International Maternal Pediatric Adolescent AIDS Clinical Trials Unit and the Adolescent Trial AIM Network.

The new project involves two clinical trials with aprepitant, one in HIV-infected adult patients receiving antiretroviral therapy, and the other combining the agent with the anti-HIV drug ritonavir in patients failing standard HIV therapy.

“NK1R antagonists in general have a lot of potential for new HIV treatments, but we still have a lot to learn about what they do and how they work,” says Dr. Douglas. “Our hope is that we can learn more about these promising agents, and rapidly translate our findings to a new therapeutic agent for HIV infection.”
ENHANCING SURVIVAL, QUALITY OF LIFE

Through HIV Clinical Research

Richard Rutstein, M.D.

About 30 years ago, children infected with HIV were expected to live only a few short years. Substantial advances in understanding the inner workings of the virus and developing effective drug therapies have since extended the life expectancy of those infected. Children with HIV can now expect to live — and live well — far into adulthood. And just as importantly, these new therapies, when given to HIV-infected pregnant women, can prevent almost all newborn infections.

Understanding the complex steps involved during infection with HIV to develop methods of preventing infection is only part of the HIV research agenda. Another, equally important, factor involves research into the most effective and manageable care for those already infected with the virus.

The improvement in the quality and length of life of those with HIV can be attributed to a remarkable collaborative global research effort, of which Children’s Hospital is proud to be a contributing member.

Richard Rutstein, M.D., medical director of the Hospital’s Special Immunology Service, has cared for HIV-infected children for 25 years, the last 20 at Children’s Hospital. He leads numerous clinical research studies looking at new anti-retroviral agents, the effects of the drug regimen on patients, and the impact of HIV-related illnesses on the patients’ future health and long-term survival.

The success of the worldwide AIDS research initiative is evident in the dramatic decrease in perinatal HIV infection. Dr. Rutstein and his colleagues reported that among families followed at the Special Immunology Family Care Center, the rate of transmission of HIV from mother to infant dropped from 20 percent to less than 1 percent when the women were treated with a three-drug regimen. Their findings led to the present perinatal HIV treatment programs.

“This means that HIV perinatal prevention programs are by far the most cost-effective and efficacious perinatal programs to date,” says Dr. Rutstein. “All pregnant women should be offered HIV testing early in pregnancy, and again in the third trimester.”

Today, Dr. Rutstein and his colleagues are part of national multisite research networks funded by the National Institutes of Health, the Centers for Disease Control and Prevention, and the Agency for Healthcare Research and Quality. These multisite networks of pediatric/adolescent and pediatric/adult HIV treatment centers follow segments of the HIV population to provide extensive longitudinal data on the clinical outcomes of those infected. This research will continue to guide investigators on the path for future translational research efforts that can vastly impact and enhance the health and longevity of infected individuals.

Much of the clinical research conducted by Dr. Rutstein and his team as part of these multisite efforts focuses on new drug treatment strategies and safety monitoring studies.

HIV clinical research at Children’s Hospital continues to flourish today despite several global challenges. Those challenges at the heart of this HIV clinical research involve providing less costly and less toxic therapies while ensuring long-term survival through adherence to an increasingly arduous and difficult-to-follow anti-retroviral drug regimen.

Another challenge for investigators and healthcare providers is to ensure access to affordable HIV medicines to the populations hardest hit by the virus.

“The number of infected children and teens in the United States represents a small percentage of infected cases worldwide,” says Dr. Rutstein. “We need to maintain our focus in finding ways to bring therapies to those populations where HIV has the greatest impact and where efficient and affordable access to healthcare is suboptimal.”

Visit The Center for Pediatric and Adolescent AIDS Web site at:
http://www.chop.edu/consumer/jsp/division/service.jsp?id=27706
At the root of CHOP Research's success are the step-by-step discoveries that move the standard of pediatric care to new heights. Each year CHOP Research investigators make phenomenal progress by answering vital questions that, left unanswered, block the path toward eradicating pediatric disease. More than 600 articles published during the fiscal year communicate the findings of the passionate pursuit of discovery maintained by Children's Hospital investigators and staff. Many of these publications, which showcase the Institute's growing expertise in all pediatric subspecialties, were published in influential journals such as *Journal of the American Medical Association*, *Nature*, and *Nature Medicine*.

Despite a flat federal budget for biomedical research and global economic strain, the number of grant awards to CHOP Research increased 13.5 percent over the last fiscal year and the Institute remains one of the leaders in pediatric funding from the National Institutes of Health. This financial support enables CHOP investigators to continue to shape the future of pediatric care.
## Possible 'Master Switch' for Juvenile Arthritis Located

A gene region known to play a role in some types of adult rheumatoid arthritis is also present in childhood arthritis, and may act as a “master switch” that helps turn on juvenile idiopathic arthritis (JIA), according to a study led by Terri Finkel, M.D., Ph.D., Edward Behrens, M.D., and Hakon Hakonarson, M.D., Ph.D. The genome-wide association study identified the genetic variant on chromosome 9 in a region housing TRAF1 and C5. This finding, published in *Arthritis & Rheumatism*, may be a clue to the specific disease pathway that leads to arthritis, and may help investigators create targeted treatments for JIA.


## Asthma Gene Affects White, but Not African-American Children

Variants in the ORMDL3 gene, known to raise the risk of childhood asthma in European children, are associated with childhood-onset asthma of any severity in white American children but not in African-American children, according to a genotyping study led by Hakon Hakonarson, M.D., Ph.D. This study, which appeared in the *Journal of Allergy and Clinical Immunology*, sheds light on the complex genetic interactions of asthma, which may pave the way for new customizable treatments.


## Genetic Understanding of Type 1 Diabetes Expands

Using thousands of samples in a genome-wide association study, investigators led by Hakon Hakonarson, M.D., Ph.D., added two gene locations that raise the risk of type 1 diabetes to the increasing knowledge of the disease's genetic risk. These genes, UBASH2A and BACH2, are active in immune cells that play key roles in autoimmune disorders such as type 1 diabetes. Published in *Diabetes*, the findings of this study will contribute to improved predictive tests and preventive strategies for type 1 diabetes.


## Two Genes Found to Contribute to Childhood IBD

Hakon Hakonarson, M.D., Ph.D., and Robert Baldassano, M.D., used a genome-wide association study to find two newly identified gene variants that increase the risk of childhood-onset inflammatory bowel disease (IBD), which is often more severe than adult-onset IBD. The study identified one variant near the TNFRSF6B gene on chromosome 20 and one near the PSMG1 gene on chromosome 21. These genes, reported in *Nature Genetics*, are particularly strong candidates to be added to the list of genes already known to affect IBD and may help to build the foundation for personalized treatments tailored to a patient’s genetic profile.


## Protein Helps Control Blood Cell Production

In a study that may help improve treatments for blood disorders, Wei Tong, Ph.D., found that the protein Lnk regulates hematopoietic stem cell (HSC) production by interacting with JAK2, another protein involved in stem cell production, making JAK2 unavailable to become activated by the growth factor thrombopoietin.

Published in the *Journal of Clinical Investigation*, the study also found that mice that lack Lnk have HSC levels that are 10 times higher than normal. Surprisingly, the expanded HSC population in these mice includes a higher proportion of stem cells likely to contribute to a successful bone marrow transplantation.


## Auditory Processing Is Delayed in Autistic Children

Using magnetoencephalography (MEG) to look at brain activity, investigators led by Timothy Roberts, Ph.D., found that children with autism spectrum disorders (ASDs) respond to vowel sounds and tones a fraction of a second more slowly than non-autistic children, which may lead to a cascade of delay and overload in further processing of sound and speech. This finding, published in the *International Journal of Psychophysiology*, is the first step toward developing “neural signatures” that can link recorded brain activity to specific behaviors in children with ASDs and may allow clinicians to more accurately diagnose and treat ASD subtypes.

**New Technique Locates Crohn's Disease Genes**

Genes that contribute to Crohn's disease were uncovered in a study that combined genome-wide association with a statistical tool that identifies genes interacting on the same biological pathways, published in The American Journal of Human Genetics. The most significant gene variants identified are located on the interleukin 12 (IL12) pathway, which controls cell receptors involved in the development of Crohn's disease. This study, led by Hakon Hakonarson, M.D., Ph.D., may lead to drug therapies that target the IL12 pathway.


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**Visual Inspection of Jaundice Does Not Estimate Bilirubin Levels**

Ron Keren, M.D., M.P.H., found that the longstanding practice of visually inspecting newborn babies for signs of jaundice is an unreliable method of predicting the risk of developing hyperbilirubinemia. Visual inspection was especially non-predictive in late-preterm infants, who are at greatest risk of significant hyperbilirubinemia. Published in Archives of Disease in Childhood: Fetal and Neonatal Edition, these results indicate that universal bilirubin screening may be more beneficial than selective screening based on visual assessment of jaundice.


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**Early Switch From IV to Oral Antibiotics Effectively Treats Bone Infection**

Switching treatment from intravenous antibiotics to oral antibiotics is just as effective as continuing IV therapy when treating the bacterial bone infection acute osteomyelitis, according to a study led by TheoKlis Zaoutis, M.D., M.S.C.E. Published in Pediatrics, this finding indicates that hospitals can orient their clinical guidelines for uncomplicated acute osteomyelitis toward early transition to oral medication, a treatment option that is more convenient for children and families and avoids the risk of complications associated with central venous catheters.


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**Follow-up Concussion Care Essential Before Resuming Activity**

Children hospitalized with concussions should not resume regular sports or playtime activities before having a follow-up exam, according to a study led by Michael Nance, M.D., that used a computer-based testing program to assess children with concussions. The study, published in Annals of Surgery, found that nearly all children admitted to the hospital with a concussion had some abnormal brain function at the time of initial testing, indicating the importance of a follow-up exam even if symptoms are no longer apparent.


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**Congenital HI Treatment Shows Promise in Animal Study**

Investigators have used a peptide called exendin-(9-39) to normalize blood sugar levels in mice genetically engineered to have the same beta cell defect found in children with the most severe form of congenital hyperinsulinism (HI), a rare but potentially devastating genetic disease in which insulin levels become dangerously high. The study team also found that exendin-(9-39) normalizes blood sugar through a direct effect on insulin secretion. Led by Diva De Leon, M.D., and published in the Journal of Biological Chemistry, these findings may lead to an innovative medication for children with congenital HI.


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**BRAF Gene May Initiate Low-Grade Brain Tumors**

Investigators led by Jaclyn Biegel, Ph.D., found a potential target for effective therapies in children with low-grade brain tumors composed of glial cells, known as gliomas. As published in Brain Pathology, genome-wide arrays of tumor samples uncovered a duplication in chromosome 7q34; additional analysis revealed alterations in the BRAF oncogene that may play a role in the initiation of these tumors. The results of this study are the first to identify a consistent pattern of genetic abnormalities in low-grade gliomas.


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**Conclusions**

- The findings suggest new avenues for research and potential therapeutic targets in Crohn's disease, osteomyelitis, and congenital hyperinsulinism.
- Early transition to oral antibiotics is effective for treating acute osteomyelitis.
- Follow-up concussion care is essential before resuming activities.
- Exendin-(9-39) may offer a potential treatment for congenital hyperinsulinism.
- BRAF gene alterations may play a role in low-grade brain tumors.
Pregnancy Weight Gain Influences Weight of Child

According to a study led by Brian Wrotniak, P.T., Ph.D., children whose mothers gain more than the recommended amount of weight during pregnancy are more likely to be overweight at age seven than children of mothers who gained adequate or insufficient weight. The results of this study, published in the American Journal of Clinical Nutrition, indicate that helping pregnant women meet the recommended weight gain may be a new strategy for preventing pediatric obesity. These findings are particularly relevant since nearly half of U.S. women exceed the guidelines for recommended weight gain during pregnancy. PubMed Abstract: http://www.ncbi.nlm.nih.gov/sites/entrez/18541573

Studies Discover Autism Gene Regions and Biological Pathways

Two studies led by Hakon Hakonarson, M.D., Ph.D., have moved the field of autism research significantly ahead by identifying genes with important contributions to the disorder. Both studies, each published in Nature, used genome-wide association tools to identify genetic variants that affect the risk of a child developing an autism spectrum disorder (ASD) and detected genes implicated in the development of brain circuitry in early childhood.

One study is the first to identify common genetic variants associated with autism. It found that children with ASDs were more likely than healthy controls to have gene variants on chromosome 5 in a region between cadherin 9 (CHD9) and cadherin 10 (CHD10), genes that carry codes to produce neuronal cell-adhesion molecules. These molecules help shape the developing brain’s structure and connections among brain regions, which may be an underlying problem in ASDs. The variants may contribute to as many as 15 percent of ASD cases in a population.

The second study identified deletions or duplications of DNA, known as copy number variations, that increase a child’s risk of having an ASD. The variants were enriched in genes that belong to two biological pathways involved with neuronal cell-adhesion molecules. One cluster of genes includes the family of neuronal cell-adhesion molecules identified in the first study. The other cluster is involved in the ubiquitin degradation pathway that process and degrade neuronal cell-adhesion molecules. Both networks play critical roles in the development of neuronal connectivity within the central nervous system.

The findings of these studies converge with evidence that children with ASDs may have reduced connectivity among neural cells and abnormal development of the brain’s frontal lobes. Ongoing research will capitalize on an increased understanding of how ASDs arise with the goal of improving clinical treatments. PubMed Abstract: http://www.ncbi.nlm.nih.gov/sites/entrez/19404256

ALK Gene Mutations Are Main Cause of Neuroblastoma

Yael Mosse, M.D., and John Maris, M.D., identified gene mutations that are the main cause of the inherited version of neuroblastoma and contribute to the more common, non-familial form of neuroblastoma. These findings help define the genetic events that can lead to the broad range of outcomes associated with the disease, which can spontaneously disappear with minimal treatment or be relentlessly aggressive.

Using genome-wide arrays to analyze the DNA of 10 families with neuroblastoma, the study team first discovered that a region of chromosome 2 was associated with the disease. Further sequencing of that region identified mutations in the anaplastic lymphoma kinase (ALK) gene in eight of the 10 families. The study team then found ALK mutations in 12 percent of 194 tumor samples from the aggressive, high-risk form of the disease.

This study, published in Nature, is the first to identify mutations in ALK and is one of the few examples of a cancer caused by mutations in an oncogene. These findings enable the study team to develop the first genetic tests for families affected by the inherited form of this disease and to begin testing drugs in development that treat the ALK gene in adult cancers. PubMed Abstract: http://www.ncbi.nlm.nih.gov/sites/entrez/18724359
Abnormal Blood Sugar Levels Likely in Overweight Siblings of Children With Type 2 Diabetes

Obese siblings of children with type 2 diabetes are at four times greater odds of having abnormal glucose levels indicative of pre-diabetes or diabetes compared to other obese children, according to a study led by Sheela N. Magge, M.D., M.S.C.E. Published in The Journal of Pediatrics, this is the first study to examine the risk of abnormal glucose levels among siblings of children diagnosed with type 2 diabetes during childhood.

The study team looked at 62 obese children with a body mass index greater than the 95th percentile, 20 had a sibling diagnosed with type 2 diabetes during childhood and 42 did not. The groups were similar in age, gender, racial distribution, and pubertal status.

While the study showed that the sibling group was more likely than other obese children to have abnormal glucose levels, specifically impaired glucose tolerance or type 2 diabetes, it did not show any significant differences in insulin resistance as measured by the homeostasis model assessment.

Clinical experience suggests that children with type 2 diabetes often have an obese sibling. Because abnormal glucose levels indicate that a child has or is at risk for diabetes, this study shows that obese siblings of children with type 2 diabetes could benefit from screening tests and diabetes prevention education.


Protein Essential for Nervous System Development

Two studies led by Robert Kalb, M.D., and published in the Journal of Neuroscience demonstrate the key role the protein GluR1 plays in controlling the growth of dendrites in the developing nervous system. These findings, achieved in animal models, provide a greater understanding of how neural architecture develops normally and may serve as a basis for eventual treatments of nervous system injuries.

The first study showed that GluR1 is present on the surface of nerve cells during the most vigorous period of dendrite growth shortly after birth and is lost as neurons mature and dendrites stop growing. Suppressing GluR1 activity in mice reduced dendrite growth and led to poorly developed connections between neurons, resulting in decreased strength and endurance, while increasing its expression led to extended stamina.

The molecular pathways by which GluR1 binds with SAP97, a scaffolding protein, to control dendrite growth shortly after birth were described in the second study. This study suggests that GluR1 transports SAP97 to the membrane of nerve cells where it can receive pro-growth signals to build dendrites.


**Contract Awarded to Study Duration of Antibiotic Use to Treat UTIs**

Antibiotics are becoming less effective against infectious diseases because bacteria are increasingly resistant to commonly used antimicrobial drugs. The widespread threat of infections with resistant bacteria has the potential to affect the health of individuals and society as a whole. One strategy to reduce this resistance is to decrease the frequency and duration of the use of antimicrobial drugs.

The National Institute of Allergy and Infectious Diseases awarded Theoklis Zaoutis, M.D., M.S.C.E., associate chief of the Division of Infectious Diseases and associate director of the Center for Pediatric Clinical Effectiveness, a grant to help answer key questions about the necessity of antimicrobial treatments, proper doses, and appropriate treatment intervals.

The study will determine the optimal duration of antibiotic treatment of urinary tract infections (UTIs) in children, one of the most common serious bacterial infections of childhood. The initial award is $1.5 million, with a six-year total of $13.8 million if clinical trial milestones are met.

The largest clinical trial to compare a short course with the standard course of antimicrobial treatments for pediatric UTIs, the study will enroll more than 700 children to look at the effectiveness of antibiotic treatments as long as 10 days to as short as 3 days.

Because the current standard duration of antibiotic therapy recommended to treat UTIs is not evidence-based, this study will allow doctors to improve pediatric care while reducing unnecessary use of antibiotics.

**Award Supports Mentorship for Cancer Researchers**

Anne Kazak, Ph.D., Division of Oncology, was awarded an Established Investigator Award in Cancer Prevention and Control from the National Institutes of Health to enable her to focus additional efforts on mentoring and research. Dr. Kazak, a well-established cancer investigator dedicated to understanding pediatric cancer survivorship, has mentored numerous investigators who have gone on to establish successful academic careers and federally funded research projects.

The 5-year award supports the mentorship Dr. Kazak provides to trainees, fellows, and junior faculty from a variety of backgrounds who are working on projects related to the psychosocial aspects of cancer. The award also extends the scope of two existing grant-supported projects to increase the number of opportunities for psychosocial oncology research and to advance Dr. Kazak’s overall research goals.

The first project looks at the connections between posttraumatic stress in young adult cancer survivors and their adherence to recommended survivorship treatments; the second pilots adaptations to interventions developed for families of patients who are newly diagnosed with cancer.

In addition, the grant supports Dr. Kazak’s efforts to create mini-courses for multidisciplinary research trainees. The courses are designed to attract and retain investigators interested in conducting psychosocial research and interventions in pediatric cancer and other serious pediatric illnesses. The first course developed was a writing workshop, future courses will focus on developing study measurements and working with families who are dealing with pediatric cancer.

**Contract Awarded to Study Infant Feeding and Early Development**

Virginia Stallings, M.D., Division of Gastroenterology, Hepatology, and Nutrition, was awarded a $4.86 million contract from Social Scientific Systems Inc. (SSS), on behalf of the National Institute of Environmental Health Sciences, to conduct the Infant Feeding and Early Development (IFED) study.

This observational cohort study will compare a variety of developmental changes during early infancy and toddlerhood among children on one of three feeding regimens: breast milk, cow-milk based formula, or soy-protein based formula. By enrolling some mothers during pregnancy, the study also aims to examine whether prenatal exposures have an impact on early development.

During the infant phase of the study, approximately 250 infants will be followed from birth, boys until 7 months of age and girls until 9 months of age. The study team will assess the growth and development of infant participants by physical exam, specimen analyses, and ultrasound.

The toddler phase will focus on children aged 12 months to 24 months. The researchers will evaluate language acquisition, toy preferences, and developmental markers such as breast tissue and bone density in more than 750 toddlers from the three feeding groups. The findings of this study may have an impact on future feeding recommendations.

Children’s Hospital will serve as the IFED study’s clinical site and SSS will be the coordinating center. As lead investigator of the clinical site, Dr. Stallings has assembled an interdisciplinary team who will help conduct the IFED study.

Children’s Hospital IFED co-investigators are Babette Zemel, Ph.D., Division of Gastroenterology, Hepatology, and Nutrition; Richard Bellah, M.D., Division of Body Imaging; Judith Bernbaum, M.D., Division of Neonatology; Andrea Kelly, M.D., Division of Endocrinology; and Jerilynn Radcliff, Ph.D., Division of Psychology.
Research is critical to improving the health of children. Too often, however, our best evidence fails to inform real world practice.

PolicyLab aims to ensure optimal child health and well-being by informing programmatic and policy changes through interdisciplinary research.

A new Center of Emphasis at Children’s Hospital, PolicyLab was founded on the beliefs that research should be informed by community needs and priorities and that evidence should inform the decisions of policymakers.

In essence, PolicyLab’s leaders and experts believe that real-time, practical, and sustainable solutions are needed to improve the well-being of vulnerable children.
“By involving all stakeholders in the search for solutions, PolicyLab fosters collaborative thinking and builds capacity for future program and policy advancement,” says Kathleen Noonan, who serves as the center’s managing director and policy director. “We strive to create novel opportunities to advance the well-being of children, diminish health disparities, and use healthcare resources effectively.”

The PolicyLab team, which includes investigators, a vast program staff with extensive methodological and policy expertise, and a Healthcare Analytics Unit, is working on research and policy projects affecting adolescent health, behavioral health, child welfare, complex chronic conditions, and healthcare service delivery.

In addition to leading research studies with a more intentional focus on program and policy change, PolicyLab will convene local and national stakeholders in critical discussions on child health and well-being and will disseminate “Evidence to Action” briefs highlighting PolicyLab’s research topics in the context of local and national policy issues. Combined, these efforts enable PolicyLab to affect needed program and policy change that improve child health and well-being in Philadelphia and beyond.
Taking a More Scientific Approach to Nursing Practice

Nursing at Children’s Hospital encompasses far more than taking care of a patient’s moment-to-moment needs, monitoring the response to therapies, and providing comfort and support to patients and families. Nursing is more than tradition in practice; it is an active, engaging endeavor at the center of patient care that simultaneously leads to countless research questions.

The Hospital’s Center for Pediatric Nursing Research and Evidence Based Practice aims to fully integrate collaborative nursing research into practice to improve the outcomes for patients and families. The effort involves an evidence-based approach, ensuring there are adequate data and reliable sources to support the best practices in pediatric nursing.

Led by nurse researchers Sharon Barton, Ph.D., R.N., P-CNS; Katherine Finn Davis, Ph.D., R.N., C.P.N.P.; and Beth Ely, Ph.D., R.N., the center stimulates scientific inquiry among nurses in all practice areas. The nurse researchers serve as leaders, mentors and consultants to Hospital nurses, supporting them in their quest to ask scientific questions and translate the results of those inquiries into improved clinical practice.

“Nursing research at Children’s Hospital has experienced a great evolution over the past several years,” says Dr. Barton. “Nurses ask clinical questions and their inquiries are guided by their peers and the support of nurse researchers. Their questions become research studies or evidence-based practice projects and quality improvement.”

Current studies in nursing research focus on pain management, skin injury, infant feeding, side effects of radiation therapy, clinician decision making about sedation, and medication reconciliation, among others. Scientific inquiries by Children’s Hospital nurses have led to several improvements in clinical practice and multiple opportunities for further investigation.

One of the research projects spearheaded by nurses at Children’s Hospital involved an evaluation of skin injuries in hospitalized patients including those related to immobility, medical devices, and diaper use. A comprehensive one-day prevalence study conducted by more than 60 nurses resulted in thousands of data points that have generated new research questions into the causes of skin injuries and evidence-based approaches for prevention and treatment.

“By encouraging clinical questions at the bedside and teaching nurses the necessary skills through mentoring, we can stimulate nursing research and evidence-based practice to make a tremendous positive impact on patient care and outcomes,” says Dr. Davis.

In addition to providing logistical and resource support to ensure research studies are scientifically sound, the Center for Pediatric Nursing Research and Evidence Based Practice provides financial support. The center makes several grant awards a year for evidence-based practice and nursing research studies, which often stem from nurses’ clinical experiences, observations, and interests.

“We are helping to change the landscape of nurses’ involvement in research and evidence-based practice and how nurses think about and contribute to the collective scientific knowledge applied to nursing practice,” says Dr. Ely.

Visit The Hospital’s Center for Pediatric Nursing Research and Evidence Based Practice Web site at:
http://www.chop.edu/service/nursing/research/
Affinity Groups Connect Investigators Working Toward Common Goals

Research at Children’s Hospital is targeted at eradicating disease, yet sometimes the quickest path to this goal does not follow traditional routes, such as working within the confines of an academic discipline. The Research Affinity Group (RAG) structure at CHOP Research provides the opportunities and resources for investigators to interact with others who share a common research objective, regardless of their background or specialty.

The dynamic nature of CHOP Research necessitates that this structure is constantly refined to meet the changing needs of an ever-evolving research community. During the fiscal year two new RAGs were established, the Mitochondria RAG and the Health and Behavior RAG.

The Health and Behavior RAG was created to facilitate research designed to address the direct and indirect effects of behavior on virtually all pediatric diseases, with the ultimate goal of enhancing the effectiveness of pediatric care for children and their families. Treatments and preventative approaches for behavioral outcomes of disease, such as quality of life, functional impairments, and cognitive difficulties, can reduce disease morbidity and enhance well-being.

Led by Anne Kazak, Ph.D., Division of Oncology, and Joel Fein, M.D., M.P.H., Division of Emergency Medicine, the Health and Behavior RAG enhances the existing research infrastructure for the unique needs of behavioral researchers and clarifies how behavioral researchers can effectively use the resources available to them. In addition, the RAG brings together a dense social network of nationally prominent investigators from highly specialized disciplines to naturally promote and strengthen research collaborations and provide opportunities for mentorship.

Visit The Health and Behavior Research Affinity Group Web site at:
http://www.research.chop.edu/research/affinity_groups/health_behavior/

The Mitochondria RAG was launched to confront the complex connection between mitochondrial biology and human disease. Mitochondrial disease is the most common inborn error of metabolism and disorders of the mitochondria contribute to a number of common diseases, such as diabetes, hearing loss, stroke, liver and kidney diseases, neurodegenerative diseases, cancer, and possibly autism.

Because mitochondrial biology is so complex, no one researcher is an expert in every aspect. The Mitochondria RAG, led by Marni J. Falk, M.D., Division of Human Genetics and Molecular Biology, and Neal Sondheimer, M.D., Ph.D., Division of Child Development, Rehabilitation, and Metabolic Disease, brings trainees, young investigators, clinicians, and experts across medical fields together with leaders in today’s mitochondrial research community and the pioneers who made the foundational discoveries upon which today’s research is based. Through these efforts, the RAG is creating unexpected opportunities for investigators to collaborate on establishing a deeper understanding of mitochondrial biology and devising effective clinical therapies.

Visit The Mitochondria Research Affinity Group Web site at:
http://www.research.chop.edu/research/affinity_groups/mitochondria/
Providing optimal medical care for children requires focusing not only on the what and how of treatment but also the why — the hopes, goals, and reasons that guide the decisions made by caregivers. Understanding the "why" of care, while always important, is especially crucial whenever healthcare providers and parents don't see eye to eye on the best treatment approach for a child, or when considering the differences between cutting-edge therapy and clinical research.

The Department of Medical Ethics, established in 2008, works to ensure that all ethical decisions are made based on the soundest available evidence and practices, and to ingrain the habit of considering the "whys" of treatment into every aspect of patient care.

Led by Chris Feudtner, M.D., Ph.D., M.P.H., the department works to make ethics more inclusive, proactive, teachable, and research-guided. Through this process, advances in the ethics of clinical care build upon an increasingly engaged staff and an ever-stronger evidence base.

Dr. Feudtner approaches medical ethics informed by his extensive research on the epidemiology and healthcare experience of children with complex chronic conditions. He focuses specifically on palliative, end-of-life, and bereavement care, as well as hospital inpatient care.

"Many clinical ethical dilemmas arise when healthcare providers and parents do not look at or feel about a child's healthcare situation in the same way, resulting in fundamentally different views that would play out as different courses of action," says Dr. Feudtner. "One aspect of the department's research is aimed at understanding the best methods to facilitate discussions that advance mutual understanding and move care forward in the best direction."

To this end, Dr. Feudtner and his colleagues are conducting research into the ethical issues related to end-of-life care decisions and the use of cutting-edge therapies, among other topics.

Some of the research conducted to date has focused on the psychological and "motivational structure" for human behavior, including understanding the preferences of parents, as well as differences in values and beliefs of families and healthcare staff.

Other ethical questions can include gift giving and the relationship between providers and family members, the allocation of scarce resources, and human subjects research.

"Through rigorous scientific methods we can develop evidence-based and robust forms of decision support to help our caregivers make sound ethical decisions," says Dr. Feudtner.
Dietary Branched-Chain Amino Acids as a Possible Treatment for Traumatic Brain Injury

AKIVA COHEN, PH.D.

Traumatic brain injury, or TBI, represents the primary cause of death and disability in children and young adults. Occurring approximately three times a minute, it affects nearly 2 million people a year in the United States alone. According to the Centers for Disease Control and Prevention, every year TBI leads to more than 2,600 deaths, 37,000 hospitalizations, and 435,000 emergency department visits for children up to age 14.

TBI can occur in a variety of events ranging in severity from an automobile accident to a seemingly innocuous bump on the head that can occur during a child’s normal play. However, even injuries considered mild — with limited cognitive effects, like a temporary change in mental status — can set into a motion a cascade of events inside the brain that can lead to long-lasting problems.
Akiva Cohen, Ph.D., Division of Neurology, is investigating changes in the limbic system of the brain that lead to TBI-induced cognitive impairments. The center of this investigation involves changes in the levels of branched-chain amino acids after TBI.

Using lateral fluid percussion injury coupled with behavioral testing and other laboratory techniques, Dr. Cohen and his colleagues noticed a significant decrease in the levels of these critical branched-chain amino acids in the hippocampus, a part of the brain often injured in TBI that plays a role in higher cognitive functioning such as emotion, learning, and memory. These amino acids are essential for the synthesis of both excitatory (glutamate) and inhibitory (GABA) neurotransmitters. Normal hippocampal function is dependent on the balance between the excitatory and inhibitory systems.

Refurbishing the optimum levels of these amino acids therefore becomes key to minimizing the cognitive effects of mild to moderate TBI by restoring hippocampal function.

Their innovative research has lead to the development of a potential approach to actively and quickly restore the necessary balance between excitatory and inhibitory neurotransmission to the hippocampus before long-term effects can take hold.

"Re-establishing the normal concentration of branched-chain amino acids after injury may lead to the restoration of the balance between excitatory and inhibitory neurotransmission necessary for normal hippocampal function, leading to cognitive improvement after TBI," says Dr. Cohen.

Dr. Cohen and his colleagues believe that the dietary consumption of these critical branched-chain amino acids, mixed with water and delivered over a period of several days, may bring about this balance and restore the levels of branched-chain amino acids to normal after a mild-to-moderate TBI.

“It is our hope that after further investigation we may have a relatively easy, rapid and cost-effective way to prevent any devastating, long-term cognitive dysfunction caused by traumatic brain injury,” says Dr. Cohen.
Improving the health of children is the ultimate ambition of every research program at Children’s Hospital. However, even the most extraordinary discovery may require years of development to become a product that has an impact on children across the globe.

Transitioning a foundational discovery with the potential to prevent or treat a disease into a tangible product available to patients is often best achieved by commercializing the innovation. Companies that license rights to the intellectual property of CHOP Research investigators invest concentrated resources to develop raw brilliance into polished products for the marketplace.

Specialists in the relationship between academic researchers and industry partners are essential to establishing partnerships that will successfully develop new diagnostic tests, imaging techniques, and therapeutic approaches.

The Office of Technology Transfer supports these relationships by identifying discoveries that have commercial potential, finding industry partnerships that will propel the innovation toward commercialization, and managing the critical documents that protect the innovation during this process.
Polyurethanes are widely used in medical applications such as synthetic heart valves, vascular grafts, and pacemaker electrodes. However, their use is limited because of three major complications: calcification, thrombosis, and chemical degradation. Division of Cardiology researchers Robert Levy, M.D., Stanley Stachelek, Ph.D., and Ivan Alferiev, Ph.D., have developed a method that uses low temperatures to modify polyurethanes, which eliminates these complications. Polyurethanes modified using this method do not cause in vivo calcification and thrombosis nor do they carry the risk of chemical breakdown. This technique represents a substantial improvement over existing synthetic methods and results in a highly biocompatible material that is amenable to cellular attachment and growth.

The following patents were issued during fiscal year 2009 for technologies developed by CHOP Research investigators.

**US Patent Number 7,408,014 B2**

Polyurethanes are widely used in medical applications such as synthetic heart valves, vascular grafts, and pacemaker electrodes. However, their use is limited because of three major complications: calcification, thrombosis, and chemical degradation. Division of Cardiology researchers Robert Levy, M.D., Stanley Stachelek, Ph.D., and Ivan Alferiev, Ph.D., have developed a method that uses low temperatures to modify polyurethanes, which eliminates these complications. Polyurethanes modified using this method do not cause in vivo calcification and thrombosis nor do they carry the risk of chemical breakdown. This technique represents a substantial improvement over existing synthetic methods and results in a highly biocompatible material that is amenable to cellular attachment and growth.

**US Patent Number 7,553,659 B2**

Garrett Brodeur, M.D., Division of Oncology, has discovered that portions of the CDH5 gene are absent in neuroblastoma. This gene, which plays a role in neural development and pediatric brain tumors, may prove to be a valuable marker for determining the effectiveness of treatment modalities for neuroblastoma. It may also be a valuable target for new drugs developed to treat this intractable cancer.

**US Patent Number 7,405,292**

Building on a previously patented invention, Terri Finkel, M.D., Ph.D., Division of Rheumatology, developed short interfering RNA (siRNA) sequences that inhibit HALP, a gene that plays a role in helping HIV-infected T cells survive attack by the immune system, and that increase cellular apoptosis. The interaction between these siRNA sequences and HALP may reduce the number of HIV-infected T cells, thus providing a new strategy for the treatment of HIV infections.

**US Patent Number 7,468,513**

Martin Charron, Ph.D., Division of Nuclear Medicine, has created a system for acquiring multidimensional tomographic image data from single-photon emission computed tomography systems (SPECT) that enhances the resolution of SPECT images in a shorter period of time and with reduced exposure to radioactive tracers compared to the current system. This system provides 3-D, high-resolution functional data about metabolism in the brain, heart, kidneys, and other organs, and reduces the amount of time it takes for patients to have the scan.

**US Patent Number 7,394,053**

An imaging technique developed by Roberto Accorsi, Ph.D., Division of Radiology, could reduce the need for invasive tissue biopsies. The technique uses both radiographic and optical image detection methods to create a 3-D view of a tumor site. This innovation will facilitate cancer diagnoses and sentinel lymph node mapping procedures that determine the extent of a cancer’s spread.

**US Patent Number 7,435,548**

Hakon Hakonarson, M.D., Ph.D., Division of Human Genetics and Molecular Biology, and Michael Grunstein, M.D., Ph.D., Division of Pulmonary Medicine, developed a method to screen for drugs that may treat asthma and other inflammatory conditions such as atopy, rheumatoid arthritis, and chronic obstructive pulmonary disease. This innovation, which builds on a previously patented technology, may also identify genes involved in the inflammatory process, and may potentially lead to improved treatments for these conditions and methods to predict the likelihood that a patient will respond to a specific drug.
One serious aspect of cystic fibrosis is the inability of the pancreas to produce a sufficient amount of enzymes needed to break down dietary fats. Pediatric patients with cystic fibrosis often suffer from growth failure due to malnutrition. Diagnosing dietary fat malabsorption is cumbersome, requiring patients to collect their stool samples and record their diet for three days. Virginia Stallings, M.D., Division of Gastroenterology, Hepatology, and Nutrition, developed an alternative diagnostic that involves taking small blood samples before and after administrating digestive fatty acid-containing solutions to the patient. The results of the blood tests determine the patient’s fat absorption rates and thus the patient’s pancreatic function. This test is somewhat analogous to a glucose tolerance test and is much easier for a patient to undergo compared to the current diagnostic procedure.

George Rothblat, Ph.D., Division of Gastroenterology, Hepatology, and Nutrition, developed an experimental model system that measures the movement of cholesterol in and out of liver cells. This measurement of cholesterol flux in a cell is an effective system for evaluating cholesterol-modulating drug candidates.
Children’s Hospital prides itself on its unwavering commitment to innovative patient care, state-of-the-art research, and talented and dedicated professionals and support staff who believe in and advance the Hospital’s and Research Institute’s missions and goals every day.

But the success of the Hospital and the Research Institute does not rest solely with a commitment to excellence and motivated and gifted people. For more than 150 years, the Institution’s endeavors and accomplishments have been inexorably entwined with philanthropy.

Through these gifts — both large and small — Children’s Hospital is continuously positioned to realize its mission.
One of the greatest, most significant philanthropic gifts to research rests with endowed chairs, a deeply meaningful and permanent form of giving that allows the chairholders to engage in vigorous scientific discovery and advance the health of children across the globe.

Over the last seven years alone, during the Hope Lives Here campaign, 35 new endowed chairs were created, supporting research and groundbreaking programs at Children’s Hospital. There are now 74 fully funded chairs and another 12 have been pledged by donors. During the fiscal year, the Hospital’s board of trustees established the following endowed chairs:

The Children’s Hospital of Philadelphia
Endowed Chair in Adolescent Medicine

Colman Family Endowed Chair in Pediatric Inflammatory Bowel Disease, awarded to Robert N. Baldassano, M.D.

Steven D. Handler Endowed Chair in Medical Ethics, awarded to Christopher Feudtner, M.D., Ph.D., M.P.H.

Robert and Dolores Harrington Endowed Chair in Pediatric Cardiology, awarded to Jack Rychik, M.D.

Stanley Plotkin Endowed Chair in Pediatric Infectious Diseases, awarded to Jeffrey M. Bergelson, M.D.

Jennifer Terker Endowed Chair in Pediatric Cardiology, awarded to Robert E. Shaddy, M.D.

Wawa Endowed Chair in International Adoption, awarded to Susan Friedman, M.D.

Frank E. Weise III Endowed Chair in Pediatric Hematology, awarded to Gerd Blobel, M.D., Ph.D.
Despite a challenging economic landscape, CHOP Research continues to recruit and retain outstanding investigators in every therapeutic area. Numerous new investigators joined CHOP Research during the past fiscal year, moving the Institute closer to its goal of improving the health of children throughout the world.

Oncology investigators are unraveling the mysteries of both common and rare cancers; infectious disease research teams are reinvigorating the hope of an HIV vaccine; injury prevention investigators are finding new approaches to keeping children safe; and geneticists and disease experts are working together to target the genes that contribute to a multitude of complex disorders.

The excellence of our research community is the foundation of the Institute's continued research successes. As evidence of the Institute's extraordinary achievements, members of the CHOP research community have received numerous awards. Those featured here — a fraction of the honors bestowed on our world-class investigators — honor exceptional contributions to an improved understanding of disease, dedication to navigating complex roads to discovery, and demonstrated abilities and drive for future research success.

Celebrating a Long Path of Achievement

Peter Gruber, M.D., Ph.D., Division of Cardiothoracic Surgery; Jake Kushner, M.D., Division of Endocrinology; and Valder Arruda, M.D., Ph.D., Division of Hematology, were elected to the American Society for Clinical Investigation, an honor society of physicians who have accomplished outstanding achievements relatively early in their careers.

Alexander Fiks, M.D., M.S.C.E., Division of General Pediatrics, received a Young Investigator Award from the Academic Pediatric Association/Agency for Healthcare Research and Quality for his project, “Shared Decision Making in Pediatrics: A National Perspective.”

Janet Lioy, M.D., Division of Neonatology, received the Mead Johnson Academic Community Outreach Award, which is given to an individual who has made significant contributions to neonatal outreach in the community. Dr. Lioy was also awarded the March of Dimes Salute to Women of Achievement Award for her dedication to neonatal care education and advancements.

Timothy Roberts, Ph.D., Division of Radiology Research, received the 2009 Princeton Lecture Series Fellowship award at the 15th annual Eden Institute Foundation/Princeton Lecture Series as a tribute to his career in the field of autism.

The Society for Healthcare Epidemiology of America honored Theoklis Zaatouis, M.D., M.S.C.E., associate chief, Division of Infectious Diseases with their Pediatric Investigator Award in recognition of his exemplary contributions to infection control and healthcare epidemiology.

Ian Krantz, M.D., Division of Human Genetics and Molecular Biology, was nominated to the National Organization of Rare Disorders Hall of Fame for his work on Cornelia de Lange syndrome (CdLS) that has raised awareness of CdLS, paved the way for diagnostic tests, and enhanced the understanding of how CdLS works.

The American Philosophical Society presented Jordan Orange, M.D., Division of Allergy and Immunology, with the Judson Daland Prize for his outstanding achievements in patient-oriented research that have led to fundamental insights into defects of the innate immune system and natural killer cells.

Jack Rychik, M.D., Division of Cardiology, received the 2009 Feinbaum Award from the American Society of Echocardiography, which is granted to a luminary investigator in the field of echocardiography.

Kevin Osterhoudt, M.D., M.S.C.E., Division of Emergency Medicine, received the American College of Medical Toxicology Award for Significant Contributions to the Educational Pursuits of Medical Toxicology.

Terri Lipman, Ph.D., C.R.N.P., F.A.A.N., Division of Endocrinology, was nominated as an Edge Runner by the American Academy of Nursing for her innovative work on improving the accuracy of linear growth assessments in children. Dr. Lipman was also named as the Miriam Stirl Term Endowed Chair of Nutrition in the University of Pennsylvania School of Nursing.

Elizabeth Weller, M.D., Division of Child and Adolescent Psychology, received the Special Chairman’s Award from the University of Pennsylvania Department of Psychiatry.

The American Academy of Pediatrics awarded David Sherry, M.D., Division of Rheumatology, with the James T. Cassidy Award, in recognition of his outstanding service as a pediatric rheumatology educator, especially his excellence in mentoring fellows.

Hakon Hakonarson, M.D., Ph.D., Division of Human Genetics and Molecular Biology, received the 2009 Scripps Genomics Medicine Award for Pioneering Discoveries in Pediatric Genomics.
Lisa Meltzer, Ph.D., Division of Pulmonary Medicine, received the Investigator Award from the American Academy of Sleep Medicine, Childhood Sleep Disorders and Development Section.

The Foundation Fighting Blindness presented J. Fraser Wright, Ph.D., with the Board of Directors Award for his contributions toward developing a highly innovative vision-restoring gene therapy, which the foundation called “one of the most important advances ever made in retinal and ophthalmological research.”

Antonella Cianferoni, M.D., Ph.D., Division of Allergy and Immunology, received the American Partnership for Eosinophilic Disorder’s HOPE Junior Investigator Award for her project, “Genomics and Biomarkers of Eosinophilic Esophagitis.”

The career and accomplishments of H. Fred Clark, X.X., Division of X, were featured in a “Portrait of a Leading Vaccinologist” by Human Vaccines, a leading vaccination journal.

Paul Weinberg, M.D., Division of Pathology and Laboratory Medicine, received the Robert Dunning Dripps Memorial Award for Excellence in Graduate Medical Education from the University of Pennsylvania.

The Fibromuscular Dysplasia Society of America presented Kevin Meyers, M.D., Division of Nephrology, with their Founders Award.

Katherine Bevans, Ph.D., Division of General Pediatrics, was honored by the National Association of School Psychologists as an Early Career Scholar.

Samir Shah, M.D., M.S.C.E., Division of Infectious Diseases, was awarded the Excellence in Research Award from the Society of Hospital Medicine Excellence.

John Maris, M.D., chief, Division of Oncology, received the Leonard Berwick Memorial Teaching Award from the University of Pennsylvania School of Medicine for integrating basic and clinical science in his teaching. Dr. Maris also was elected to the Interurban Clinical Club, a group of leaders in internal medicine from a selection of East Coast medical schools.

Jeffrey Barrett, Ph.D., Division of Clinical Pharmacology, received the Bio-IT World Best Practice Award, Judges Prize, for Pediatric Knowledgebase, a tool designed to help physicians individually manage patients' drug therapy.

Joshua Friedman, M.D., Division of Gastroenterology, Hepatology, and Nutrition, was named Researcher of the Year by the Pennsylvania Chapter of the American Liver Foundation.

Valerie Brown, M.D., Ph.D., Division of Oncology, was awarded a Kimmel Scholar Award by the Sidney Kimmel Foundation for Cancer Research. The award was given to young scientists who established themselves through publications in peer-reviewed journals known for their quality, prominence, and influence in cancer research.

Anne Kazak, Ph.D., Division of Oncology, received the 2009 American Psychological Foundation Cummings PSYCHE Prize in recognition of her significant and enduring contributions to expanding the role of the psychologist as a primary care provider.

Alix Seif, M.D., M.P.H., Division of Oncology, received the Young Investigator Award from the American Society of Pediatric Hematology/Oncology.

Anna Meadows, M.D., received the National Leukemia/Lymphoma Society’s highest honor, the Return of the Child Award, for her many contributions to the research and therapy of childhood cancer.

Division of Oncology investigators Brian Lestini, M.D., Ph.D., and Robin Perry, M.D., were both selected for an American Society of Clinical Oncology Young Investigator Award.

Beverly Lange, M.D., Division of Oncology, received a Children Oncology Group Lifetime Achievement Award.

Craig Bassing, Ph.D., Division of Cell Pathology, was selected for the 2008 Lassin Family Cancer Research Award from the University of Pennsylvania Abramson Cancer Center.
Audrey Evans, M.D., retired after an exceptional 60-year career dedicated to improving the care of children with cancer. Dr. Evans joined Children’s Hospital in 1969 as the first director and chief of the Division of Oncology. She immediately began contributing to advances in care that have led to the enormous growth and success of the department’s clinical and research programs.

Among her many achievements, Dr. Evans developed the Evans Neuroblastoma Staging System to assign treatment based on tumor stage, described the spontaneous regression of some cases of neuroblastoma, established a series of international neuroblastoma research meetings that has evolved into the prestigious Advances in Neuroblastoma Research biennial international conferences, and helped to form and lead the first Childhood Cancer Cooperative Group whose efforts dramatically increased cure rates in a variety of childhood cancers.

In addition, Dr. Evans recognized the importance of incorporating nursing, psychology, and social work into oncology programs, an innovative approach that has affected the care of every child with cancer.

Dr. Evans has impacted generations of patients at Children’s Hospital and throughout the world. She has received an outstanding number of awards in the field of pediatric oncology, most recently the 2009 Pitcher of Hope Award, presented annually to a CHOP professional who shows extraordinary commitment to caring for children with cancer.

In her retirement, Dr. Evans will remain an active part of national and international childhood cancer programs.
Robert Berg, M.D., joined Children’s Hospital as the new chief of the Division of Critical Care Medicine and the Russell Raphaely Endowed Chair in Critical Care Medicine. Dr. Berg is an international leader in research and program development for cardiopulmonary resuscitation (CPR) and advanced life support.

Dr. Berg brings to Children’s Hospital his 20 years of experience as a pediatrician specializing in critical care medicine at The University of Arizona College of Medicine where he was chief of Pediatric Critical Care and, most recently, associate dean for Clinical Affairs. His more than 150 peer-reviewed articles on cardiac arrest, CPR, and defibrillation include numerous landmark studies in *The New England Journal of Medicine* and the *Journal of the American Medical Association*. Dr. Berg is the only pediatrician recipient of the Award for Lifetime Achievement in Cardiac Resuscitation Science from the American Heart Association.

In his new role at Children’s Hospital, Dr. Berg will continue his CPR and life support research while leading the world-renowned critical care medicine program and overseeing the Pediatric Intensive Care Unit, the first such multidisciplinary unit in the United States.
Building the Future of Research

The Research Institute’s reputation as the preeminent institution conducting translational research for children received a significant boost when it recently opened the doors to its new state-of-the-art, environmentally responsible research facility.

The Colket Translational Research Building, the first of several buildings slated for the Hospital’s new South Campus, is named for Ruth M. and Tristram C. Colket Jr. in appreciation of their $25 million donation toward Children’s Hospital’s goal to advance translational research — moving basic science investigations into real-life treatments and cures.
The $400 million research tower comprises four new laboratory floors; a two-story ground floor housing a lobby, cafeteria, conference space; and four administrative office floors, three of which are convertible to future laboratory use. The building is designed to expand vertically to 23 stories to provide for future growth.

The research tower followed an initial phase of construction involving the development of four stories below grade, providing infrastructure and laboratory support space as well as an expandable central utility plant to support the entire development of Children’s Hospital’s new South Campus. The South Campus — sitting on a portion of the former Philadelphia Civic Center site — consists of nearly eight acres of land directly across from Children’s Hospital’s current clinical and research facilities.

The new 11-story, 450,000-square-foot research building provides flexible state-of-the-art laboratory space that will not only advance the Hospital’s world-class research program but will also enable the Hospital to recruit top-level investigators.

“This new building provides the space, equipment, and technology required to advance pediatric medicine, and will attract the best and brightest investigators, who will have greater resources and flexibility to conduct their research,” says Philip Johnson, M.D., chief scientific officer and executive vice president for Translational Medicine and Science.
In addition, the Colket Building is a “green” building, having achieved Leadership in Energy and Environmental Design, or LEED, certification. LEED is an internationally recognized rating system for environmentally responsible buildings.

Design approaches that led to the certification include thermal windows; light-colored roofing and paving materials to reduce the heat-island effect that can create a warmer microclimate in urban areas; an energy-recovery system for the heating, ventilating and air conditioning system; the use of highly reflective materials around the windows to reduce the amount of solar radiation through the windows; and the use of wood furniture and casework made of materials that meet the criteria of the Forest Stewardship Council, which encourages socially responsible forest management practices.

“The Colket Translational Research Building represents the future of The Children’s Hospital of Philadelphia and a healthier future for children everywhere,” says Steven M. Altschuler, M.D., the Hospital’s president and chief executive officer. “Medical research has never been more promising, and I am confident that the greatest advances in pediatric research will occur in this state-of-the-art facility.”
Research by the Numbers

The Research Annual Report, 2009

Sources of Grants and Contracts

- NIH: 78%
- Foundations: 3%
- State: 3%
- Industry: 4%
- Clinical Trials: 5%
- Other: 6%

New Awards (grants/contracts)

- # of awards: 100, 200, 300, 400, 500, 600
- ($ Million): 100, 150, 200, 250, 300, 350, 400

Total Research Operating Expenses

- ($ Million): 100, 150, 200, 250, 300

Publications

- Journal Articles: 100, 200, 300, 400

Total Research Space

- Thousands (Gross Square Feet): 0, 50, 100, 150, 200, 250, 300, 350, 400
- Locations: Abramson Research Center (373,851), 3535 Market Street (139,819), Colket Translational Research Building (83,299), 3550 Market Street (2,408), Main Building (3,900)
CHOP Research Institute Leadership

Philip R. Johnson, M.D.
Chief Scientific Officer
Executive Vice President,
Translational Medicine and Science
Director, the Research Institute

Tom Curran, Ph.D.
Deputy Scientific Director

Peter Adamson, M.D.
Director, Office of Clinical and
Translational Research

Mary Tomlinson
Deputy Administrative Director
Vice President, Research Administration

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Science Committee

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Anne Faulkner Schoemaker, Vice Chair
Fred Biesecker
Richard R. Carr
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Philip R. Johnson, M.D.
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Asuka Nakahara
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Tom Curran, Ph.D.
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Ellen Hyman-Browne
Diego Jaramillo, M.D.
Meg Jones
Virginia Stallings, M.D.
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