Research Annual Report 2005

The Joseph Stokes Jr. Research Institute of
The Children's Hospital *of* Philadelphia

Heritage *of* Hope
150 years
The Children's Hospital *of* Philadelphia

Embarking on a New Era

"... very large numbers of specialties moved towards the solution of each individual patient's problem through highly diversified laboratory and clinical research."

- Joseph Stokes Jr., M.D., 1967

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It is with great enthusiasm that we introduce the premier annual report for the Joseph Stokes Jr. Research Institute of The Children's Hospital of Philadelphia.

Stokes Institute has a rich and distinguished "bench to bedside" research history. The Institute serves as the home for more than 250 world-class investigators conducting innovative research in the laboratories and clinics across our campus. And, as you will see within the pages of this report, our investigators continue to advance the basic understanding of pediatric diseases and to develop new therapies that will benefit our patients and their families for generations to come.

We've witnessed substantial growth in the Hospital's research program over the last decade. With such growth comes the need to assess the external factors affecting our continued development, evaluate our current program and facilities, and challenge ourselves to continue on our path toward pediatric research preeminence.

To position the Stokes Institute as the premier pediatric research center in the world, we have made significant changes during the past year with the guidance and support of the Institute's Board Committee. We've organized the Hospital's research program under Research Affinity Groups toenhance multidisciplinary collaboration; more aggressively recruited talented investigators; expanded our training and educational programs; and continued to build the research infrastructure to further support our investigators and research staff.

We are fortunate to have recruited Philip R. Johnson Jr., M.D., to guide our way into the future as the Hospital's new chief scientific officer and director of the Stokes Institute. Dr. Johnson assumed the role of chief scientific officer in January 2005. His predecessor, David Pleasure, M.D., stepped down to focus on his renowned research in pediatric neurology, which flourished in his 30 years of service to Children's Hospital.

Dr. Pleasure realized his goal of fortifying the Hospital's scientific environment while managing annual double-digit growth. His legacy as director includes establishing the Stokes Investigator Program and reorganizing the academic structure through affinity groups. He also helped establish centralized core facilities and was instrumental in recruiting numerous scientists to the institution.

To build on the foundation put in place by his distinguished predecessor, Dr. Johnson brings his extensive experience in strategic planning, facilities expansion and faculty recruitment as we map the future of pediatric healthcare at Children's Hospital.

We are excited about the future of research at Children's Hospital. We view research as our product pipeline, and that pipeline — built on the Hospital's 150 years as a leader in pediatric healthcare — has never been fuller. So please enjoy this inaugural issue of the Stokes Institute's Annual Report. We look forward to sharing our milestones as the Hospital continues its growth and evolution toward pediatric research preeminence.

Steve M. Altschuler, M.D.
President and Chief Executive Officer

Tristram C. Colket Jr.
Chair, Joseph Stokes Jr. Research Institute Board Committee


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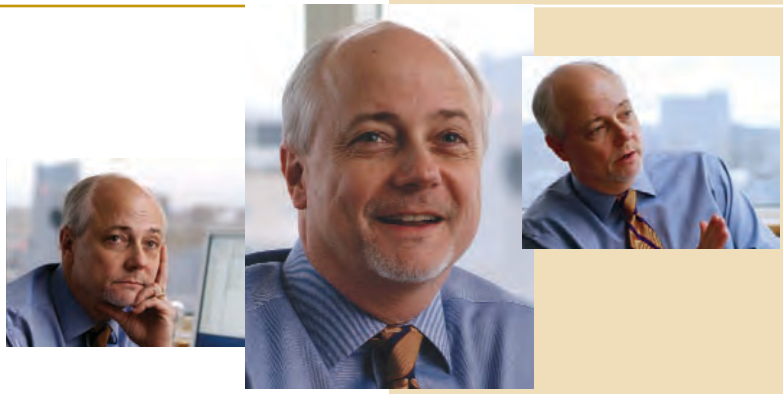


Embarking on a New Era of Research at The Children's Hospital of Philadelphia

For more than 80 years, The Children's Hospital of Philadelphia has built a reputation as a pioneer in pediatric research. Vaccines, novel therapies, and other interventions developed and tested at Children's Hospital have saved the lives of many children throughout the world and improved the health of countless others. This legacy continues today, embodied in our rotavirus vaccine and our TraumaLink program.

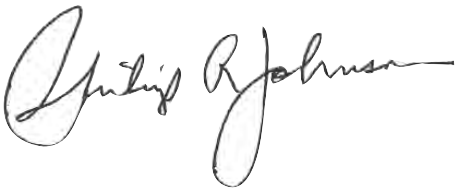
The continued success of the Stokes Institute depends not only on building upon the past, but also on planning for the changes and initiatives necessary to achieve preeminence. The future of research at Children's Hospital is directly linked to controlled and deliberate growth, a process that involves constant review and refinement of our research programs.

Growth isn't just about increasing the amount of research funding, constructing buildings, or winning the war for talent. While these activities are all necessary, they are not sufficient. Growth also involves embracing the entrepreneurial spirit — the notion of "going first and being first" — that has sustained Children's Hospital for 150 years.

To that end, we must continue to pioneer new therapies, integrate novel technologies, and tackle the toughest healthcare issues that face our patients and their families.

We can, and must, learn from every patient and family who walks through our doors for care. This is the foundation of the "bench to bedside" nature of our research program. In today's lingo, this is known as translational research. But Children's Hospital was in this business long before that phrase was coined. We must continue to lead the way in harnessing the data derived from patient care to guide and drive laboratory and clinical investigation.

Research is, and will continue to be, a cornerstone of the Hospital's mission and perhaps the key element in our overall goal of improving pediatric health worldwide. At the Stokes Institute at Children's Hospital, we are embarking upon a new era of research that will change the direction and intensity of our efforts while enhancing the care for our patients and families. I am sincerely humbled to be part of this great aspiration, and look forward to the next 150 years of innovation at Children's Hospital.



Philip R. Johnson Jr., M.D.
Chief Scientific Officer and Senior Vice President
Director, Joseph Stokes Jr. Research Institute

Pursuing Research Preeminence

Research Affinity Groups: A unique structure that fosters collaboration and allows for continued growth

Stokes Institute, with its mission to be a leader in pediatric research, has witnessed phenomenal growth over the last decade. This growth is evident not only in the number of laboratory and clinical investigators conducting innovative research but also in the unique and cutting-edge programs that are the hallmark of research at Children's Hospital.

Stokes Institute, recognizing the challenges that often accompany growth, looked for a unique way to manage the needs of its investigators, foster interdisciplinary collaboration and better position the Institute to compete for decreasing federal research funding.

The solution: Research Affinity Groups.

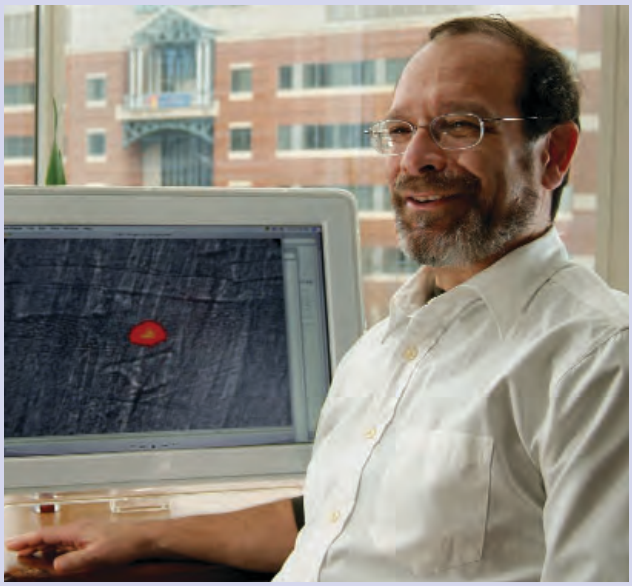
A new organizing principle of the Stokes Institute, the Research Affinity Group concept reflects the increasingly interdisciplinary and multidisciplinary nature of many key research questions. In addition, the affinity group structure aligns with the emerging national consensus that multidisciplinary centers are essential to advancing the nation's research agenda.

The Institute designed the Research Affinity Group structure to build on areas of existing strength, identify new and important research areas, and explore important, broad and interdisciplinary scientific questions that may have an impact on children's health.

The groups allow Stokes researchers to collaborate across disciplines more easily to address issues of central importance to children's health. This collaboration has the potential to link multitalented investigators widely dispersed throughout the Institute who have common research interests.

The following pages highlight each of Stokes Institute's 13 Research Affinity Groups.

1922
Research "Department" is established in the basement at Bainbridge Street — a 14-by-16-foot room with one centrifuge.



Cardiovascular Research Group Leader: Mortimer Poncz, M.D.

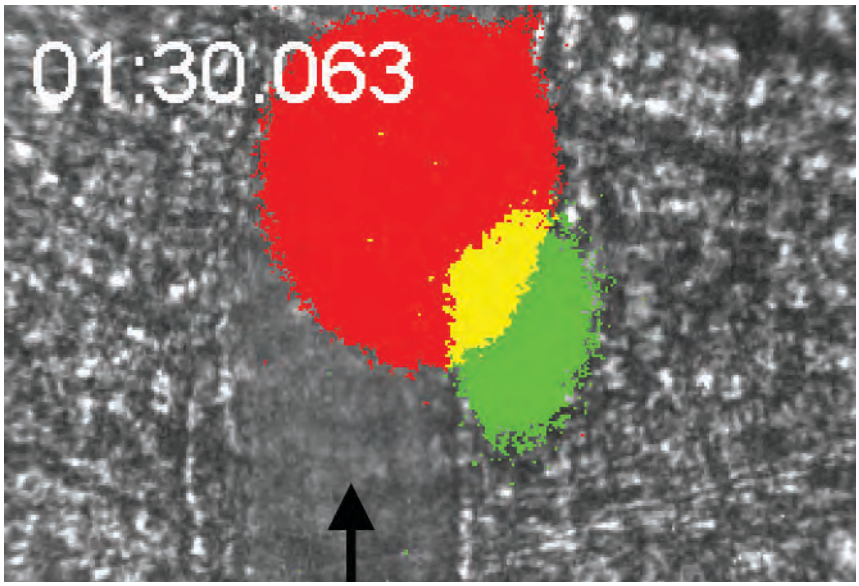
While atherosclerosis, thrombosis and stroke are not traditionally diseases associated with pediatric patients, there is growing concern in the pediatric healthcare community about cardiovascular diseases. This concern has increased for a number of reasons, such as a better recognition of the pediatric causes of these adult diseases, an increase in sedentary lifestyles and altered eating habits, and a awareness of disease processes.

In addition, although it saves the lives of more and more children, modern medical care often entails invasive procedures that introduce foreign bodies — often plastic catheters — into patients. This process can lead to a marked increase in observed blood clots, or thrombi. Iatrogenic thrombi, clots that occur as a secondary consequence of providing medical care, are a major concern and complication in the management of many life-threatening pediatric illnesses.

Recent thrombosis and hemostasis research at Children's Hospital has focused on the basic mechanisms involved in the so-called "liquid clotting phase" and in clot formation. Hospital investigators also work to develop models for translating current knowledge into gene therapy-based strategies to treat patients with bleeding and clotting disorders.

In addition, the Hospital's cardiology research has focused on developing new materials for grafts and stents; designing novel strategies for local gene therapy to blood vessels and the heart; and establishing a better understanding of normal cardiovascular development during embryogenesis. The focus of the lipid research group has centered on lipoprotein and cholesterol metabolism and atherosclerosis development.

In the past, the Hospital's research programs in hemostasis and thrombosis, cardiology and vascular biology, and lipid metabolism and atherosclerosis functioned independently. Recognizing the common interests between these research endeavors, the members of the Cardiovascular Research Affinity Group focus on a common theme: atherosclerosis, vascular biology and thrombosis.



Fibrin clot (green) and platelet plug (red) in thrombus, growing at the site of laser injury in a small vein lacking circulatory Factor VIII. The overlap of the clot and plug is in yellow.

To further its research efforts in this critical area, the affinity group established an atherosclerosis, vascular biology and thrombosis modeling system to promote the establishment of common multiuser models. Within this organization, the group established a system for measuring new blood growth, watched clot formation under a microscope, and developed a controlled flow chamber to observe the interaction between platelets and endothelial cells.

To encourage growth in this new pediatric research focus, the Cardiovascular Affinity Group is pursuing activities including sharing instruments, establishing a new cardiovascular seminar series, founding a yearly retreat for fellows to present their research efforts and coordinating these efforts with colleagues at the University of Pennsylvania.

1929
Joseph Stokes Jr., M.D., becomes physician-in-chief. He goes on to transform Children's Hospital into a world leader in teaching and research.

Cell and Gene Therapy

Group Leader: Katherine High, M.D. Investigator, Howard Hughes Medical Institute

Cell and gene therapy and stem cell research offer unprecedented opportunities for developing new medical therapies for serious diseases that affect children. Current research in these areas may contribute to a new approach for treating disease — regenerative medicine, in which defective genes, cells or even entire organs are replaced.

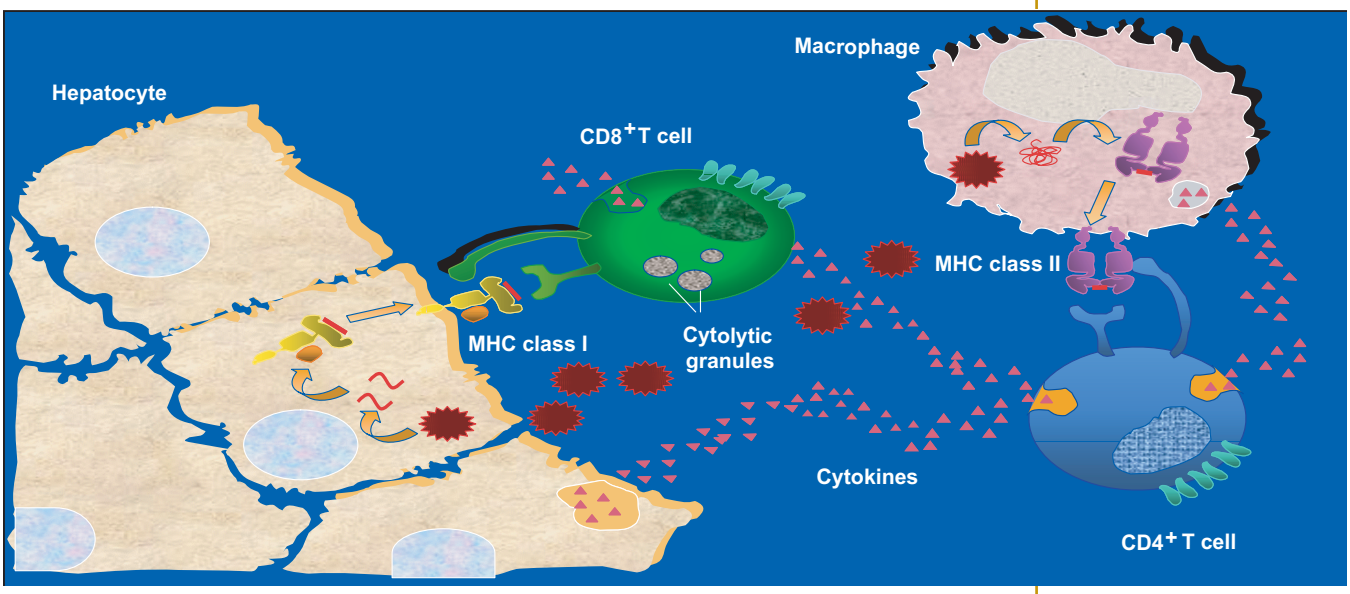
One of the most exciting frontiers in modern medicine is the concept of using a gene to treat a genetic disease. Researchers have made dramatic progress in innovative gene therapy strategies that could cure, or even prevent, disease. The idea of introducing corrective genes into cells to stop diseases such as hemophilia, cystic fibrosis and congenital blindness at the source is rapidly becoming a reality.

Cell therapy is an older discipline that has been modified to include blood transfusions, organ and bone marrow transplantation, and modern adoptive transfer of white blood cells to treat cancer. Recent developments have been focused on using stem cells to replace defective tissues and cure disease. While this work is in the earlier stages of research, the possibility of taking a person's own cells and using them as stem cells to treat that person's disease is an exciting frontier.

A sizable group of people at Children's Hospital are focused on these areas of investigation and are members of the Cell and Gene Therapy Research Affinity Group, which aims to develop new treatment methods for children with inherited and infectious diseases.

The affinity group fosters a multidisciplinary approach among investigators working to discover new gene and cell therapies in search of cures for debilitating and life-threatening childhood disorders. This approach may lead not only to a variety of applications in the treatment of inherited disorders such as hemophilia, muscular dystrophy and cystic fibrosis, but also to the treatment of acquired and complex disorders, including diabetes, heart disease, infectious diseases, neurodegenerative disorders and cancer.

One of the most notable activities of this affinity group is the extremely high-quality seminar series that attracts distinguished outside speakers who are active in the cell, gene and stem cell research field. Speakers not only hold public seminars, but also visit with individual lab members to discuss specific research projects. In addition to affinity group seminars, the group actively pursues collaborative funding.



Summary of immune responses during AAV gene therapy.

Cell and gene therapy affinity group members have successfully competed for NIH Program Project grants, including an award entitled "Gene Therapy for Hemophilia," which investigates the use of vectors introduced into either skeletal muscle or circulating blood platelets as a means of treating hemophilia.

Another program project is "Immune Responses in Gene Therapy for Hemophilia," which focuses on the body's immune responses in the setting of gene therapy for hemophilia.
In addition, members of the affinity group collaborated to submit an application for cell and gene therapies for muscle disorders. The grant was successfully funded by a competitive Stokes Institute grant, using monies provided to the Hospital by the Commonwealth of Pennsylvania under the national tobacco settlement.

1936
Discovery of the whooping cough vaccine, the first in a series of vaccines pioneered at Children's Hospital that has worldwide impact on childhood disease.

Child Health Services Research

Group Leaders:
Louis Bell, M.D., and
Jeffrey H. Silber, M.D., Ph.D.

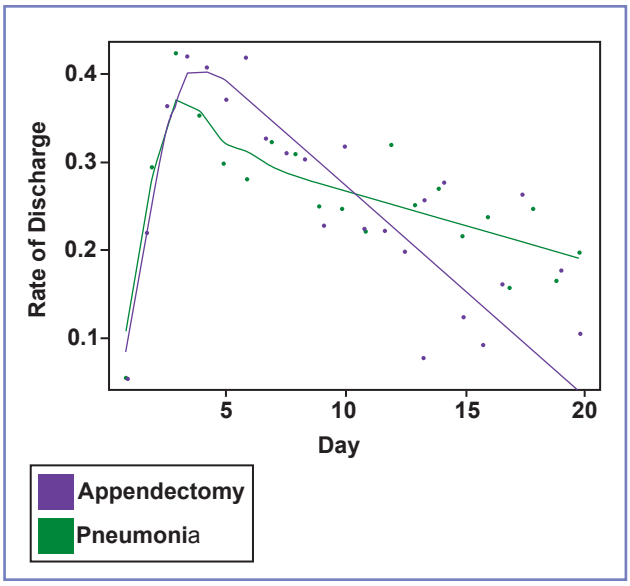
Despite remarkable advances in biomedical research and the treatment of disease, evidence exists that the complex systems of pediatric healthcare and other child-oriented services do not perform well, resulting in poor outcomes for child health while incurring high costs. It is critical that investigators understand this performance gap to learn how to close it and provide good health outcomes for all children.

Racial and socioeconomic disparities in child health continue to be well-documented. Recent legislative attempts to expand health insurance coverage for children in the United States have left 10 million children uninsured — and these children are half as likely to have visited a physician as children with insurance. The cost and quality of pediatric care varies across geographic regions, types of hospitals and various systems of care. Adding to the problem, therapies and interventions known to be effective — like medications to control asthma attacks — are underused. Each of these problems and many others adversely affect the health of children.

The Child Health Services Research and Epidemiology Research Affinity Group is dedicated to studying the cause and distribution of disease and quality of health in children. It also aims to improve children's health and well-being by analyzing the causes and distribution of disease and quality of healthcare and other child-oriented services.

Because a multitude of factors influence these outcomes, research by members of the Child Health Services affinity group typically involves many disciplines, including economics, psychology, biostatistics and medicine. For example, researchers in the group developed and applied methods from their respective disciplines to improve the quality of pediatric health-services research. They also applied multivariate matching techniques and econometric modeling to claims data, surveys and administrative databases.

Other examples of the affinity group's recent efforts include projects aimed at understanding the organization of behavioral healthcare for children with attention deficit and hyperactivity disorder; improving the long-term care of children with asthma; improving screening and early recognition of childhood autism; and identifying the best strategies for preventing poor outcomes in common pediatric diseases.



Researchers have defined a hospital stay that is "too long" or "prolonged" based on the typical pattern of hospital discharge.

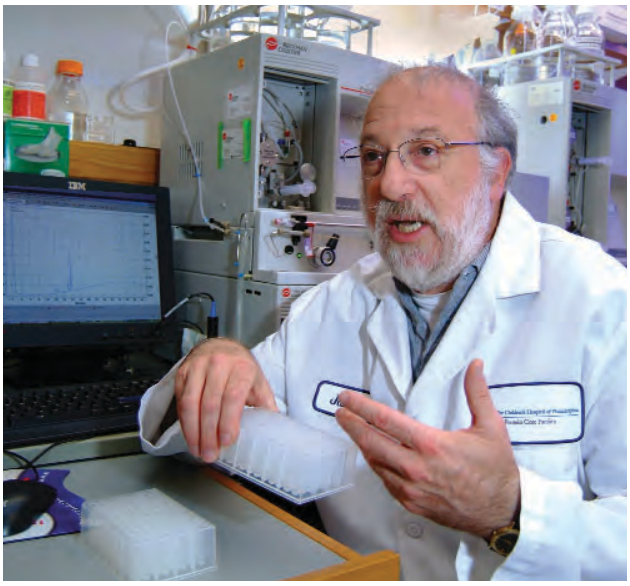
Affinity group investigators have also examined variations in the quality of care premature infants receive and the resulting outcomes; the impact of maternal obesity on neonatal outcomes; optimal discharge time of premature infants from the neonatal intensive care unit; and the impact of medication errors in the pediatric intensive care unit.

In addition, investigators have focused on understanding the impact of peer influences that lead teenagers to risky behaviors; the impact on healthcare access for underserved children and families; racial disparities in outcomes; and the difference in outcomes of similar patients across different types of healthcare providers. Members of the Health Services affinity group also explored methods to reduce surgical post-operative mortality rates and analyzed the influence of obesity on surgical outcomes.

1940s — 1950s

Vaccines for influenza and mumps are discovered by husband-and-wife team of Drs. Werner and Gertrude Henle. Additionally, along with Joseph Stokes Jr., M.D., they develop the first convincing demonstration of vaccination against influenza and mumps — 100,000 eggs a year were used in the study of viral diseases. They are also the first to prove the effectiveness of gamma globulin in preventing paralytic polio and the first to develop a method to prevent hepatitis.

Left page: Louis Bell, M.D.
Right page: Jeffery H. Silber, M.D., Ph.D.



Defective Proteins and Disease

Group Leader: Yair Argon, Ph.D.

Most diseases are caused by malfunctions of a protein. A defective receptor may preclude proper function of pancreatic cells, an altered protein may lead to malignant transformation, or the inability of a hormone to be secreted may lead to abnormal organ development. Understanding the changes in the expression or function of proteins is, therefore, key to developing therapies.

Gaining such understanding, however, is no small feat, because each of the 30,000 genes in human DNA can encode more than one form of a protein, increasing the complexity of the information contained in DNA. In addition, not every pathologic change is due to a single gene mutation. In many diseases, the alteration is an atypical realignment of interacting proteins.

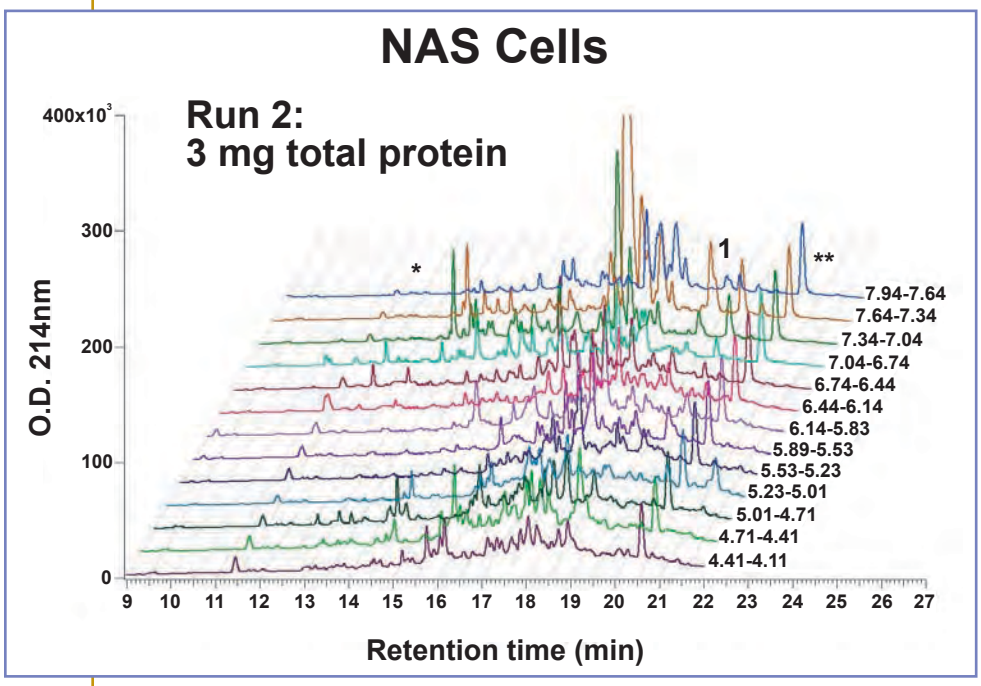
Research conducted in the Defective Proteins and Disease Research Affinity Group focuses on this problem by investigating how proteins function, how they interact, and how they differ between normal and diseased tissues.

Several investigators in the affinity group measure how receptors on the surface of cells transmit information that leads to growth and differentiation of the endocrine or immune systems. Their work intersects with that of another group of investigators who are interested in viral infections, since viruses often "hijack" normal cellular proteins.

Another critical area of the affinity group's investigation lies with markers of disease, or protein patterns that are expressed differently in people with a particular disease. Some investigators are relating modifications common to many proteins, such as additions of phosphate or nitrate, to alterations in the functions of key metabolic enzymes in normal and defective neonatal development.

Yet a third focus is the question of how proteins misfold, lose their proper structure and therefore become dysfunctional. Three research groups are studying how a special set of cellular proteins, called molecular chaperones, either protect other proteins from misfolding or correct the defect in the context of cystic fibrosis, systemic amyloidosis and thalassemia.

A new focus of the group is proteomics, or cataloging all the proteins present in a given tissue at a particular stage of pathology. Knowing these protein patterns will greatly enhance the current wealth of genetic information about a variety of diseases.



Separation of complex protein mixtures by multidimensional chromatography.

A new technique developed by the affinity group separates complex protein mixtures by multidimensional chromatography into hundreds of discrete fractions, and has already improved upon the enumeration of proteins that are present in diseased and normal tissues. Being able to identify rare proteins may uncover those that play important roles in an individual disease.

These research advances already hold the promise of discovering signature patterns — proteins that are found consistently in patients with a specific disease — that will become diagnostic tools.

The Defective Proteins and Disease Research Affinity Group provides a forum for investigators from a variety of divisions to work together, improving the effectiveness of their research. Shared instruments in the Protein Core Facility, a seminar series featuring outside speakers, a monthly in-house lab meeting and a multi-investigator seed project all allow group members to interact and gain feedback on ongoing research.

1954

"Rheumatic Fever and Virus Research Building" the first research building is built for $800,000, including equipment. It is more commonly known as "The Research Building."

Developmental Biology and Pediatric Disorders

Group Leader: Jeffrey Golden, M.D.

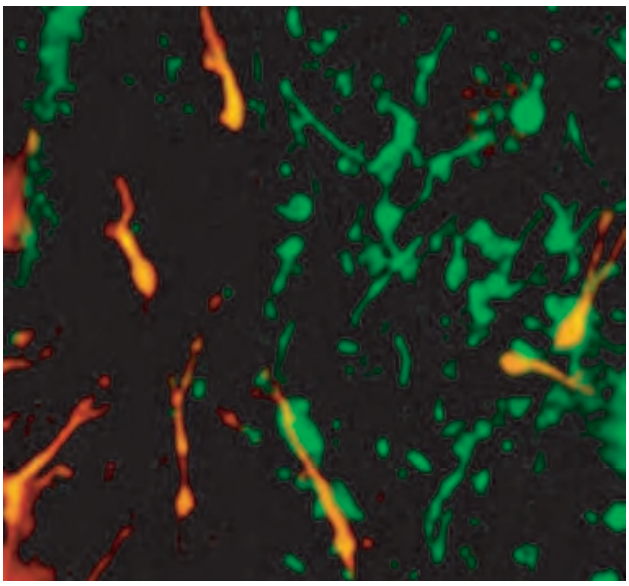
Understanding the pathobiology of pediatric diseases within a developmental framework is paramount to the diagnoses, management and cure of many childhood diseases. Understanding developmental biology is, therefore, crucial to the Hospital's mission of being the leader in caring for children. Accomplishing this goal requires basic research focused on elucidating the mechanisms of developmental processes.

The Developmental Biology and Pediatric Disorders Research Affinity Group strives to meet the goal of providing cutting-edge basic and translational research in developmental biology and training the next generation of pediatric physician-scientists. This affinity group augments and elevates existing research efforts in developmental biology at Children's Hospital and aspires to implement the "bench to bedside and back to the bench" paradigm inherent when developmental biology research is tightly linked to the care of children.

As a new program, developmental biology has focused on building an infrastructure to support ongoing and new research. This infrastructure comes under three main headings: teaching, faculty recruitment and interdisciplinary research. The affinity group initiated a seminar series to provide a venue for Hospital investigators to interact with outstanding developmental biologists. This monthly series, now in its second year, has hosted a variety of internationally renowned developmental biologists, new investigators with exciting research programs, and outstanding local investigators at Children's Hospital, the University of Pennsylvania and The Wistar Institute. A second goal for this seminar series is to provide a forum for junior faculty, postdoctoral fellows and students to meet with and learn from potential colleagues and mentors.

The affinity group also provides a data/journal club as an informal forum for students and postdoctoral fellows to present their own research or to critically review recently published papers. This series, also attended by the faculty, allows students and fellows to present their preliminary research for constructive feedback or to critically evaluate published studies, both important exercises for those in training.

The affinity group's second major focus has centered on faculty recruitment. The group conducts highly competitive national searches to identify outstanding candidates in developmental biology research.



Interneurons (green) that have been labeled with a dye migrating in a living brainslice.

1950 — 1960s

With his research on the prevention of polio, Dr. Lewis L. Coriell begins to lay the groundwork for the development of the Salk vaccine. Dr. Coriell and associates also invent a laminar airflow system to keep operating rooms sterile.

The final focus of this new program revolves around interdisciplinary research. Establishing and maintaining cutting-edge research in the highly competitive and rapidly changing field of developmental biology requires access to state-of-the-art equipment and techniques as well as economies of scale, all of which are made possible by sharing ideas and resources. The affinity group initiated several programs to facilitate research at Children's Hospital.

The first initiative was the creation of the Transgenic Core, which provides all Hospital investigators with access to consultation and application of transgenic and mutagenesis experiments. Another initiative involved establishing common space for intermittently performed functions such as the use of chemical benches, thermocyclers, gel electrophoresis and documentation, and microscopy.

This shared space takes advantage of economies of scale and encourages each lab both to use its own space more efficiently and to share the cost of equipment that can be used in several labs. These common spaces also provide areas where people from different labs are in regular contact, fostering interaction.

Although the Developmental Biology Research Affinity Group is a young program, it has made significant strides toward creating an intellectual environment that will support outstanding scientific investigation. Continued growth and productivity will occur within this small but interactive cadre of scientists. Most importantly, this program will provide insight into development and developmental disorders, critical to the care of children and the essence of Children's Hospital.

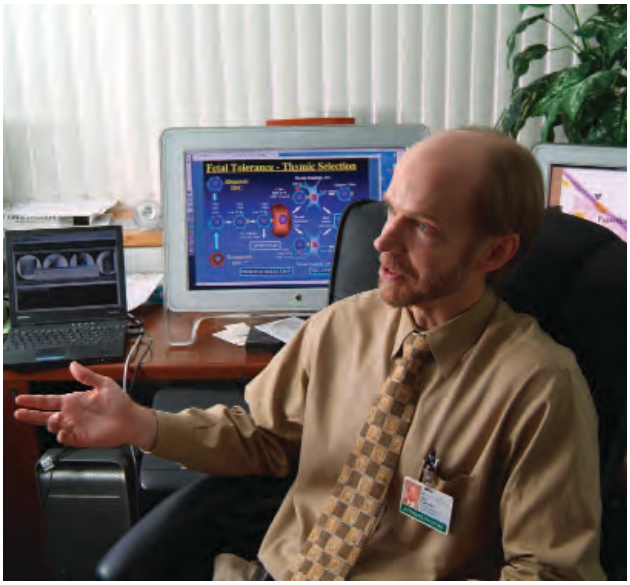
Fetal Therapy Research
Group Leader:
Alan Flake, M.D.

The convergence of technologies in modern medicine suggests that within the next decade essentially all anatomic and genetic diseases could be diagnosed early in gestation. Early diagnosis could enable physicians not only to treat fetal disease, but also to anticipate childhood and adult disease.

The Fetal Therapy Research Affinity Group investigates the possibilities for treating many disorders during fetal development, which may provide a therapeutic window of opportunity for treatment.

As part of its mission, this affinity group facilitates interaction between a diverse group of Children's Hospital investigators interested in fetal biology and therapy. The group brings together investigators for mutually beneficial discussion, collaborative studies and, ultimately, the application of successful clinical therapies. Investigators focus on fetal diagnosis and treatment, maternal aspects of fetal therapy, new methods of minimally invasive surgical or fetoscopic intervention, treatment of anatomic malformations, and fetal stem cell or gene therapy.

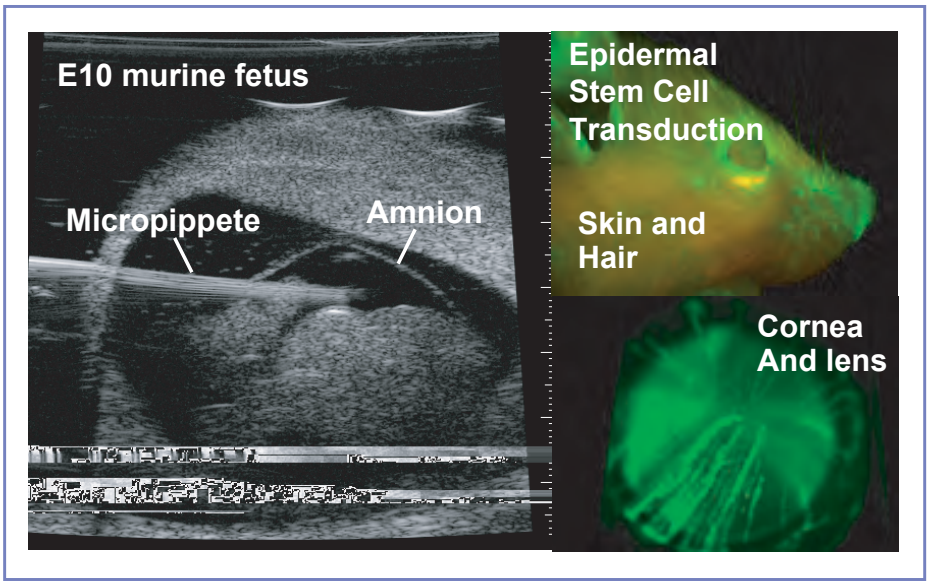
Recent fetal therapy research has focused on a number of common fetal anatomic malformations, most notably prenatal surgical closure of myelomeningocele (MMC), a condition in which the backbone and spinal canal do not close before birth. Children's Hospital is one of three surgical centers in an ongoing federally sponsored clinical trial designed to compare prenatal surgical closure of MMC with standard postnatal treatment.



As part of this research endeavor, the affinity group recently developed an experimental MMC model that closely parallels the human form of the disease. This model is expected to allow for a more in-depth study of MMC and perhaps lead to new treatment strategies.

Another area of research focus in the affinity group centers on congenital diaphragmatic hernia, a defect in the diaphragm that allows the abdominal organs to enter the chest cavity. Hospital investigators are studying the potential for using fetal tracheal occlusion as a treatment for lung hypoplasia, as well as pharmacological and gene therapy approaches to pulmonary vascular hypertension. To this end, fetal therapy investigators are developing models of congenital lung malformation and abdominal wall defects.

In collaboration with the Hospital's Center for Fetal Diagnosis and Treatment and the Fetal Heart Program of the Cardiac Center, the Fetal Therapy Research Affinity Group is developing techniques for fetal cardiac intervention, specifically to open ventricular outflow tract obstructions to allow cardiac remodeling and prevent underdevelopment of the heart. Further investigations into experimental models of human anatomic defects may provide new insights into the pathophysiology of these disorders and allow for the development of new therapeutic approaches.



Early gestational gene transfer by ultrasound-guided intraamniotic injection of lentiviral vector.

In utero gene therapy studies also involve investigations of early gestational injection methods using a high-resolution ultrasound system that allows microinjection into the amniotic space. This has resulted in high efficiency transduction of epithelial stem cells in experimental models.

Hospital researchers are also investigating stem cell and gene therapy *in utero*. With the clinical goal of treating sickle cell disease and other hematologic disorders, investigators continue their aggressive pursuit of strategies to increase engraftment of hematopoietic stem cells in the fetus and have made substantial progress toward improving donor cell homing to, and engrafting in, the fetal liver. Part of the stem cell research project involves strategies of highly selective myeloablation of the fetus using innovative reagents that specifically target hematopoietic stem cells and progenitors.

1963
Stanley Plotkin, M.D., develops rubella (German measles) vaccine; clinical trials are conducted.

Genes, Genomics and Pediatric Disease

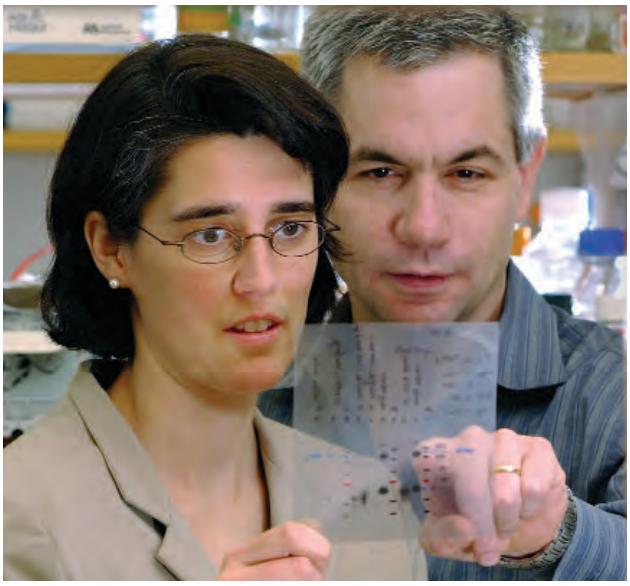
Group Leaders: Nancy Spinner, Ph.D., and John Maris, M.D.

Genetics is a discipline that has unique implications for pediatric medicine and affects all aspects of childhood healthcare. The field has undergone tremendous growth in recent years as new technologies have allowed for increasingly precise probing of the genome. The recent completion of the Human Genome Project provided the essential roadmap for these studies while innovative genetic models of human disease and high-throughput technologies such as DNA microarrays have provided the tools necessary to exploit this information.

Genetics and genomic research at Children's Hospital is multifaceted and spans many divisions. These research efforts are conducted in the Genes, Genomics and Pediatric Disease Research Affinity Group. The affinity group houses an outstanding program focused on the molecular genetic basis of human disease. Major recent advances include identifying the gene for Cornelia de Lange syndrome, a rare developmental disorder, and identifying the role of mutations in a cellular signaling pathway, known as Notch2, in human disease.

Investigators also focused on continuing their study of the 22q11.2 deletion syndrome — an abnormality of chromosome 22 that can lead to a myriad of health problems; increasing the understanding of a fatal nervous system disorder called Batten disease; and gaining strides in unraveling the role of mutations in a tumor-suppressing gene known as hSNF5/INI1 in causing certain pediatric tumors. Also, investigators have been engaged in large collaborative research efforts focused on the interactions between human genes and environmental exposures.

Another area of investigation for affinity group members is neurogenetics. Investigators have focused on studying the cause of several neurologic disorders, including various muscular dystrophies. They have been actively involved in the clinical and research components of neurogenetics in order to understand the mutated genes and pathways and translate that understanding to diagnosis and treatment.



Page 16 (left to right): Nancy Spinner, Ph.D., with student Athma Pai. Page 17 Researcher Kristina Cole and John Maris, M.D.

Cancer is a genetic disease, and many Hospital investigators have focused on the genomics and proteomics of common pediatric cancers. In the past year, investigators have made major advances in understanding neuroblastoma, an aggressive cancer that occurs in infants and young children. Research strides in neuroblastoma include the development of a more precise algorithm for predicting prognosis based on genetic alterations in the cancer cells. This work is being applied nationwide within the Children's Oncology Group Clinical Trials network, a National Cancer Institute-supported group that coordinates cancer clinical trials at 238 member institutions, including the cancer centers of all major universities and teaching hospitals.

Children's Hospital investigators have made significant progress in understanding the underlying abnormalities in pediatric solid tumors and leukemias and translating these findings to the clinic. For example, by demonstrating that many neuroblastomas are dependent on activation of a gene called Trk, a specific inhibitor of Trk has been developed with a local pharmaceutical company and is now in clinical trials for children with neuroblastoma.

1965

The balloon catheter is invented by William Rashkind, M.D., the "father of interventional cardiology," allowing the first nonsurgical treatment of certain heart defects.

Because genomic medicine is by definition multidisciplinary, the formation of a research affinity group was a natural extension of ongoing collaborative research efforts at Children's Hospital. Monthly affinity group meetings provide a forum to share and critique research programs and to develop strategic goals. The affinity group also has a successful monthly seminar series that draws international experts. This group also provides a forum for establishing and extending collaborations with colleagues at the University of Pennsylvania.

Finally, in the last year the affinity group organized an external advisory committee of international experts to critique its program and provide advice on genetics and genomics research at Children's Hospital and the University of Pennsylvania.

Metabolism, Nutrition and Physical Development

Group Leaders: Babette Zemel, Ph.D., and Rebecca Simmons, M.D.

Disorders of nutrition and metabolism affect the majority of patient populations cared for at Children's Hospital. Failure to thrive, obesity and bone deficits are common complications in a wide variety of chronic conditions. Malabsorption, inflammation, reduced physical activity, altered dietary intake and medical treatments often have a profound effect on nutrient metabolism, growth, body composition, and health and disease outcomes. In addition, many of the major chronic diseases of adulthood, such as diabetes, hypertension, osteoporosis, cardiovascular disease and some cancers are nutrition-related and have antecedents in childhood.

The goal of the Metabolism, Nutrition and Physical Development Research Affinity Group is to identify the causes and consequences of metabolic and nutritional disorders of childhood and to identify effective strategies for disease prevention and treatment. An additional goal is the prevention of obesity and nutrition-related diseases in adulthood that have their origins in infancy and childhood.

The group boasts many multidisciplinary research projects across a wide range, including gastroenterology, hepatology and nutrition, endocrinology, psychiatry, cardiology, hematology, nephrology, rheumatology, pulmonology, neurology, nursing, child development and neonatology. Obesity is a common theme across many of the specific areas of research.

The obesity epidemic across all groups of children is a growing concern and is increasingly becoming a problem in the pediatric patient population. Major research efforts include evaluating the behavioral and medical treatments for obese adolescents, the school-based obesity intervention programs, the effect of obesity on bone strength, prevention and the treatment of diabetes, and the effect of obesity on sleep apnea, asthma and other pulmonary complications, and disorders of lipid metabolism. Recently, the Commonwealth of Pennsylvania's Health Research Formula Fund State Tobacco Resettlement Act funded the Hospital's project "Risk Factors for the Pediatric Metabolic Syndrome" to evaluate the contribution of obesity, obstructive sleep apnea, fasting insulin levels and family history of diabetes to overall glucose tolerance, insulin sensitivity, and lipid and blood pressure abnormalities.

Abnormalities of growth and body composition in children with chronic diseases is another major research theme. Various research projects are underway to describe the timing, magnitude, causes and consequences of growth failure and altered body composition in children with sickle cell disease, cystic fibrosis, Crohn's disease, renal insufficiency, juvenile rheumatoid arthritis, Down syndrome, intractable epilepsy, liver disease, lupus erythymatosis and cardiac malformations.

Left page: Babette Zemel, Ph.D.
Right page: Rebecca Simmons, M.D.

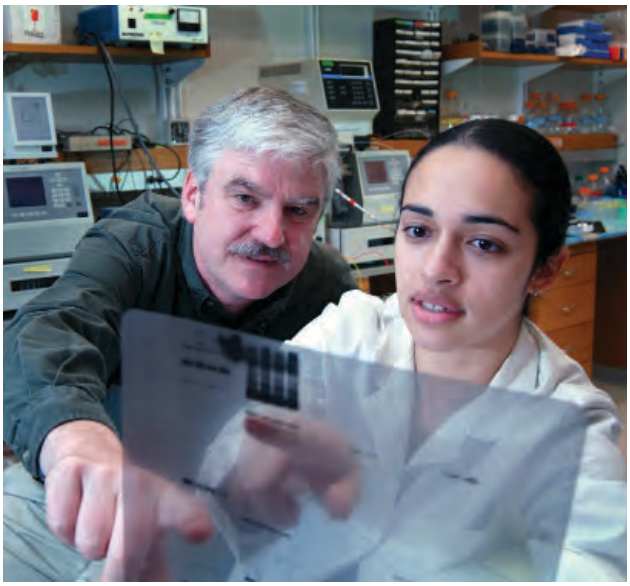
1965
The Clinical Research Center (CRC) is established for hard-to-diagnose, hard-to-treat pediatric diseases and use of new treatments. CRC is the forerunner of the General Clinical Research Center, which has been continuously funded by the National Institutes of Health for more than 40 years.

The program of research in the area of lipoprotein metabolism and atherosclerosis seeks to understand the contribution of reverse cholesterol transport — the process by which excess cholesterol is transported to the liver for excretion from the body — to the role of high-density lipoprotein (HDL) in preventing plaques in arteries. Recently, emphasis has been on the HDL receptors, known as scavenger receptor class B, type I (SR)-BI and ATP binding cassette transporter AI (ABCA1), and understanding the mechanisms by which they modulate cholesterol transport at cell surfaces. These proteins are thought to prevent plaque build up in arteries because both can mediate the removal of excess cholesterol from cells.

Progress is being made in defining the structure of apolipoprotein apoA-I, the principal protein of HDL, which is involved in binding to the lipid transporter ABCA1 and construction of HDL particles. Investigators continue to work on defining the structures of HDL precursors.

Affinity group members also developed and used an assay for evaluating reverse cholesterol transport in models that express SR-BI in the liver and demonstrated that hepatic SR-BI expression is a positive regulator of reverse cholesterol transport. Studies in models lacking apoA-I indicated that the increased atherosclerosis can be attributed to both impaired reverse cholesterol transport and increased inflammation. These studies are continuing to provide novel understanding of the mechanisms by which HDL protects against the development of atherosclerosis.

The affinity group has several seminar series to promote interdisciplinary interactions and generation of innovative lines of research. The Nutrition Seminar Series meets weekly and hosts both internal and external speakers on a wide array of nutrition-related topics.



Mind Brain Research
Group Leader:
Michael Robinson, Ph.D.

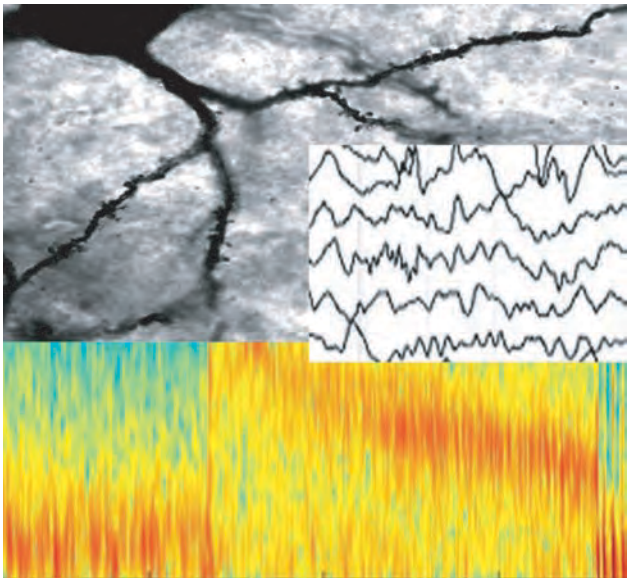
A startling number of children are afflicted with diseases of the nervous system, including epilepsy, stroke, head trauma, autism and attention deficit hyperactivity disorder. In addition, many genetic disorders, such as inborn errors of metabolism, manifest with primary brain dysfunction. Concern for pediatric health related to these diseases has heightened because of evidence that the incidence of some of these disorders has increased over the past three decades.

Although some of these disorders, like stroke, have traditionally been associated with the elderly, recent studies suggest children are also at risk. Research indicates that the incidence of stroke during the first year of life is as high as that observed during the sixth decade. Additionally, the Centers for Disease Control and Prevention estimates the incidence of autism is as high as 1 in 166 births, and up to 5 percent of children experience at least one seizure. These disorders collectively place a significant strain not only on children and their families, but also on society.

Children's Hospital follows the largest and most diverse population of children with neurologic, psychiatric and developmental disabilities in the country. Outstanding clinical and basic researchers complement the clinical care programs throughout the Hospital.

The Mind Brain Research Affinity Group facilitates the development of targeted investigation and fosters the interactions necessary to translate research rapidly into best clinical practices. The affinity group identified four areas of research as priorities for mind brain researchers: neuroprotection, epilepsy, stress biology and autism/complex neurobehavioral disorders.

Recently, mind brain investigators established a pediatric stroke program and obtained funding to organize a multisite study of the incidence and outcomes of stroke in children and adolescents. Researchers also developed a new program project grant to investigate the changes in neurons that lead to epilepsy and to understand how a ketogenic diet — high in fat, and low in carbohydrates and protein — reduces seizure frequency.



Page 20 (left to right): Michael Robinson, Ph.D., and lab technician Elizabeth Genda. Above: Abnormal neuron with immature synopsis, intracranial brain wave recordings and frequency analysis.

In addition, the affinity group obtained funding to provide continued support for the Institutional Mental Retardation and Developmental Disabilities Research Center, which has been active for the past 15 years. This center strives to coordinate and enhance mental retardation research at Children's Hospital and the University of Pennsylvania. It provides services to more than 90 NIH-funded projects with an aggregate value of more than $12 million.

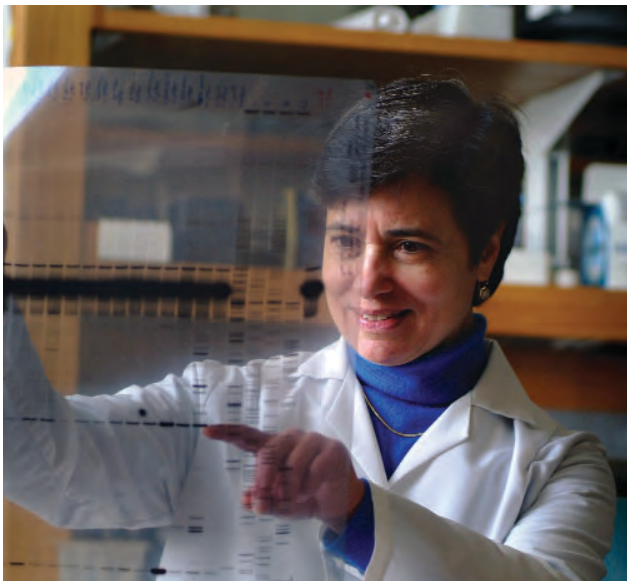
Children's Hospital researchers also helped to develop a Center for Dynamic Imaging and developed the Center for the Management of Attention Deficit Hyperactivity Disorder. By creating clinical centers that focus on specific disease groups, investigators can develop disease-based research models that may be used to produce targeted treatment approaches for a variety of conditions.

1967

Drs. Werner Henle and Gertrude Henle, along with Dr. Klaus Hummeler, discover the association between infectious mononucleosis and the Epstein-Barr virus, which ultimately proves that a common virus may produce malignancy.

The mind brain research community is strengthened by the neurodevelopmental disabilities training grant that supports postdoctoral fellows; the Leadership Development through Interdisciplinary Training, commonly known as LEND; and the yearly fellows' poster day, where postdoctoral trainees present their research to the community. The group also organizes seminar series and meetings to attract esteemed scientists from around the world.

Normal and Malignant Hematopoiesis
Group Leader: Carolyn Felix, M.D.



Gene and protein networks that signal blood cell maturation from primitive bone marrow progenitor cells, as well as networks that regulate the balance of cell growth and death, are especially relevant to hematopoiesis. Research at Children's Hospital into this field focuses on networks that regulate the development of specific blood cell elements in normal and diseased states.

The Normal and Malignant Hematopoeisis Research Affinity Group aims to address problems in these networks to develop targeted prevention and more effective treatments for disordered hematopoiesis, leukemia and lymphoproliferative diseases in children.

The progenitor cells in the hematopoietic system give rise to heterogeneous cell populations — red and white blood cells, as well as platelets — that execute specific functions. Technologies like gene expression profiling and proteomics have revealed global pictures of the networks that distinguish specific blood cell elements in normal and malignant states. Current research in the affinity group involves deciphering which elements in these networks can be targeted for new treatments and, ultimately, for preventing diseases of the hematopoietic system.

The Normal and Malignant Hematopoeisis Research Affinity Group brings together investigators engaged in clinical, translational and basic research who are skilled in oncology, hematology, stem cell transplantation, cytogenetics, biochemistry, epidemiology, pharmacology, pathology, immunology, cell biology and bioinformatics. Linking new technologies and integration holds promise for better diagnosing, treating and preventing pediatric diseases of the hematopoietic system.

Recent hematopoesis research at Children's Hospital has focused on leukemia, the most common childhood cancer, and its two major subtypes: acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). Whereas most children diagnosed with ALL can be cured, the prognosis remains poor for the 20 percent of patients diagnosed with AML.

Hospital researchers have focused on synergistic studies with the long-term goal of developing preventative strategies and leukemia-specific treatments for various forms of pediatric AML. A particular form of AML, which occurs as a complication of anticancer chemotherapy, has an especially poor prognosis. One project has examined how disruption of the cellular protein called topoisomerase II causes chromosomal breakage that leads to this particular form of AML. A mechanistic understanding of the cause of this form of AML could lead to safer chemotherapy regimens and protective compounds.

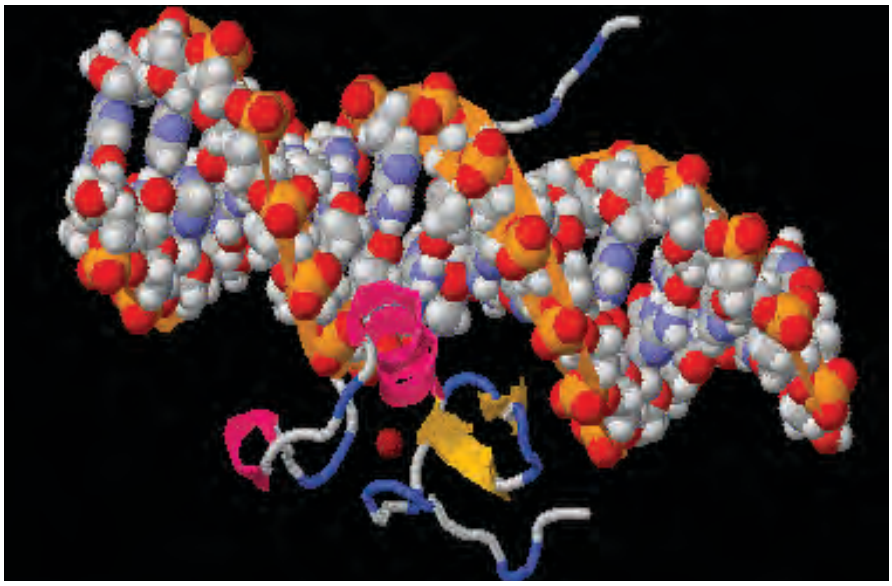


Image of GATA-1 created by Chime SquareTM Animations, a molecular graphics resource at Southern Illinois University.

Another focus of hematopoesis research in the affinity group is GATA-1, a critical transcription factor protein that programs the expression of genes in blood-cell development. Patients with Down syndrome are especially susceptible to AML, and the GATA-1 transcription factor is abnormal in the form of AML associated with Down syndrome.

Investigators in this affinity group are also pursuing a strategy to reduce the complications and mortality from infections associated with intensive AML treatment regimens by determining individual genetic variations that underlie infection risk.

Other affinity group research has focused on dissecting signaling pathways in immune cells called NKT cells to determine their role in the immune response, which may prove relevant to the development of immunity against tumors.

These interdisciplinary projects ultimately have the potential to advance the current knowledge of normal and malignant hematopoiesis, as well as to translate knowledge of the science of hematopoiesis to reduce morbidity and mortality in heterogeneous forms of leukemia in children.

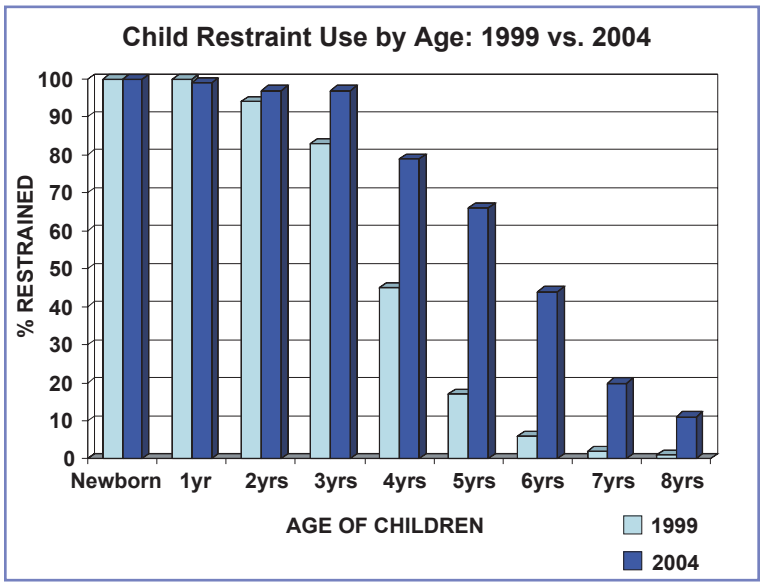
Activities of the research affinity group, including a rich seminar series and annual retreat, facilitate the progress of an ever-expanding web of researchers with a common interest in broad areas of hematopoiesis within the Stokes Institute and the Children's Hospital's campus and beyond. This avenue of combining expertise in specific areas from new interchanges beyond the clinic and the individual laboratory will speed the Hospital's advances in promoting bench-to-bedside research.

Pediatric Injury Research
Group Leader:
Flaura Winston, M.D., Ph.D.

Unintentional injuries are a major concern for pediatric patients. Accidental injury is the leading cause of death for children older than 1 year of age, outnumbering the other leading causes combined, including cancer, congenital anomalies and homicide. Information on the causes for this high rate of injury is valuable for parents, educators, policymakers and product manufacturers.

Pediatric injury research at Children's Hospital has focused on sources of injury such as automobile crashes, home safety, sports and bicycling, and abuse, neglect and violence, among others. The Pediatric Injury Research Affinity Group brings together physicians, nurses, engineers, behavioralists, epidemiologists and outreach professionals from throughout the Hospital to conduct focused research on the root causes of injury as well as to develop and test interventions that prevent or minimize the impact of injury.

Pediatric injury research experienced tremendous growth in the past year, particularly in the area of automobile crash injury prevention. The Hospital's crash-investigation team was designated a member of the Crash Injury Research and Engineering Network, a multidisciplinary research network that provides the National Highway Traffic Safety Administration, the auto safety engineering community and the medical profession with the ability to jointly study real-world cases of serious injuries sustained in car crashes. With a five-year grant and facilitation from the National Science Foundation (NSF), the Hospital also established a unique NSF Industry/University Cooperative Research Center called the Center for Child Injury Prevention Studies (CChIPS) — the only NSF center devoted to injury prevention. The center unites Children's Hospital and University of Pennsylvania researchers with automotive and insurance industry members to translate research findings into tangible innovations in safety technology and public education programs. Currently, there are six founding industry members who contribute research dollars to support the CChIPS agenda: Britax Child Safety Inc., Nissan North America Inc., State Farm Insurance Companies, Takata Corp., Toyota Motor North America Inc. and Volkswagen of America Inc.



The Hospital has continued its longstanding research partnership with State Farm through Partners for Child Passenger Safety (PCPS), an ongoing research and advocacy program funded through 2007. Since its launch in 1997, PCPS researchers have published nearly 50 scientific articles and seven publicly available reports, and they have created a multimedia Web site, www.chop.edu/carseat, available in English and Spanish.

Other Pediatric Injury Research Affinity Group investigators have received federal, corporate and foundation funding to support work in a wide range of areas, including suicide prevention, bullying prevention, community injury prevention, child prevention of persistent traumatic stress after injury, child crash-test-dummy design, injury biomechanics, and teen driver safety and training, among other topics.

1972

The Joseph Stokes, Jr. Research Institute is created. It includes 70,000 square feet dedicated to research.

Pharmacologic Basis of Pediatric Therapeutics

Group Leader: Jeffrey Barrett, Ph.D.

Pharmacotherapy is generally concerned with the safe and effective management of drug administration. It implies an understanding of drug pharmacokinetics and pharmacodynamics — how the body uses the drugs and the physiologic effects of medications — to optimize a patient's response to treatment through effective dosing.

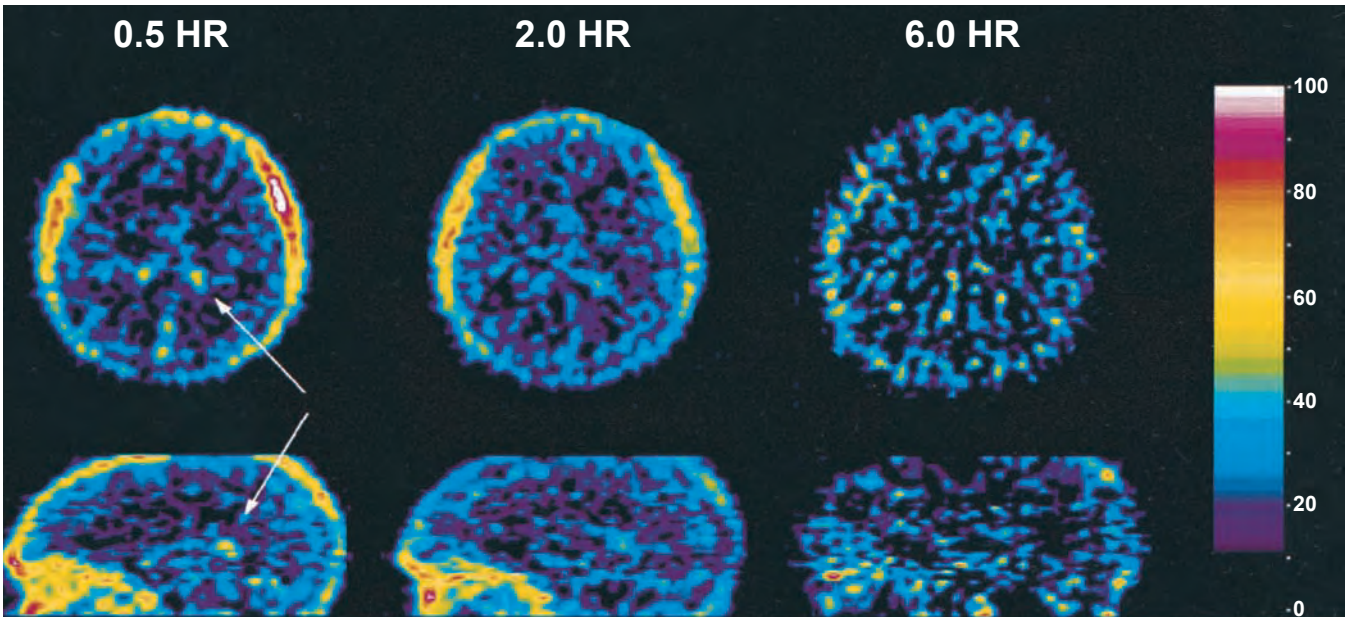
Pediatric pharmacotherapy presents several challenges: developmental changes in children may alter drug kinetics, pathophysiologic differences may alter pharmacodynamics, and the cause of a disease in a child may be different from that in an adult. Other factors may also result in great variation in safety and efficacy outcomes. The situation becomes more complex for critically ill children and neonates given the paucity of well-controlled pediatric clinical trials.

Four axioms define the current state of pediatric therapeutics: limited opportunities exist to study pediatric populations; funds for such endeavors are sparse; some assumptions regarding adult pharmacotherapy are portable to pediatric populations while others are not; and the diversity of various pediatric subgroups based on age, indication, disease or illness makes generalizing across such groups problematic and potentially dangerous.

The emphasis of the Pharmacologic Basis of Pediatric Therapeutics Research Affinity Group centers on the premise that more informative clinical trials are needed in targeted populations for which the medical need is greatest. Such investigations are more productive when therapeutic area knowledge regarding clinical indications, drug actions, developmental status and other factors that may alter drug kinetics or dynamics are assembled into quantitative models that describe the intended clinical setting. The addition of research tools and techniques to improve the quality and information content of data collected from such investigations are also essential elements to the study of pediatric pharmacology.

The affinity group's efforts have therefore focused on assessing drug utilization within the inpatient hospital setting, and developing robust, analytical methods to support pharmacokinetic studies. As part of its effort, the affinity group also integrates modeling and simulation approaches to facilitate clinical trial simulation before protocols are finalized.

This recipe has been used for several collaborative investigations with Anesthesia/Critical Care Medicine, Neonatology, Infectious Disease and Oncology with agents including dexmedetomidine, clonidine, fluconazole and actinomycin-D.



PET images of the brain showing (18F) trovafloxacin uptake over time.

Moreover, the affinity group, with its heightened understanding of clinical-trial modeling and simulation techniques, guides such investigations and provides mentorship opportunities for Children's Hospital investigators seeking to learn these techniques. The group maintains close collaboration with the NIH-governed Pediatric Pharmacology Research Unit (PPRU) network, which has reviewed and endorsed several investigations.

The Pharmacologic Basis of Pediatric Therapeutics Research Affinity Group's other collaborations include pharmacometrics training and analysis with the Metrum Research Group, an informatics approach to pediatric pharmacotherapy with the U.S. Food and Drug Administration, and mechanisms for studying drug utilization with the National Institute of Child Health and Human Development.

In the coming year the affinity group will explore microdialysis, a technique to measure drug levels in tissues, and positron emission tomography scanning as research tools to further expand quantitative pharmacologic investigations.

Members of the group are also exploring the use of discrete-event simulation (a probability-based modeling approach to simulate trial outcomes) as a technique to optimize patient enrollment and study-design strategies.

The affinity group participates in a biweekly e-journal club sponsored by the Metrum Research Group and will host a spring symposium highlighting new technologies.

Page 26 (left to right): James Lee, lab technician and Jeffrey Barrett, Ph.D.

Vaccines and Immunotherapies

Group Leader:
Terri Finkel, M.D., Ph.D.
Co-leaders:
Steven Douglas, M.D., and Paul Offit, M.D.

Researchers harnessed the protective powers of the immune system for medicinal purposes with the development of modern vaccines more than 50 years ago. Nevertheless, infectious diseases remain a leading cause of death for children around the world, and researchers are exploring new ways to use vaccine technology to eliminate this threat.

The immune system sometimes continues its attack long after it eliminates the invading disease. Immune system dysfunction is involved in autoimmune disorders as varied as asthma, inflammatory bowel disease and rheumatoid arthritis. Autoimmune disorders often develop during childhood and remain as debilitating chronic illnesses that last a lifetime. As discoveries in the laboratory shed light on the healing potential of the immune system, vaccines will be developed to correct autoimmune disorders by halting the immune system's mistaken attack on the body itself.

New vaccines also are being developed to help the immune system recognize and eliminate cancer. Unlike infectious diseases, against which the immune system is prepared to defend, cancer evades detection. Unfortunately, traditional treatments designed to kill cancer also destroy healthy cells, leaving the immune system weak and the body defenseless.

Recognizing that numerous diseases involve a component of immune system dysfunction, the Vaccines and Immunotherapies Research Affinity Group — including researchers from such diverse fields as cancer research, gene therapy, immunology, infectious disease, rheumatology and vaccine development — are applying shared knowledge to better understand the immune system and its powers to protect and heal.

Recent infectious disease research at the Hospital has focused on developing a safe and effective vaccine against rotavirus, the most common cause of diarrhea and dehydration in children. Hospital investigators have developed a new oral vaccine delivery system that could one day eliminate the need for needles, making vaccines easier and more cost-effective to administer, especially in the developing world.

Another infectious disease with global impact is HIV. Standard vaccines for HIV have so far proven ineffective because the virus has evolved to include sophisticated methods for evading detection by the immune system. Hospital researchers have worked to understand how HIV invades cells and evades detection and used that information to design compounds and delivery systems that target the cells HIV invades.

The Rotavirus Vaccine, RotaTeq®*, and delivery system developed by Children's Hospital researchers and Merck & Co.*

Researchers are also working to understand the high vaccine failure in children with certain genetic disorders causing immunodeficiency and autoimmunity, and are developing strategies for enhancing vaccine delivery.

Refining treatments for neuroblastoma, the most common and deadly form of solid-tumor cancer in children, has been another focus of this research affinity group. Until recently, the standard of care for children with neuroblastoma — a combination of surgery, chemotherapy and stem cell transplantation — resulted in survival rates of only 35 percent. Investigators have focused on new ways to boost the natural immune response of patients during recovery from stem cell transplantation, a time when patients are extremely vulnerable to life-threatening infections or a relapse of their cancer.

In addition, Children's Hospital researchers have focused on better understanding autoimmune disorders, the role of genetics, and the ways in which infectious diseases alter immune-system functioning. Investigators have begun to work to develop immune therapies for juvenile rheumatoid arthritis, dermatomyositis and lupus using an immune therapy designed for treating lymphoma.

1973
Hospital named by the federal government as one of only three pediatric cancer research and treatment centers.

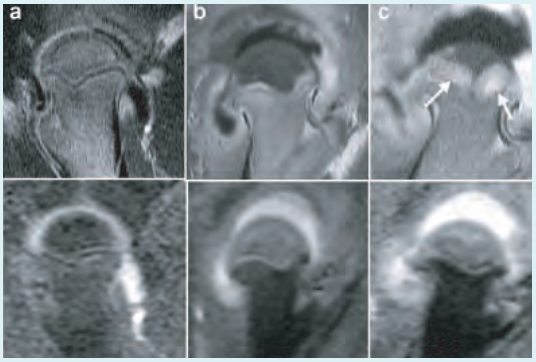
Page 28 (left to right): Terri Finkel, M.D., Ph.D., Paul Offitt, M.D., and Steven Douglas, M.D.

Progress Notes

Innovation on the Way to Intervention

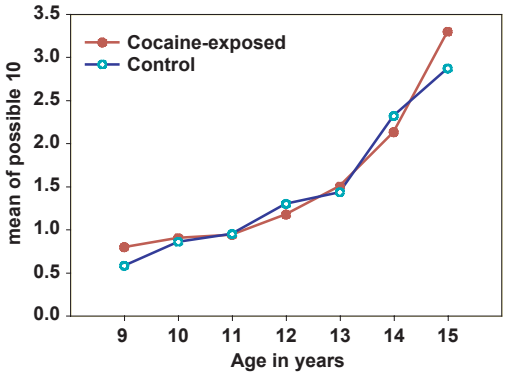
The close relationship between patient care and the vibrant research community at Children's Hospital makes it possible to have a direct link from the bench to the bedside. The highlights here, only a sampling of what's being accomplished at the Hospital, demonstrate the progression from recognizing a clinical or biological issue, developing a research direction, conducting basic research, applying the results in the clinical setting and evaluating those results. Each step is essential as we progress toward answering the research questions that ultimately will affect children's health.

Imaging



Diego Jaramillo, M.D., M.P.H., chair, Department of Radiology, is investigating the early diagnosis of growth disorders using MRI.

Prevention

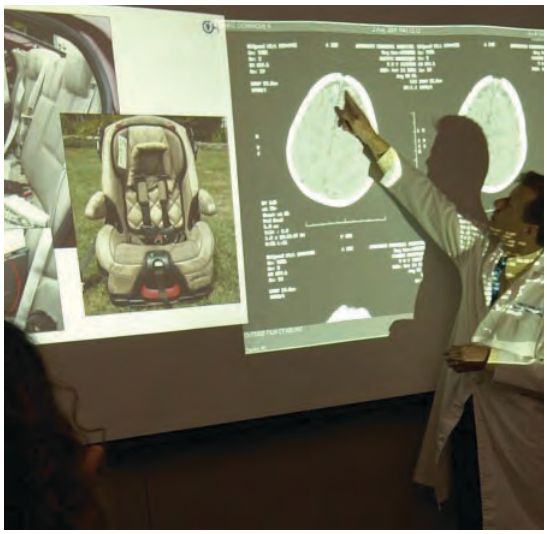


Hallam Hurt, M.D., Division of Neonatology, is exploring the neurocognitive precursors to adolescent drug use.

1978

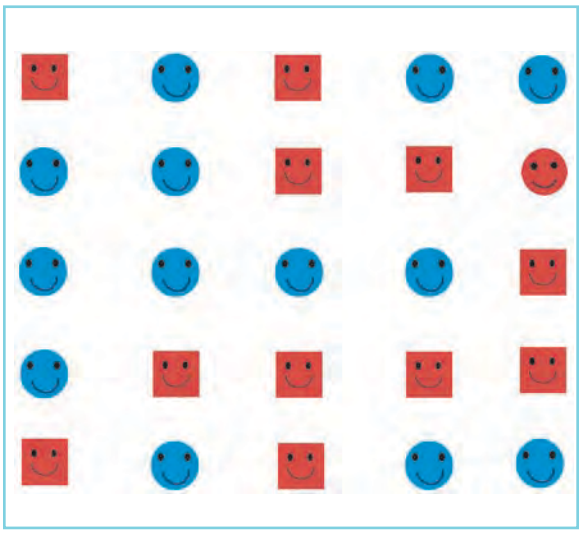
Dr. William Rashkind and colleagues develop an umbrella-like device for nonsurgical repair of certain heart defects.

Injury



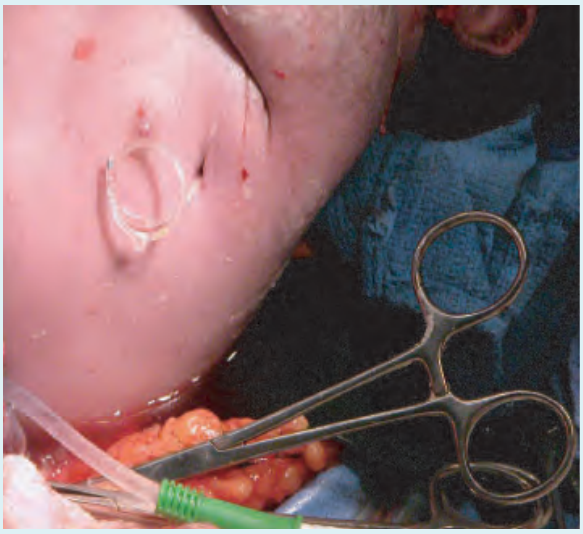
Dennis Durbin, M.D., and colleagues in the Division of General Pediatrics are expanding the Hospital's renowned crash investigation and engineering research by participating in the Crash Injury Research and Engineering Network. Through this multidisciplinary research network, the National Highway Traffic Safety Administration and medical professionals jointly study real cases of serious injuries sustained in car crashes.

Stroke



In an example of critical foundation-supported research, **Sabrina Smith, M.D., Ph.D.**, Division of Neurology, is using funds from the Child Neurology Foundation for a new study on language acquisition and visuospatial function in children who have suffered from a stroke.

Fetal Surgery

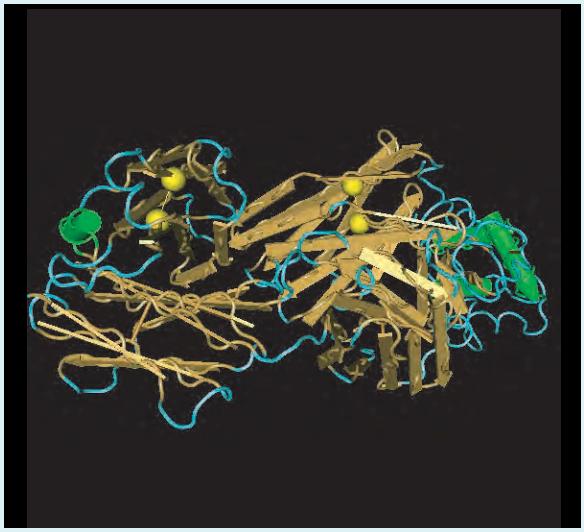


Treating high-risk fetal lung lesions using *ex utero* intrapartum therapy (EXIT) — a late-pregnancy procedure for a fetus with large head or neck tumors or severe heart or lung problems — was the focus of a study by Surgeon-in-Chief **N. Scott Adzick, M.D.**, pediatric surgeon **Holly Hedrick, M.D.**, and colleagues in the Hospital's Center for Fetal Diagnosis and Treatment. After reviewing the records of numerous patients after resection of lung lesions during the EXIT procedure, which involves maintaining placental blood flow and gas exchange, Dr. Adzick and his colleagues found that the procedure allows for controlled resection of large fetal lung lesions at delivery, avoiding acute respiratory problems related to air trapping and normal lung compression. The results of the study were published in the *Journal of Pediatric Surgery*.

Hedrick HL, Flake AW, Crombleholme TM, Howell LJ, Johnson MP, Wilson RD, Adzick NS. The *ex utero* intrapartum therapy procedure for high-risk fetal lung lesions. *J Pediatr Surg*. 2005 Jun;40(6):1038-43.

1983
Dr. Charles Stanley leads his research team to discover MCADD (medium-chain acyl-coA dehydrogenase deficiency), an inherited disease that may go undetected until it causes childhood brain damage or death.

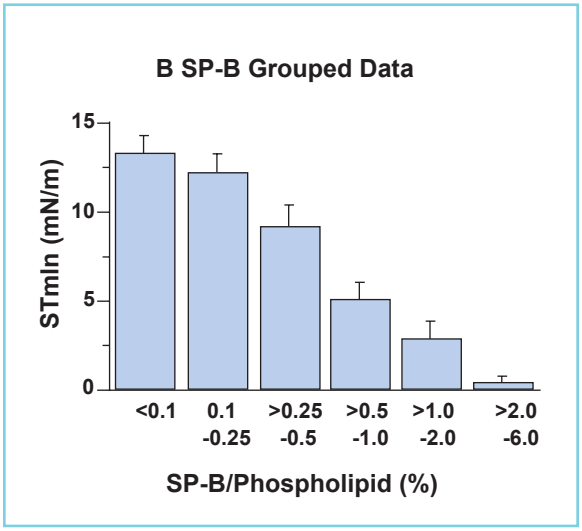
Host Defense



The immune cells that make and secrete the antibodies used to fight infections have to tightly control the synthesis of these proteins. An important control is how well they are folded, and the cells destroy improperly folded antibodies so they are not helpful in fighting infection. Pathologist **Yair Argon, Ph.D.**, found that to achieve this control, immune cells coordinate the formation of two disulfide bonds between amino acids called cysteines, unlike the more common case, where these bonds are formed one by one. These findings were published in *The Journal of Biological Chemistry*.

Elkabetz Y, Argon Y, Bar-Nun S. Cysteines in CH1 underlie retention of unassembled Ig heavy chains. *J Biol Chem*. 2005 Apr 15;280(15):14402-12.

Surfactant



Many premature babies suffer respiratory problems during their first few weeks of life due to an insufficient amount of a lung substance called surfactant. Neonatologist **Philip Ballard, M.D., Ph.D.**, led a study that found that even after infants begin producing their own surfactant, it often fails to function properly in premature infants who continue to have lung disease after the first week of life. The study results, which were published in *Pediatric Research*, show that infants with continued lung disease often have abnormal surfactant function and diminished amounts of surfactant protein B, an important component of surfactant. Surfactant abnormalities are more likely to occur during periods of respiratory infection and worsened respiratory status. Dr. Ballard and his colleagues are conducting a pilot trial of surfactant therapy.

Merrill JD, Ballard RA, Cnaan A, Hibbs AM, Godinez RI, Godinez MH, Truog WE, Ballard PL. Dysfunction of pulmonary surfactant in chronically ventilated premature infants. *Pediatr Res*. 2004 Dec;56(6):918-26.

Genetics

Expression phenotypes with the strongest evideice of linkage from genome scans

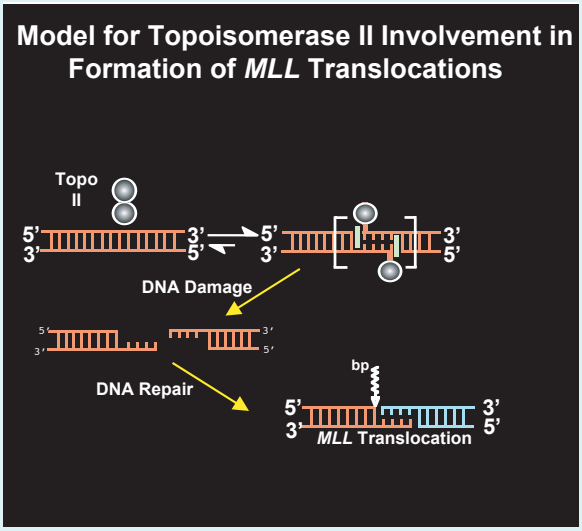
P-value	Gene	Location	*Cis/trans*
$<10^{-11}$	*ICAP-1A*	2q25	*Cis**
$<10^{-11}$	*TM7SF3*	12p11	*Cis**
$<10^{-10}$	*HSD17B12*	11p11	*Cis*
$<10^{-10}$	*CHI3L2*	1p12	*Cis*
$<10^{-10}$	*PSPHL*	7p11	*Cis*
$<10^{-10}$	*DSCR2*	21q22.2	*Trans*
$<10^{-10}$	*CBR1*	21q22.1	*Trans*
$<10^{-10}$	*HOMER1*	5q14	*Trans*
$<10^{-9}$	*DDX17*	22q13	*Cis*
$<10^{-9}$	*ZP3*	7q11	*Cis*
$<10^{-9}$	*IL16*	15q25	*Cis*
$<10^{-9}$	*ALG6*	1p31	*Trans*
$<10^{-9}$	*TNFRSF11A*	18q22	*Trans*

*The most extreme *P*-values occurred at SNPs located >5Mb from the gene, but linkage evidence within 5Mb of target gene was also highly significant ($P<4.3 \times 10^{-7}$).

Vivian Cheung, M.D., Division of Neurology, led a study that involved performing a genetic analysis of genome-wide variation in human gene expression. The investigators used microarrays to measure gene expression levels and performed genome-wide linkage analysis for expression levels of 3,554 genes in 14 large families. They found evidence of linkage to specific chromosomal regions. The combination of microarray techniques and linkage analysis allows the genetic mapping of determinants that contribute to variation in human gene expression. The study was published in the journal *Nature*.

Morley M, Molony CM, Weber TM, Devlin JL, Ewens KG, Spielman RS, Cheung VG. Genetic analysis of genome-wide variation in human gene expression. *Nature*. 2004 Aug 12;430(7001): 743-7.

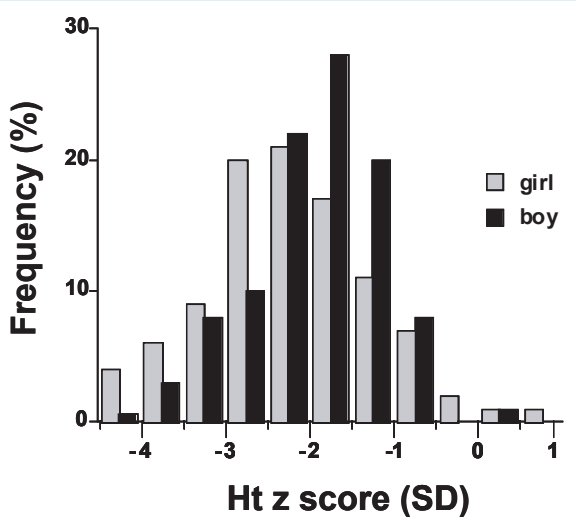
Leukemia



A group of anticancer drugs known as topoisomerase II poisons convert an enzyme that relaxes supercoiled DNA into a DNA-damaging enzyme. Some studies suggest that these drugs target areas of the DNA associated with different forms of leukemia. Incidence of a form of leukemia known as acute promyelocytic leukemia (APL) has increased in patients who are already being treated for a different form of cancer. This incidence has risen during the same period that the use of topoisomerase II poisons as a cancer treatment has increased. Oncologist **Carolyn Felix, M.D.**, led a study published in the *New England Journal of Medicine* that found topoisomerase II poisons contribute to DNA breaks associated with APL.

Mistry AR, Felix CA, Whitmarsh RJ, Mason A, Reiter A, Cassinat B, Parry A, Walz C, Wiemels JL, Segal MR, Ades L, Blair IA, Osheroff N, Peniket AJ, Lafage-Pochitaloff M, Cross NC, Chomienne C, Solomon E, Fenaux P, Grimwade D. DNA topoisomerase II in therapy-related acute promyelocytic leukemia. *N Engl J Med*. 2005 Apr 14;352(15):1529-38.

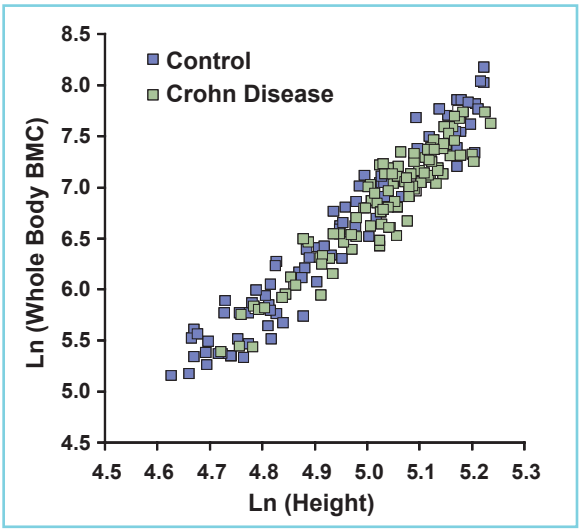
Growth



A study led by endocrinologist **Adda Grimberg, M.D.**, found that twice as many boys as girls are referred to medical specialists for evaluation of short stature and poor growth, which may reflect society's gender bias about stature and may have serious health consequences. The investigation, published in *The Journal of Pediatrics*, revealed that girls who were referred were more likely to have an underlying disease affecting their height, and were less likely to be within normal height ranges. Girls who were referred for evaluation were significantly shorter than the referred boys when compared to same-sex children in the general population and to predictions based on their parents' health. These findings were highlighted in *The New York Times* in February 2005 and in numerous media venues throughout the United States and abroad.

Grimberg A, Kutikov JK, Cucchiara AJ. Sex differences in patients referred for evaluation of poor growth. *J Pediatr*. 2005 Feb;146(2):212-6.

Bones



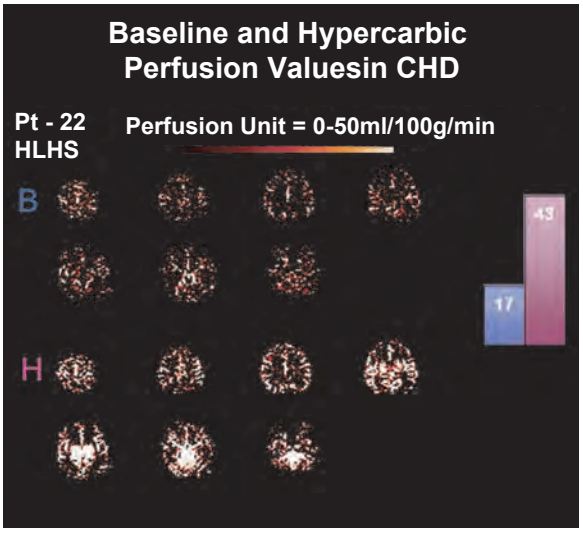
Nephrologist **Mary Leonard, M.D.**, led a study that found that children who take steroids for a kidney condition called nephrotic syndrome do not suffer bone loss, a common side effect of steroid treatments in adults and in steroid treatment of some childhood diseases. The study, published in the *New England Journal of Medicine*, suggests steroid-related weight gain in children with nephrotic syndrome may contribute to bone strength and mass.

Leonard MB, Feldman HI, Shults J, Zemel BS, Foster BJ, Stallings VA. Long-term, high-dose glucocorticoids and bone mineral content in childhood glucocorticoid-sensitive nephrotic syndrome. *N Engl J Med*. 2004 Aug 26;351(9): 868-75.

1988

Dr. Graham Quinn and associates are coleaders in proving the value of freezing retinal tissue (cryotherapy) to destroy abnormal vessel growth for the prevention of blindness in premature infants.

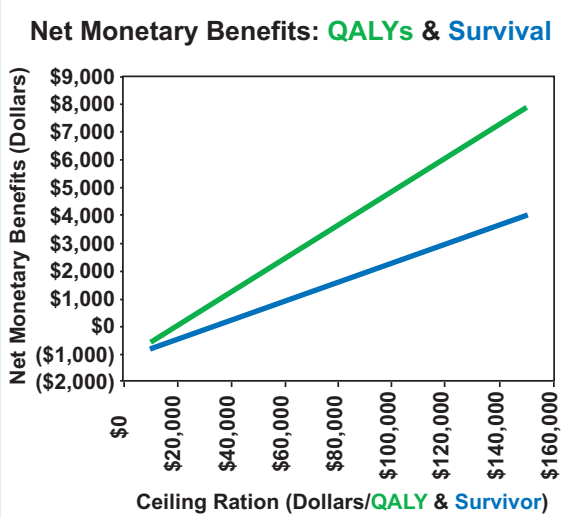
Brain Injury



Neurologist **Daniel Licht, M.D.**, found that newborns with congenital heart disease often have abnormally low blood flow in their brains before they undergo surgery. Dr. Licht and his coinvestigators used a novel magnetic resonance imaging technique, which they modified for use in infants, to conduct the first study to measure infants' cerebral blood flow before surgery. The study results, published in *The Journal of Thoracic and Cardiovascular Surgery*, indicate that reduced blood flow to the brain was associated with injury to the newborn brain, specifically a condition known as periventricular leukomalacia, a scarring of white matter in the brain.

Licht DJ, Wang J, Silvestre DW, Nicolson SC, Montenegro LM, Wernovsky G, Tabbutt S, Durning SM, Shera DM, Gaynor JW, Spray TL, Clancy RR, Zimmerman RA, Detre JA. Preoperative cerebral blood flow is diminished in neonates with severe congenital heart defects. *J Thorac Cardiovasc Surg*. 2004 Dec;128(6):841-9.

Nitric Oxide



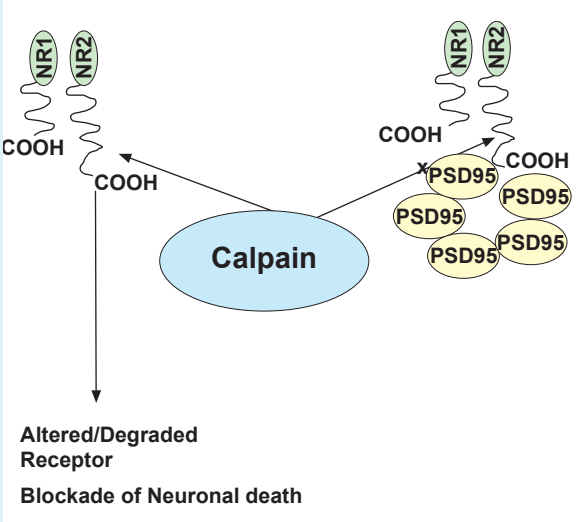
Neonatologist **Scott Lorch, M.D., M.S.C.E.**, found that inhaled nitric oxide (iNO) is a cost-effective method of treating infants with persistent pulmonary hypertension of the newborn (PPHN), a condition in which the infant's blood does not pass through the lungs, resulting in oxygen-poor blood. The results also indicate that the timing of treatment decisions could improve efficiency and cost of care for patients with PPHN treated with iNO. These results were published in *Pediatrics*.

Lorch SA, Cnaan A, Barnhart K. Cost-effectiveness of inhaled nitric oxide for the management of persistent pulmonary hypertension of the newborn. *Pediatrics*. 2004 Aug;114(2):417-26.

1990s

Dr. Robert Levy is cited for his research milestones related to the mechanisms and prevention of bioprosthetic heart valve calcification, and discoveries concerning the first report of a gene delivery stent.

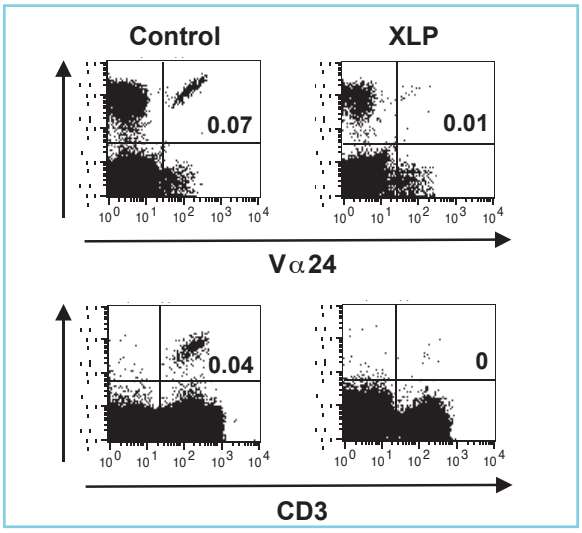
Neurobiology



Calpain is a protease — an enzyme that breaks down proteins — activated by a cellular receptor called NMDA that plays a role in neurological function and development. This receptor is composed of two subunits, NR1 and one of several forms of NR2. Calpain cleaves NR2 subunits, which then interact with a protein called PSD-95. Neurologist **David Lynch, M.D., Ph.D.**, found that interactions of the NR2 subunits with PSD-95 control the calpain-mediated breakdown of the NR2 subunit. These results, published in *The Journal of Neuroscience*, provide a mechanism for calpain's role in the turnover of NMDA receptors. The findings suggest that calpain could play a role in the damage seen in stroke and other neurologic disorders of children and adults.

Dong YN, Waxman EA, Lynch DR. Interactions of postsynaptic density-95 and the NMDA receptor 2 subunit control calpain-mediated cleavage of the NMDA receptor. *J Neurosci*. 2004 Dec 8;24(49):11035-45.

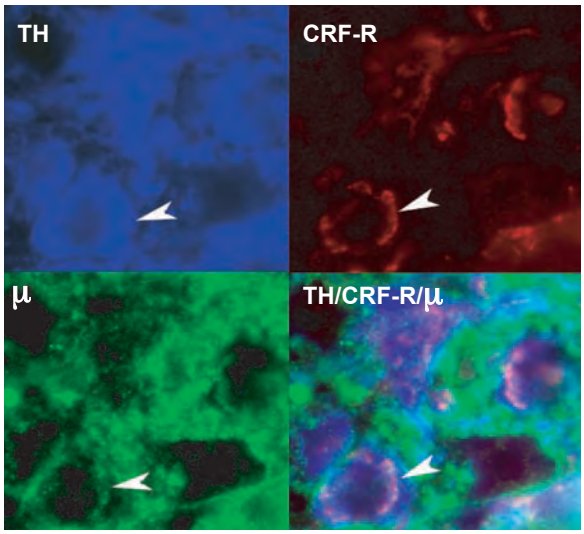
Immunity



XLP is a form of immunodeficiency caused by mutations in a gene responsible for the production of a protein known as SAP. Oncologist **Kim Nichols, M.D.**, led a study published in *Nature Medicine* that found SAP plays a crucial role in the development of natural killer T cells (NKT). Investigators found that patients with XLP do not have NKT cells, which suggests that the lack of NKT cells may contribute to the symptoms of XLP.

Nichols KE, Hom J, Gong SY, Ganguly A, Ma CS, Cannons JL, Tangye SG, Schwartzberg PL, Koretzky GA, Stein PL. Regulation of NKT cell development by SAP, the protein defective in XLP. *Nat Med*. 2005 Mar;11(3):340-5.

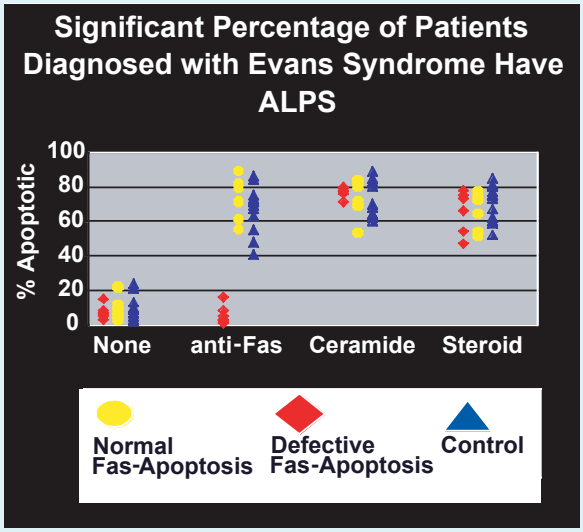
Addiction



Chronic opiate use produces long-lasting changes in the brain. One of those changes, which may then contribute to continued substance abuse, is dysregulation of the stress response. Neuroscientist **Rita Valentino, Ph.D.**, found that brain cells that regulate arousal and behavioral responses to stress (i.e., locus coeruleus neurons) become sensitized to corticotrophin-releasing factor (CRF), a stress neuromediator with chronic exposure to morphine. Her studies suggest that opiate-seeking behavior may occur to counteract the hypersensitivity of these neurons to stress. These studies also suggest that subjects that are chronically exposed to opiates may be vulnerable to stress-related disorders such as anxiety, depression or post-traumatic stress disorder. This study, published in *The Journal of Neuroscience*, is the first evidence for dysregulation of the central response to stress by chronic use of opiates.

Nichols KE, Hom J, Gong SY, Ganguly A, Ma CS, Cannons JL, Tangye SG, Schwartzberg PL, Koretzky GA, Stein PL. Regulation of NKT cell development by SAP, the protein defective in XLP. *Nat Med*. 2005 Mar;11(3):340-5.

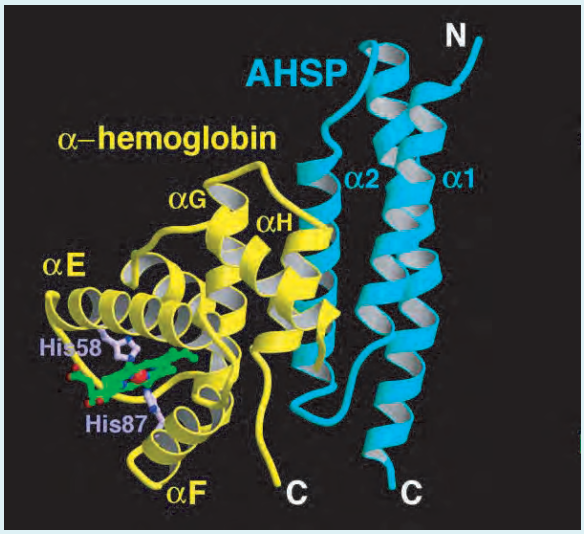
Diagnostics



Oncologist **David Teachey, M.D.**, investigated the potential overlap between two rare disorders with overlapping clinical symptoms. The results of this study, published in *Blood*, suggest a high prevalence of autoimmune lymphoproliferative syndrome (ALPS) among patients with Evans syndrome. This is a novel finding that has important implications for the prognosis and treatment of these patients. The results also indicate ALPS may be more common than previously thought. A sensitive first-line screening test was developed during this study, which uses developing immune cells, or double-negative T cells, as markers for patients who require definitive testing.

Teachey DT, Manno CS, Axsom KM, Andrews T, Choi JK, Greenbaum BH, McMann JM, Sullivan KE, Travis SF, Grupp SA. Unmasking Evans syndrome: T-cell phenotype and apoptotic response reveal autoimmune lymphoproliferative syndrome (ALPS). *Blood*. 2005 Mar 15;105(6):2443-8.

Hemoglobin



Hematologist **Mitchell Weiss, M.D., Ph.D.**, coauthored a study that reported the crystal structure of a complex between α-haemoglobin (α-Hb) and α-haemoglobin-stabilizing protein (AHSP) that when disrupted contributes to the symptoms of β-thalassemia, a common inherited anemia. The study described the structural changes that occur in αHb and AHSP when they bind. These findings, published in *Nature*, illustrate a new facet of hemoglobin homeostasis, and contribute to the body of research designed to find a treatment for β-thalassemia.

Feng L, Zhou S, Gu L, Gell DA, Mackay JP, Weiss MJ, Gow AJ, Shi Y. Structure of oxidized alpha-haemoglobin bound to AHSP reveals a protective mechanism for haem. *Nature*. 2005 Jun 2;435(7042):697-701.

Infections

Adjusted Risk Factors for ESBL-EK Infection in Hospitalized Children

Variable	Adjusted OR (95% CI)	P Value
Third-generation cephalosporin* use in previous 30 d	5.82 (1.92-17.68)	.002
Female	4.49 (1.49-13.51)	.008
Infecting organism	3.48 (1.07-11.32)	.039
Steroid use in previous 30 d	4.04 (1.30-12.50)	.016

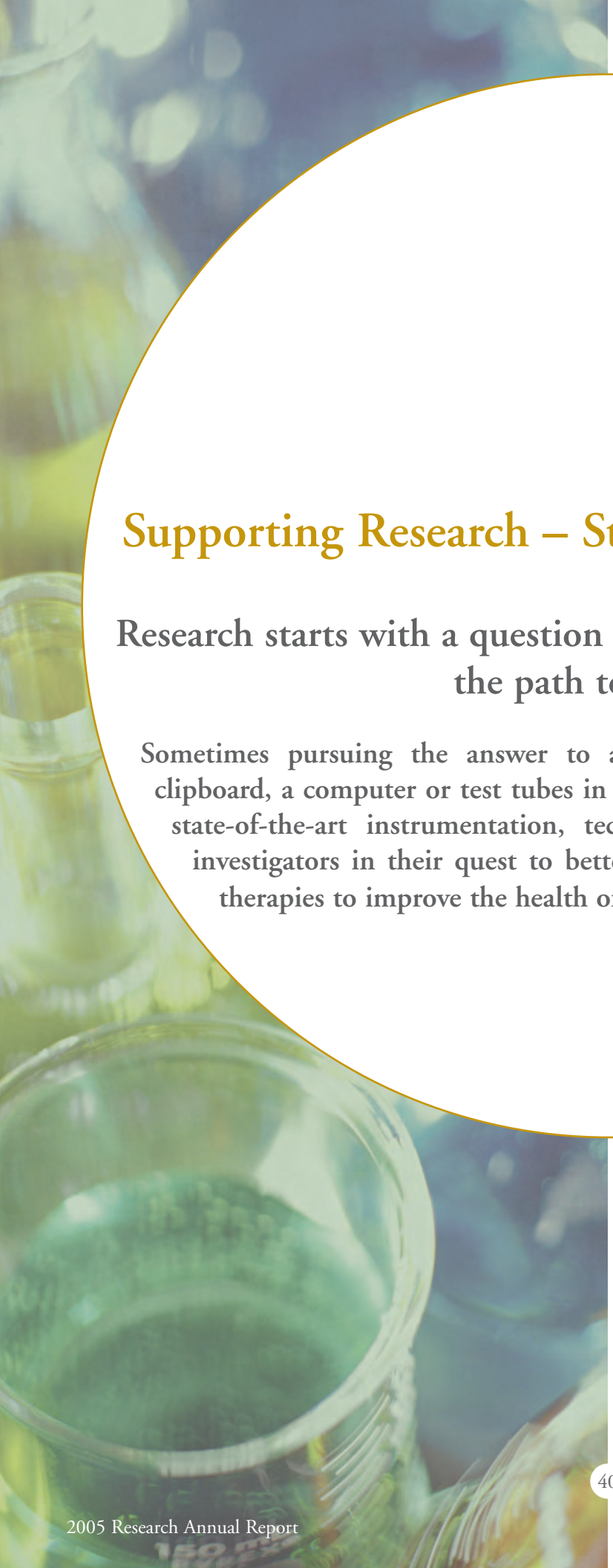
OR indicates odds ratio; CI, confidence interval.

* Third-generation cephalosporins include: cefotaxime, ceftazidime, and ceftriaxone.

The increased prevalence of infections caused by antibiotic-resistant bacteria has become a concern for hospitalized patients. Clinical epidemiologist **Theoklis Zaoutis, M.D.**, led a study that investigated the risk factors for infection with antibiotic-resistant bacteria in pediatric patients. The results, published in *Pediatrics*, indicate that a group of antibiotics, known as cephalosporins, are significantly associated with this type of infection. These results suggest that limited use of cephalosporins may reduce the number of antibiotic-resistant infections.

Zaoutis TE, Goyal M, Chu JH, Coffin SE, Bell LM, Nachamkin I, McGowan KL, Bilker WB, Lautenbach E. Risk factors for and outcomes of bloodstream infection caused by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella species in children. *Pediatrics*. 2005 Apr;115(4):942-9.

1991
The Hospital is designated a Human Genome Center by the National Institutes of Health and awarded a major federal grant for the mapping of chromosome 22 (completed in 1999).



Supporting Research – Stokes Core Facilities

Research starts with a question . . . the path to the answer is the challenge

Sometimes pursuing the answer to a research question involves using a clipboard, a computer or test tubes in a laboratory. At other times, access to state-of-the-art instrumentation, technologies and skills is critical to investigators in their quest to better understand disease and develop therapies to improve the health of children.

The Stokes Institute provides instrumentation and technical skill through 15 core facilities that service both laboratory and clinical research programs. Providing core facilities to investigators makes research more affordable, convenient and efficient.

With substantial Hospital support, the Stokes Institute has improved and broadened the core facilities available for the Hospital's research community, investing in equipment, services and other capabilities as well as supporting technical staff. Each year, the Hospital invests millions of dollars in sophisticated research instrumentation for the core facilities, which are led by scientific or faculty directors and one or more technical directors.

1992 — 1995/1999

Dr. Terri Finkel and colleagues are the first to show that HIV does more than infect T cells. The virus also seems to prime uninfected T cells for suicide, reducing the ability to fight infection. They are also the first to show that HIV renders some of the cells it infects death-resistant, thereby prolonging the life span of these virus factories.

Core Facilities Play Key Role in New Approaches to Neuroblastoma Research

Neuroblastoma, the most common and deadly of solid tumors in children, accounts for up to 10 percent of the cancers and 15 percent of the deaths from cancer in childhood. Most affected children are diagnosed with this aggressive disease before they are 5 years old.

Despite the sobering statistics, investigators have made tremendous strides over the last 20 years in unraveling the workings of neuroblastoma and developing new and more effective treatment approaches that reduce the toxic effects of the standard, highly intensive therapy. However, future novel therapies — and improvements in the survival rate — depend on identifying the key protein pathways that change a normal cell into an aggressively growing neuroblastoma.

Michael Hogarty, M.D., Division of Oncology, is addressing this fundamental question by applying global tumor proteomics to neuroblastoma. His work illustrates the critical roles of the Stokes Institute's core facilities in enabling the cutting-edge research of Hospital investigators. The cores house either instrumentation or expertise that is generally beyond the means of an individual investigator and therefore are central resources for the entire Children's Hospital community.

Dr. Hogarty and colleagues in the Division of Oncology previously performed an extensive genomic analysis that led to the classification of neuroblastoma into distinct types. Each type has signature alterations in the genome, encompassing scores and sometimes hundreds of genes (out of the more than 30,000 human genes).

The current challenge in neuroblastoma research is to discover which gene leads to the cancer state and aggressive growth of the disease. For this purpose, Dr. Hogarty initiated a research program with Yair Argon, Ph.D., who heads the Protein Core Facility. One of the core's specialties involves identifying changes in levels of expression of proteins. The core uses a new method to identify and list all the proteins whose level is dramatically lower or higher in each subtype of neuroblastoma. The list of proteins is then correlated with the list of genes implicated by the genetic analyses.

Top of page 42 (left to right): Michael Hogarty, M.D., Division of Oncology, and lab technician Kelly Goldmith.

To achieve a meaningful relation of the proteins identified by the protein core to the lists of genes, Dr. Hogarty is working closely with the Stokes Institute's Bioinformatics Core, whose expertise lies in computational tools that can quickly sift through gene lists, and information about altered patterns of their expression in normal tissues and in disease. Sometimes, the protein and gene identified are well studied, so investigators can infer their role in causing the disease. In other cases, however, the protein is unknown, leading to a key research question — what does it do?

1995

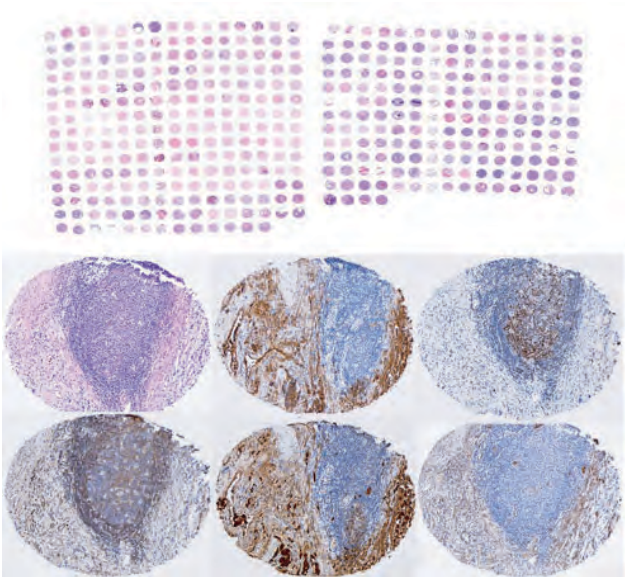
The Leonard and Madlyn Abramson Pediatric Research Center opens on the Hospital's Main Campus, consolidating all the laboratory research of the Joseph Stokes Jr. Research Institute.

Top of page: Beckman ProteinLab® PF 2D, Protein fractionation system that identifying changes in levels of expression of proteins.
Bottom of page (left to right): Bioinformatics Core members Xiaowu Gai and Juan Perin in server room with director Ge Zhang.

The computational tools in the Bioinformatics Core enable the Protein Core staff to project possible functions for an unknown protein, like its involvement in certain metabolic pathways. Investigators can then test such predictions with other Protein Core technology that measures protein-protein interactions. Bioinformatics tools also provide Dr. Hogarty with the ability to rank order the likelihood that each protein he finds is relevant for neuroblastoma.

The predictive value of a newly identified protein to neuroblastoma depends on how many times it is identified in different patients. To determine this, Dr. Hogarty will engage the services of the Pathology Core, which recently constructed a tissue microarray for neuroblastoma. Small tissue pieces from several hundred neuroblastoma tumors from patients treated at Children's Hospital, selected to represent the various subtypes of neuroblastoma, were arrayed on microscope slides and can be probed simultaneously for the presence of the candidate protein.

All the data from the protein analysis, genetic analysis and tissue microarrays will then be organized into data sets in collaboration with the Biostatistics and Data Management Core. The core will determine the statistical significance of each of the protein biomarkers, enabling Dr. Hogarty and his research team to rank the data and prioritize which proteins are worth pursuing further as possible therapy targets.



Solving a disease as complex as neuroblastoma requires many approaches, as no one technique can provide a cure. Through the availability of a host of cutting-edge technologies in the Stokes Institute's Core Facilities, Hospital researchers can now mount a multidisciplinary assault on complex childhood diseases with realistic hopes of finding the most likely causes of disease.

Top of page: Tissue microarray for neuroblastoma developed by the Pathology Core.
Bottom of page: Biostatistics director Charles Scott, Ph.D., and member Justin Valliyil.

1995

Dr. Scott Adzick leads the establishment of the Center for Fetal Diagnosis and Treatment, which is at the forefront of research and clinical practice in the emerging field of fetology.

The Biostatistics and Data Management Core has the distinction of serving as the coordinating center for the 25-center study on childhood absence epilepsy, a form of epilepsy that affects up to 15 percent of epileptic children. Characterized by brief staring-spell seizures that are frequent and unpredictable, the condition can have an adverse effect on a child's education and play.

The five-year study will recruit more than 400 children who will receive different medications for their childhood absence epilepsy.

The Core's role in this important study involves providing data and biological collections and monitoring, site coordination, double data entry, site quality assurance, monitoring, Data Safety Monitoring Board reporting, and interim and final statistical analyses.

The National Center for Research Resources Shared Instrumentation Grant provides funds for expensive equipment shared between multiple investigators. This competitive award makes it possible to purchase instruments that could not be purchased with individual investigator grants.

Stokes won a grant of nearly $300,000 to purchase a Surface Plasma Resonance Biacore 3000, which measures protein interactions. Yair Argon, Ph.D., serves as the principal investigator on the grant and assumes administrative and scientific responsibility for the equipment.

Innovation Fueling Progress

Vaccine Development Testament to Hospital's Innovation

During the last century, the life span of the average American has increased by approximately 30 years. This dramatic increase is attributed to a multitude of factors, including cleaner drinking water, better nutrition and the development of antibiotics.

Vaccines, however, are the single most significant contributor to the longer life we now enjoy.

Children's Hospital has a distinguished legacy of developing vaccines to improve the lives of children throughout the world. Pioneering research conducted at Children's Hospital by the husband-and-wife team of Drs. Werner and Gertrude Henle, as well as Lewis Coriell, M.D., and Stanley Plotkin, M.D., led to the development of vaccines for whooping cough, influenza, mumps and rubella (German measles). The Hospital served as a testing site for many of these vaccines.

Children's Hospital was privileged to collaborate on much of the innovative research conducted by world-renowned microbiologist Maurice Hilleman, Ph.D., D.Sc., (seen above) who was instrumental in the development of modern vaccines, including nine of the 14 vaccines routinely given to children today.

Dr. Hilleman, a former director of the Merck Institute of Vaccinology and a longtime advisor to Stokes Institute, passed away in April at age 85.

1995

The Division of Gastroenterology and Nutrition is at the forefront in the identification, diagnosis and treatment of Eosinophilic Esophagitis (EoE) — a new allergic GI disease in children.

During a career that spanned six decades, Dr. Hilleman contributed to the development of nearly three dozen vaccines, including those for measles, mumps, rubella, varicella and hepatitis B.

Dr. Hilleman's successful development of a vaccine for mumps started when his daughter, age 5 at the time, complained of a sore throat. After quickly determining she had the mumps, he swabbed her throat, weakened the virus strain and began working on a vaccine. As a result of his efforts, the virus has been virtually eliminated.

According to Paul A. Offit, M.D., chief, Division of Infectious Disease, Dr. Hilleman would probably consider his greatest success the hepatitis B vaccine, which was the first to use a single protein in vaccine development, the first to use DNA recombinant technology, and, since hepatitis B often leads to liver cancer, was the first to prevent a known cause of human cancer.

"Developing just one vaccine can be a lifetime's worth of work," Dr. Offit said. "That Dr. Hilleman's groundbreaking research led to numerous vaccines — many of which are among those recommended for children today — is almost inconceivable."

Dr. Hilleman conducted many of his most important vaccine studies with Children's Hospital researchers, who continue to build upon his research.

A prime example of the Hospital's bench to bedside research philosophy, recent efforts on this front involve a vaccine for rotavirus, a disease that causes approximately one-third of diarrhea-associated hospitalizations and nearly half a million deaths worldwide every year in children under five.

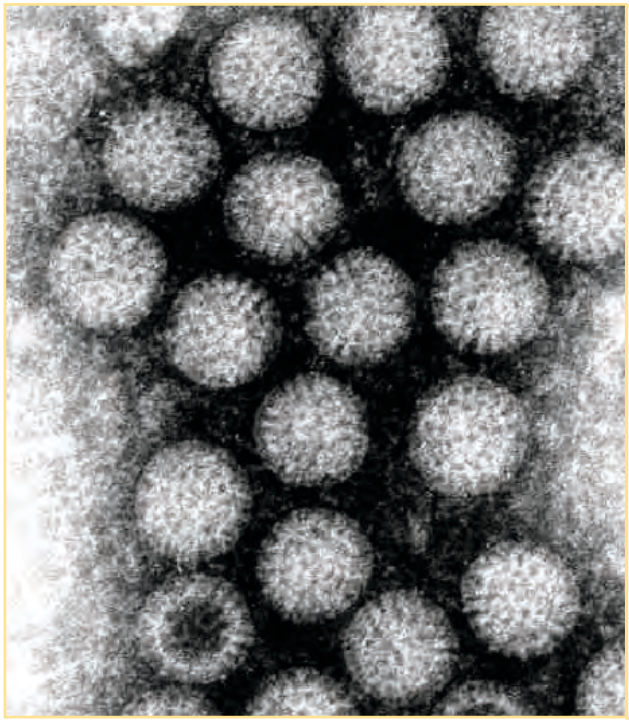
"Dr. Hilleman's contributions to vaccine development save approximately 8 million lives a year and have allowed us to live longer," says Dr. Offit, one of the chief developers of the technology that forms the basis of RotaTeq®, the rotavirus vaccine developed by Merck & Co. Inc.

As a reminder in perpetuity of the importance of Dr. Hilleman to Merck and the communities of the Hospital and University of Pennsylvania, the Merck Company Foundation made a gift to the Hospital and University to establish the Hilleman Chair in Vaccinology. Dr. Offit was chosen as the first holder of the chair.

Top of page: Paul Offit, M.D., chief, Division of Infectious Disease, and one of the rotavirus vaccine developers.

1997

Drs. Nancy Spinner, David Piccoli and Ian D. Krantz discover the gene responsible for Alagille syndrome, a disorder associated with congenital liver, heart, kidney, spine, eye and pancreatic disease.



After one of the largest safety and efficacy evaluations ever performed by a pharmaceutical company — Phase III trials that involved more than 70,000 subjects — Merck & Co. recently applied for a license for RotaTeq® with the U.S. Food and Drug Administration.

In the United States, rotavirus accounts for approximately 70,000 hospitalizations, 500,000 visits to primary care offices and 20 to 70 deaths annually.

Children's Hospital investigators Paul A. Offit, M.D.; and H. Fred Clark, V.M.D.; and Stanley Plotkin, M.D., of The Wistar Institute jointly developed the technology, which forms the basis of Merck's rotavirus vaccine. The technology was licensed to Merck in 1991.

Children's Hospital investigators have developed a multitude of technologies over the years that may ultimately improve the health of children through the development of new products and therapies.

During fiscal year 2005 alone, the United States Patent Office awarded 11 patents to Children's Hospital for technologies, all of which illustrate the translational relevance of research within the Stokes Institute.

Robert Levy, M.D., **Ivan Alferiev, Ph.D.**, and former Children's Hospital researcher **Narenda Vyavahare, Ph.D.**, received two patents for their inventions that teach mechanisms by which to make implantable bioprosthetic devices and tissues more biocompatible.
Patent numbers: US6,391,528 and US6,824,970

Robert Levy, M.D., and former Children's Hospital researcher **Narenda Vyavahare, Ph.D.**, were awarded a patent that relates to methods of stabilizing implantable bioprosthetic devices, making them less resistant to calcification.
Patent number: US6,861,211

Ivan Alferiev, Ph.D., **Ilia Fishbein, M.D., Ph.D.**, and **Robert Levy, M.D.**, received two patent awards for novel types of polyurethanes that are useful in biological systems.
Patent numbers: US6,900,282 and US6,890,998

Robert Levy, M.D., and former Children's Hospital researcher **H. Scott Baldwin, M.D.**, discovered methods for a gene therapy approach specific to the control of cardiac arrythmias. Their patent also discloses novel gene vector compositions and localized delivery formulations.
Patent number: US6,852,704

Michael Grunstein, M.D., Ph.D., and former Children's Hospital researcher Hakon Hakonarson, M.D., received a patent that includes methods for identifying genes that regulate responses to anti-inflammatory drugs, methods for drug screening, and methods for identifying genes that correlate with asthma and other inflammatory diseases.
Patent number: US6,893,828

Flaura Winston, M.D., Ph.D., and **Kristy Arbogast, Ph.D.**, received two patent awards for developing a safety handlebar and a retrofit safety handlebar that absorb energy and therefore reduce abdominal and other injuries to bicycle riders when they collide with the handlebar.
Patent numbers: US6,840,135 and US6,834,565

Drs. Winston and **Arbogast**, along with **Rajiv Menon, Ph.D.**, and **Kurt Schwinghammer, Ph.D.**, developed a sleeping occupant protection system for vehicles.
Patent number: US6,827,400

Former Children's Hospital staff nurse **Kathleen O'Neill, R.N.**, invented a device for maintaining a patient's mouth in an open position during a medical procedure.
Patent number: US6,743,017

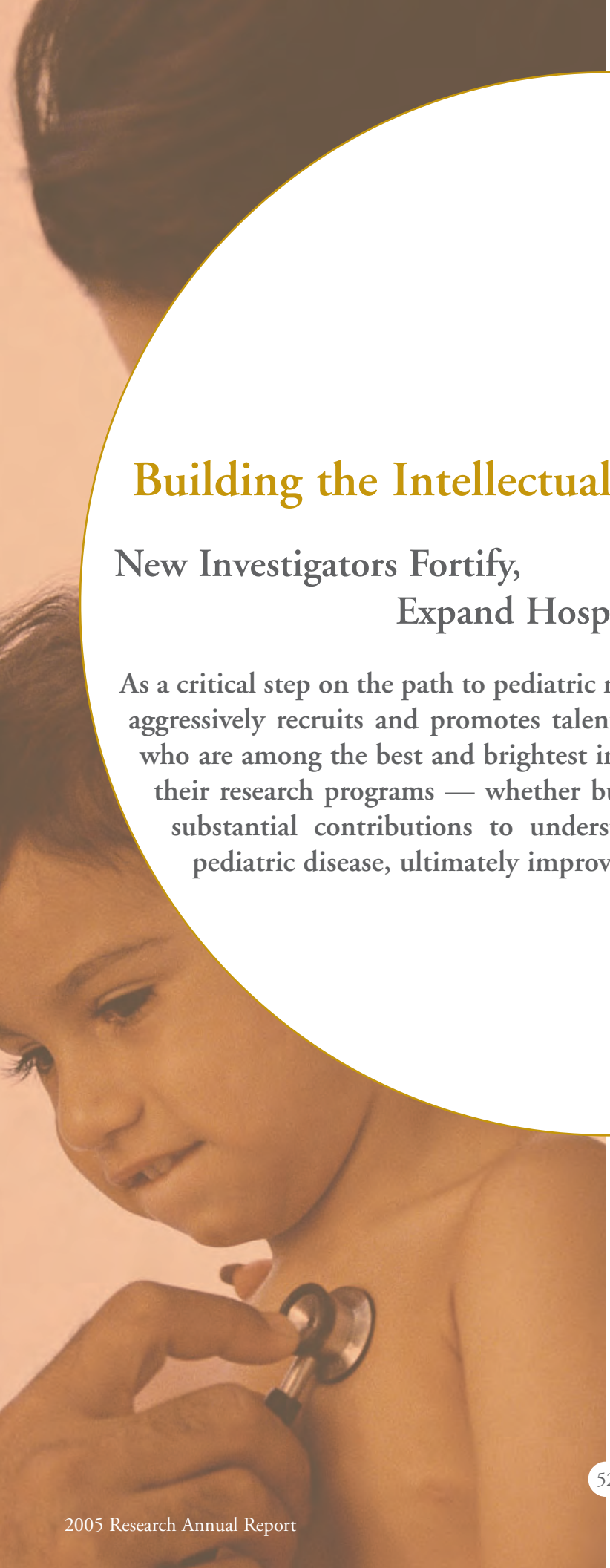
1997

Center for Outcomes Research is established to create new methods of health service research, with an emphasis on developing new pediatric outcomes measures.

Fiscal Year 2005 Tech Transfer Statistics:

Invention Disclosures Received - 29
Patent Applications Filed - 26
Patents Issued - 10
Active Licenses - 23 License Revenues - $865,000

Technology Transfer Director Kurt Schwinghammer, Ph.D.; and Chief Scientific Officer and Senior Vice President Philip Johnson Jr., M.D., director of The Joseph Stokes Jr. Research Institute.

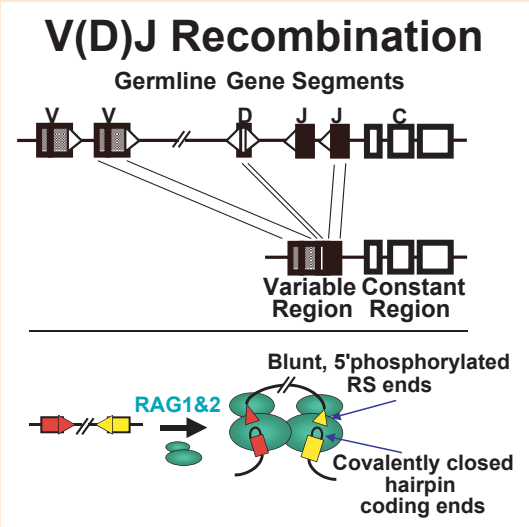


Building the Intellectual Community

New Investigators Fortify, Expand Hospital's Research Program

As a critical step on the path to pediatric research preeminence, Children's Hospital aggressively recruits and promotes talented laboratory and clinical investigators who are among the best and brightest in their fields. The Institute expects that their research programs — whether budding or in full bloom — will make substantial contributions to understanding the biology that underlies pediatric disease, ultimately improving child health.

Cancer



Craig Bassing, Ph.D., is one of the more than 20 who joined the ranks of investigators at Children's Hospital last year. A member of the Division of Cell Pathology in the Department of Pathology and Laboratory Medicine, Dr. Bassing's research interest centers on understanding the molecular mechanisms through which antigen receptor genes are assembled in developing white blood cells.

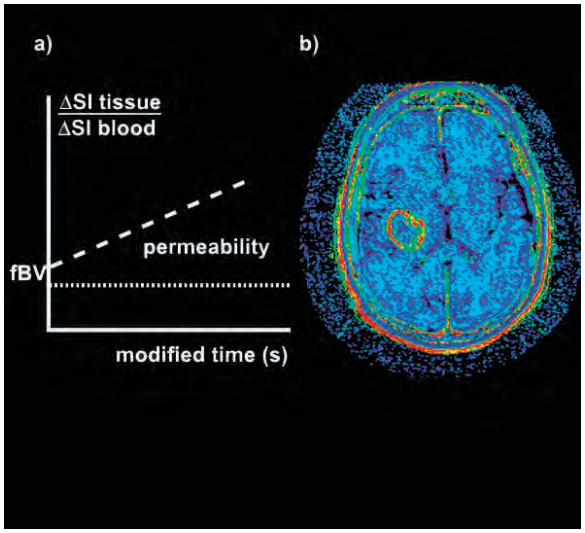
Specifically, Dr. Bassing investigates the role of chromatin modification in regulating the initiation and proper repair of the programmed DNA double-strand breaks. Errors in the process of repairing these natural breaks are often associated with diseases like cancer.

Recruited from Children's Hospital Boston, Dr. Bassing has an appointment in the University of Pennsylvania Department of Cancer Biology and was named an assistant investigator at Penn's Abramson Family Cancer Research Institute.

1997

Dr. Michael Grunstein and colleagues are the first to demonstrate that a receptor for IgE is present in airway smooth muscle, making it asthmatic in nature. They further found that a protein that is also present in airway smooth muscle can protect it from developing an asthmatic response.

Imaging



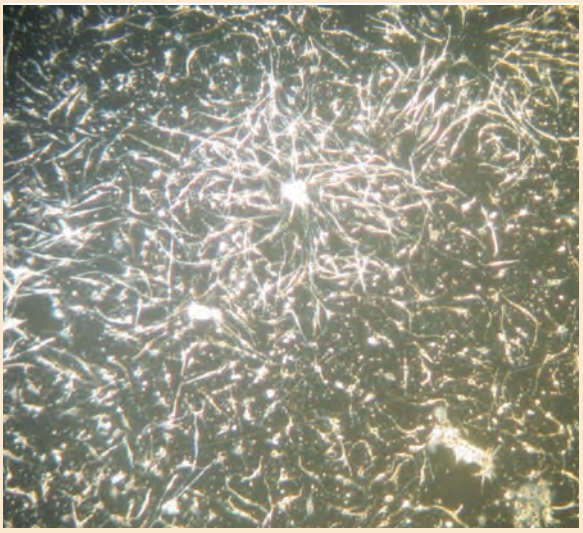
Timothy Roberts, Ph.D., joined the Department of Radiology as vice chair of research after serving as a professor of medical imaging at the University of Toronto. Dr. Roberts' research interests include brain-wave recording using magnetoencephalography; advanced, physiologically specific neuroimaging with magnetic resonance imaging; development disorders, especially autism; and neuro-oncology and imaging of microvascular permeability in cancer.

Injury

A bioengineer and researcher in pediatric trauma, **Kristy Arbogast, Ph.D.**, of the Division of Emergency Medicine in the Department of Pediatrics, focuses her research on traffic injury. As part of TraumaLink, Dr. Arbogast aims to make children safer by understanding how they are injured in everyday events — like riding in motor vehicles — as well as how the products they use during everyday events influence their risk of injury and how those products can be improved to reduce that risk.

As part of her research, Dr. Arbogast investigates products (such as cars, bicycles and playground equipment), the environment (such as skid marks or pedestrian walkways), and protective devices (such as seat belts, helmets and car seats) to determine what happens when a child is injured. Her technique uses general engineering principles to understand how the energy of an incident is transferred to a child.

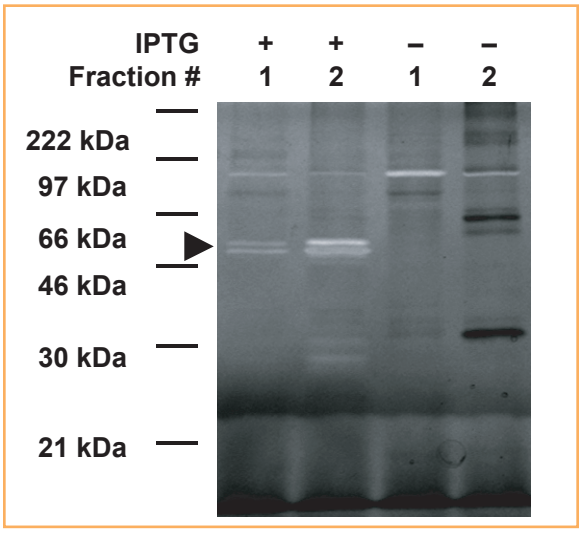
Hearing



John Germiller, M.D., Ph.D., joined the Division of Otolaryngology in the Department of Surgery as a faculty member after completing his fellowship in otolaryngology. Dr. Germiller's research centers on the factors that control the early embryonic development of the auditory nerve. The nerve is stimulated by cochlear implants that help restore hearing to many deaf children.

He specifically investigates the early growth factors that stimulate the auditory nerve and direct it to innervate the early inner ear. His goal is to identify a new auditory nerve growth factor that may be promising clinically for regenerating the auditory nerve in deaf children.

Infection



Michael Sebert, M.D., who joined the Division of Infectious Diseases, investigates the molecular basis of infections by *Streptococcus pneumoniae*, a common childhood bacterial pathogen also known as the pneumococcus. Although this bacterium is a major cause of diseases including pneumonia, otitis media, sepsis and meningitis, it most frequently is found colonizing the upper respiratory tract of humans asymptomatically. Such silent colonization is thought to precede nearly all cases of disease caused by this organism. His laboratory studies the coordinated genetic responses through which *Streptococcus pneumoniae* becomes adapted for survival in this environment. The long-term objective of his research involves defining new strategies for preventing and treating diseases caused by this pathogen.

Providing the Foundation for Tomorrow's Researchers

Training Project Focuses on Cell Injections to Treat Congenital Diseases

The field of fetal therapy is expanding rapidly, with the number of surgeries and interventions rising and the perception of the fetus as a patient gaining momentum among physicians and other healthcare professionals.

One form of fetal therapy — *in utero* hematopoietic cell transplantation (IUHCT) — has the potential to treat a large number of congenital disorders, including those diagnosed in the prenatal period, or disorders like sickle cell disease that may require bone marrow transplants after birth.

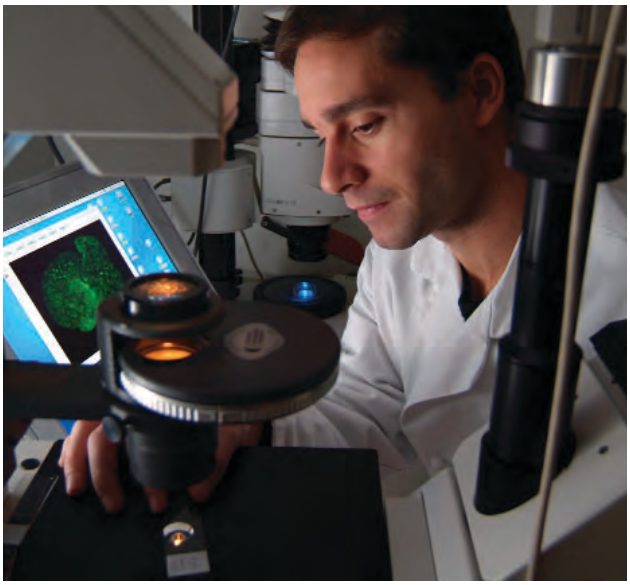
IUHCT involves injecting cells into the fetus, an ideal environment given the fetus's small size, immature immune system and a large number of migrating stem cells. The careful timing of injections and the successful engraftment of donor cells, however, have proven to be crucial to the success of the fetal cell transplantation procedure.

The research conducted by **William Peranteau, M.D.**, and his colleagues stems from a model of intravenous fetal bone marrow injection developed by surgeon Alan Flake, M.D., to better understand the immunobiology of *in utero* transplantation.

Dr. Peranteau and his team built upon the results of preliminary studies to establish an injection method that would increase the competitive advantage of the donor cell in the fetal environment.

Dr. Peranteau is one of three trainees whose work is supported by a new five-year training grant from the National Institutes of Health. The Hospital's Fetal Biology and Therapy Training Program, directed by Dr. Flake, trains clinician-scientists who are focused on fetal therapy and who can envision, develop, investigate and translate new and novel treatment strategies for the fetus.

The award ensures that trainees have protected time to develop their research skills under the direction of one of the program's mentors. Patient-oriented research opportunities, derived from the Hospital's Center for Fetal Diagnosis and Treatment, focus on fetal treatment of myelomeningocele and twin-twin transfusion syndrome. The laboratory research opportunities under the training grant include four major areas of basic research: stem cell therapy in the fetus; fetal gene therapy; fetal wound healing; and fetal anatomic malformations and lung growth.



In his stem cell therapy project under the training grant, Dr. Peranteau and his research team are investigating the ability of certain donor cells called hematopoietic stem cells to home to and engraft in the fetal liver, which plays a critical role at the time of the IUHCT procedure.

After inhibiting an enzyme called CD26 in donor cells, Dr. Peranteau and his colleagues injected the cells into their model and found that the CD26-inhibited bone marrow and enriched stems cells homed to the to the fetal liver more efficiently. The investigators went on to find that transplanting the CD26-inhibited bone marrow in the fetus led to greater engraftment of the donor cells.

Taken together, the studies conducted by Dr. Peranteau and his colleagues demonstrate that inhibiting the CD26 enzyme in donor cells increased their ability to home to specific parts of the fetus, thereby increasing the chances that the IUHCT procedure may ultimately aid in treating or curing congenital diseases in the fetus.

1997

Drs. Flaura K. Winston and Dennis R. Durbin initiate Partners for Child Passenger Safety. Their research shows that young children who use age appropriate restraints, such as a booster seats, have a 59 percent lower risk of injury in a crash. They also show that rear seats of compact extended cab pick-up trucks are particularly dangerous. These findings lead to a wide range of enhanced legislation, safety regulation, and automobile and child restraint design.

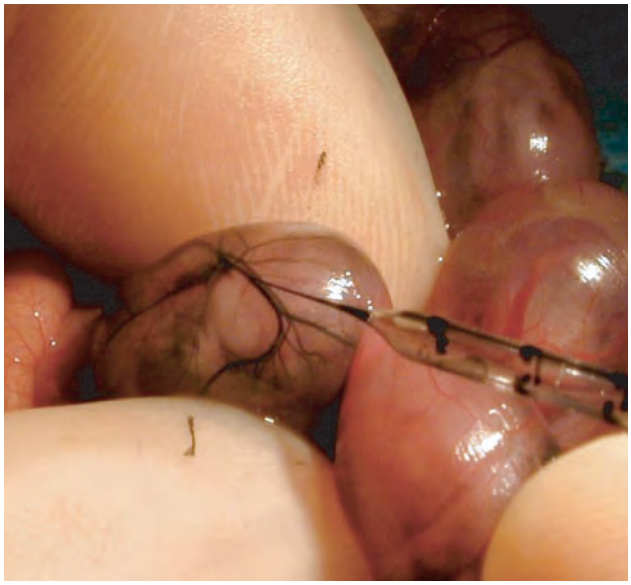


Image of in-utero *hematopoietic cell transplantation (IUHCT). Injection of allogenic bone marrow cells into the vitelline vein of a 14-day gestation model.*

Training Grants: A Valuable Resource for Investigators

Training and career development for scientists and physician-scientists is an integral element of the mission of Children's Hospital. It is through in-depth, hands-on training that the Hospital develops the next generation of investigators by exposing them to the highest scientific principles, new research techniques and the nearly limitless opportunities for clinical and laboratory research.

Federal or private grants fortify the Hospital's internal training and awards programs while offering additional opportunities for experience and training in specific areas relevant to advancing pediatric healthcare research. Numerous awards come from the National Institutes of Health, which is committed to training research investigators and has made such an endeavor part of its overall mission.

Children's Hospital is the recipient of seven highly competitive training grants that provide mentored research training as well as formal coursework, a core curriculum and training in responsible research conduct.

In addition to the fetal biology and therapy training grant, the grants awarded to the Hospital focus on both general and disease-specific areas of investigation related to pediatric healthcare research and include programs in arteriosclerosis, cardiology, career development, diabetes, hematology, neurodevelopmental disorders and stroke, and training pediatric physician-scientists.

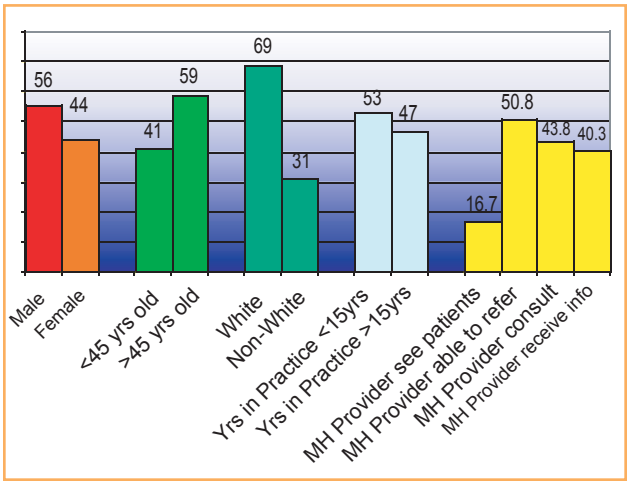
Thanks to its close association with the University of Pennsylvania, Children's Hospital trainees can also get support from the many training grants awarded to the University or can train with faculty members from relevant Hospital departments and the University of Pennsylvania, thus expanding an already rich and diverse training environment.

Fellows selected for participation in training grants are expected to devote themselves essentially full-time to research training, which generally lasts two to three years.

1998

Steven Ludwig, M.D., and N. Scott Adzick, M.D., are elected as members of the Institute of Medicine (IOM).

ADHD in Pediatric Practice



K Awards Support Future Researchers, Physician-Scientists

Many Hospital investigators are the recipients of NIH Research Career Development Awards, also referred to as "K" awards. These awards are essential to ensuring a pipeline of well-trained academic physicians and scientists by supporting their research and development activities and requiring that applicants gain additional supervised experience as they become independent research scientists.

The Hospital has 38 active K awards supporting both basic and clinical research. Such career development support helps fortify an investigator's budding career. Some researchers with K awards aim to develop better treatments for a multititude of pediatric diseases and conditions, while others explore the underlying biology that can play a role in disease.

For example, attention deficit hyperactivity disorder (ADHD) is the focus of the K award to **James Guevara, M.D., M.P.H.**, who is investigating interventional care for children with the disorder.

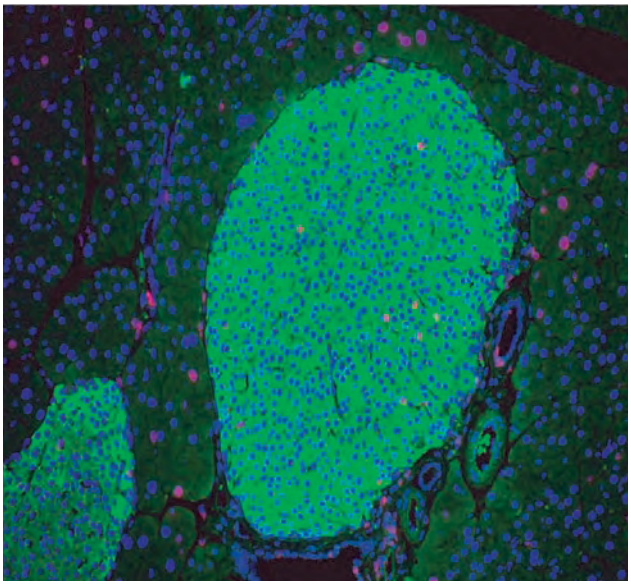
Among the most prevalent chronic health conditions among children, physicians are increasingly identifying ADHD in pediatric practice. Effective treatment for ADHD helps minimize the effects of the disorder on academic achievement, delinquency, self-esteem; and relationships with friends and family.

Dr. Guevara's K award involves studying the effects of collaborative behavioral care — the shared management of care for children between families, primary care providers, schools and mental health specialists. The award supports research on the collaborative care among primary care providers and the impact on children with ADHD. Dr. Guevara's project will also develop and pilot a collaborative care intervention with ADHD that will provide new information and interventions for patients.

Endocrinologist **Jake Kushner, M.D.**, focuses his research effort on gaining a better understanding of islet cell growth that may reveal new treatment approaches or a cure for diabetes, a significant health problem for many Americans. Insufficient insulin secretion affects patients with both type I and type II diabetes, but little is understood about the growth of islet cells, the hormone-producing cells of the pancreas.

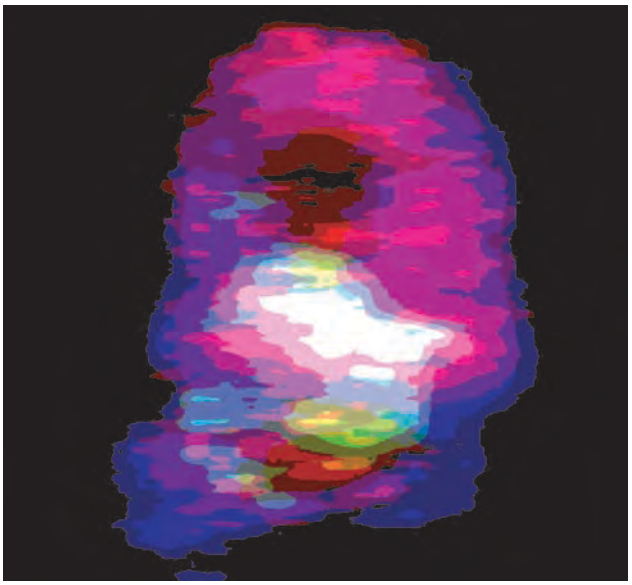
With the financial support of a K award, Dr. Kushner has been able to hone his cell biology and physiology techniques as he studies the growth of beta cells and the signals that trigger activity in these cells.

Dr. Kushner is also the recipient of the prestigious Basil O'Connor Award from the March of Dimes for his research on type II and gestational diabetes, which are highly associated with serious birth defects. The award provides funding to young scientists beginning independent research careers that may provide insight into preventing birth defects and infant mortality.



Diabetes

Immunity



Immunologist **Jordan Orange, M.D., Ph.D.**, is invested in learning more about natural killer (NK) cells, white blood cells that help the body defend against disease by detecting and destroying tumor cells and protecting against microbial pathogens. Patients who have a decreased number of NK cells or whose NK cells do not function properly are more susceptible to cancer and a variety of infectious diseases. Some researchers believe that enhancing NK cell function can improve the body's destruction of tumor cells and may improve the body's defense against viral disease.

Dr. Orange's K award allows him to investigate the processes that regulate the cytoskeleton, the internal framework that plays a critical role in cellular function. The award supports research on the receptors and signaling molecules involved in the activation and inhibition of cellular function as well as the cell's cytoskeleton. A better understanding of NK cells may help physicians prevent tumor growth and infectious disease in patients.

In addition to receiving a K award from the NIH, Dr. Orange was honored by the American Academy of Allergy, Asthma and Immunology, which chose him as the recipient of the 2005 ERT Faculty Development Award. The award supports one faculty member each year who represents the specialty of allergy and immunology and shows promise in research that will promote the specialty.

Asthma

Asthma, the most common chronic illness of childhood, is at the center of research conducted by emergency physician **Joseph Zorc, M.D.** Dr. Zorc is devoted to improving the long-term control of asthma for children seen in the Emergency Department. Many inner-city children do not receive recommended treatments that doctors know are effective for asthma, which is especially prevalent in metropolitan areas. As a result, many inner-city children receive much of their asthma care in emergency departments and never receive long-term preventative care.

Dr. Zorc's K award supports his investigation into the impact of an informational video about the benefits of preventive asthma treatment on follow-up visits to primary care providers and long-term use of asthma medication. Designed for parents of inner-city children who receive asthma therapy in the emergency department, the video provides valuable information about the benefits of follow-up care and addresses misconceptions about asthma.

1999

Dr. Beverly Emanuel's efforts contribute to the complete sequencing of chromosome 22, making it the first human chromosome to be fully sequenced. Defects in genes on chromosome 22 are implicated in certain leukemias and other pediatric tumors, mental retardation, numerous birth defects and the 22q11 deletion syndrome.

The Hospital has 38 active individual K awards with laboratory and clinical research projects. The recipients and their projects are:

Rhonda Boyd, Ph.D., Department of Psychology, "Children of depressed mothers; culture and prevention."

Valerie Brown, M.D., Division of Oncology, "Role of mTOR inhibitors and IL7 in lymphoid malignancies."

Jon Burnham, M.D., Division of Rheumatology, "The functional muscle-bone unit in JRA."

Josephine Elia, M.D., Department of Psychiatry, "Genetics of ADHD."

Ricardo Eiraldi, Ph.D., Department of Psychology, "Understanding ADHD in low-income Latino children."

Joel Fein, M.D., Division of Emergency Medicine, "Emergency Department protocol for adolescent suicide."

Cherie Foster, M.D., Division of Neonatology, "Mechanotransduction in alveolar cell development."

Joshua Friedman, M.D., Ph.D., Division of Gastroenterology, Hepatology and Nutrition, "Transcriptional control of liver development."

Adda Grimberg, M.D., Division of Endocrinology, "Role of IGFBP-3 in mediating p53-induced apoptosis."

James Guevara, M.D., M.P.H., Division of General Pediatrics, "Collaborative care approach for children with ADHD."

Fraz Ismat, M.D., Division of Cardiology, "Neurofibromin, ras & NFAT in cardiovascular development."

Andrea Kelly, M.D., Division of Endocrinology, "Pediatric obstructive sleep apnea and metabolic syndrome."

Ron Keren, M.D., M.P.H., Division of General Pediatrics, "Predicting severe neonatal hyperbilirubinemia."

Jake Kushner, M.D., Division of Endocrinology, "Cyclin D2 regulation of islet growth."

Richard Levy, M.D., Department of Anesthesiology and Critical Care Medicine, "Cytochrome oxidase inhibition in septic heart."

Daniel Licht, M.D., Division of Neurology, "Cerebrovascular physiology of infants with CHD."

Bradley Marino, M.D., Department of Anesthesiology and Critical Care Medicine, "Testing the Pediatric Cardiac Quality of Life inventory."

Kathryn Maschhoff, M.D., Division of Neonatology, "The role of Sox11 in cardiac development."

Thornton Mason, M.D., Ph.D., Division of Neurology, "Periodic limb movements in Williams syndrome."

Randolph Matthews, M.D., Ph.D., Division of Gastroenterology, Hepatology and Nutrition, "Genetic analysis of zebrafish biliary mutants."

Yael Mosse, M.D., Division of Oncology, "Genomics of human neuroblastoma."

Jordan Orange, M.D., Ph.D., Division of Allergy and Immunology, "Regulation of cytoskeletal activation of NK cells."

Susmita Pati, M.D., M.P.H., Division of General Pediatrics, "Health care access: maternal child and policy factors."

Brenda Porter, M.D., Ph.D., Division of Neurology, "Neurogenesis in pediatric temporal lobe epilepsy."

David Rubin, M.D., Division of General Pediatrics, "Health and foster care placement stability."

Sulagna Saitta, M.D., Ph.D., Division of Human Genetics and Molecular Biology, "Molecular mechanisms of cardiac outflow tract development."

Michael Sebert, M.D., Division of Infectious Diseases, "Molecular mechanisms of pnemococcal colonization."

Suresh Shelat, M.D., Department of Pathology and Laboratory Medicine, "Immunobiology of heparin-induced thrombocytopenia."

Nicolas Stettler, M.D., M.S.C.E., Division of Gastroenterology, Hepatology and Nutrition, Mentored patient-oriented research career development award, "Energy balance in children with Down syndrome."

Jason Stoller, M.D., Division of Neonatology, Pediatric Physician Scientist Program Award, "Characterization of the role of Tbx1 in DiGeorge/Velocardiofacial syndrome and potential interactions with Nkx proteins."

Rita Valentino, Ph.D., Division of Gastroenterology, Hepatology and Nutrition, "Biogenic amine system, CRF and stress."

Mei-Lun Wang, M.D., Division of Gastroenterology, Hepatology and Nutrition, "Immune modulation of intestinal goblet cell responses."

Theoklis Zaoutis, M.D., Division of Infectious Diseases, "Risk factors and outcomes of candidemia in children."

Huayan Zhang, M.D., Division of Neonatology, Physician Scientist development Award, "Hyaluronan receptors and alveolization."

Joseph Zorc, M.D., Division of Emergency Medicine, "Improving follow-up after an emergency visit for asthma."

Athena Zuppa, M.D., Department of Anesthesiology and Critical Care Medicine, "Improving drug development for the critically ill child."

In addition, Children's Hospital holds two institutional K awards. One, to Physician-in-Chief Alan Cohen, M.D., provides funding for the Hospital's Pediatric Scholars Program. The other, to Charles Stanley, M.D., chief, Division of Endocrinology, provides career development funding in the area of diabetes research.

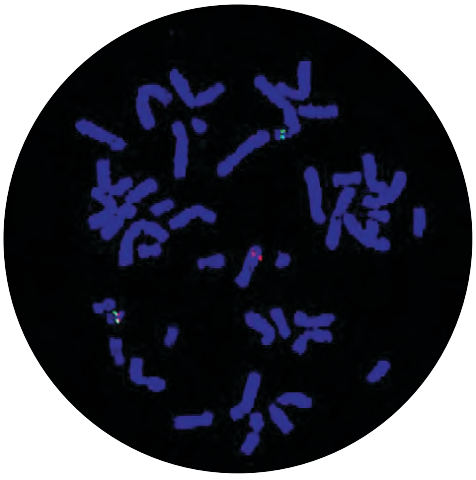
Awards/Recognition

The greatest reward for Children's Hospital investigators comes in knowing that their work — whether in the laboratory, in clinic or in an educational setting — may ultimately improve the health of children throughout the world.

The journey toward that goal may be marked by internal and external honors for Children's Hospital investigators. While all such honors are a testament to the investigators' various achievements, they are too numerous to list. The following are highlights of some of the more prestigious honors and awards bestowed on Children's Hospital investigators during the fiscal year 2005.

1999

Based on Dr. Katherine High's groundbreaking studies on AAV-mediated gene transfer for hemophilia, Dr. Catherine Manno and Dr. Alan Flake perform the first human gene transfer studies for hemophilia B using an AAV vector expressing Factor IX in people with hemophilia.



A fluorescent image of chromosomes from a person with "balanced translocation" that causes Emanuel Syndrome.

Emanuel Syndrome

Genetic Condition Named After Hospital Investigator

Children born with a condition previously referred to as Supernumerary der(22) syndrome (or partial trisomy 11/22) have an extra chromosome. The extra one is made up of parts of chromosome 22 and a part of chromosome 11, carried by one of the parents as a "balanced translocation," a condition in which a person has the right number of chromosomes but two pieces of chromosomes have switched places.

Because of the technical nature and confusion surrounding the various names for the syndrome, and in recognition of her groundbreaking research, parents of affected children petitioned to have the condition renamed Emanuel Syndrome after **Beverly Emanuel, Ph.D.**, chief of the Division of Human Genetics and Molecular Biology at Children's Hospital.

Emanuel Syndrome now has an entry in the Online Mendelian Inheritance in Man, a database of human genes and genetic disorders developed by the National Center for Biotechnology Information.

The extra chromosome in a child with Emanuel Syndrome can lead to mental, medical and physical problems, including cleft palate, heart defects, ear anomalies, genital anomalies in males, low muscle tone and varying levels of mental deficiency.

Dr. Emanuel and her colleagues have studied the risks of recurrence for Emanuel Syndrome in translocation carriers.

They also identified the points on chromosomes 22 and 11 that lead to the genetic rearrangement inherent in Emanuel syndrome and found an unexpectedly high rate of translocations in the sperm of males not affected with the condition. The renaming of Supernumerary der(22) syndrome is testament to Dr. Emanuel's continued achievements and productivity in genetic research. To further propel her renowned efforts in this area, Dr. Emanuel has embarked on an extended sabbatical to bring new ideas and methods to the next phase of her renowned research program on chromosome 22 deletion syndrome. It is her first sabbatical in more than 25 years of service to the Hospital.

Dr. Emanuel anticipates that the skills she hones and information she gathers while on leave will aid her in developing a sequence-based and microarray platform to detect chromosome 22 abnormalities.

During her sabbatical, Dr. Emanuel will attend a refresher course in molecular cytogentics and DNA microarray technology; work with a Holland-based company to develop a better testing kit to detect chromosome 22 abnormalities; and conduct extended work with a Yale University collaborator to learn the tricks of imaging chromosomes undergoing meiosis to investigate why chromosome 22 behaves poorly during meiosis, causing abnormalities.

Prestigious Pew Award Supports Emerging Bioinformatics Field

The body of data about human disease is growing so rapidly in size and complexity that broad associations between research findings and clinical applications are becoming more difficult to establish. Investigators face the daunting task of absorbing and applying information from numerous medical journals and laboratory-generated data. Just 10 years ago the challenge was to generate sufficient data for analysis; today the challenge is to analyze the reams of data that new methods, instrumentation and experiments are producing.

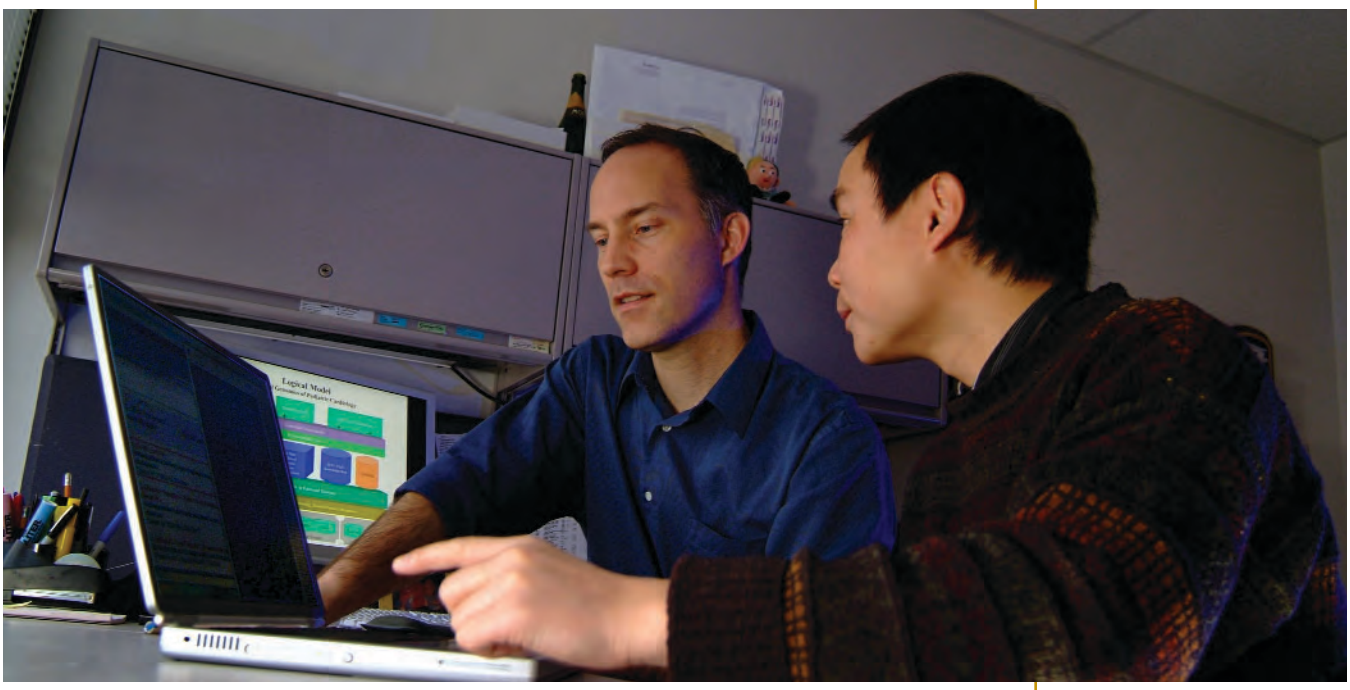
This issue becomes even more complicated when the desired outcome is to connect research findings with patient information. Finding ways to apply biomedical information is one of the nation's top healthcare priorities. The emerging field of biomedical informatics aims to create processes to integrate and use biological and medical information to assist with early diagnoses; increase preventive treatment; produce new and more targeted treatments; provide a more comprehensive understanding of disease processes; and predict the likelihood of disease in families.

Recognizing the importance of the field to the future of research, the Pew Charitable Trusts granted Children's Hospital a $1.3 million, four-year award to launch a pilot program in bioinformatics. The program, led by **Peter White, Ph.D.**, focuses on the clinical genomics of pediatric cardiology.

The cardiology project is an ideal pilot for a number of reasons. First, the recent Human Genome Project opened a new frontier in biology and medicine to link specific genetic information (genomics) with clinically observable disease descriptions (phenomics). In addition, the Hospital's Cardiac Center has conducted pioneering research over the last decade on the influence of genetics on congenital heart disease, and contributed significantly to the Hospital's designation as a Specialized Center of Clinically Oriented Research (SCCOR) in Pediatric Heart Development and Disease.

The Institute's SCCOR program is designed to speed the process by which advances in basic scientific knowledge are translated into innovative treatments for patients. Drawing on talents of multidisciplinary teams is an important feature of the SCCOR program; the Children's Hospital team includes cardiologists, cardiac surgeons and geneticists.

The information generated will help physicians and investigators better understand diseases and, ultimately, lead to improved diagnosis, treatment and prevention strategies.



This team of clinicians and researchers recently demonstrated that many children with specific types of congenital heart disease have a chromosome 22q11 deletion. In a pilot study, the investigators evaluated the operative course of patients with truncus arteriosus. Some of the patients carried a 22q11 deletion and some did not. The preliminary results indicate that the operative course of those with the deletion was notable for a longer period of ventilatory support, intensive care unit and hospital stays than those without the deletion.

The Pew-supported Clinical Genomics of Pediatric Cardiology project will use the Cardiac Center's wealth of genomic and phenomic data to develop the systems and tools needed to create an integrated knowledge base. Clinicians and investigators will then be able to browse, query and analyze data from anywhere in the Hospital's healthcare network — the laboratory, an outpatient clinic or a patient's bedside.

Top of the page: Pete White, Ph.D., with research assistant Haijun Oiu.

1999
The Clinical Trials Office (CTO) is established to facilitate clinical research studies conducted at Children's Hospital.

1999

Children's Hospital becomes one of 13 academic sites designed by the NIH as a Pediatric Pharmacology Research Unit (PPRU). PPRUs are established to conduct studies of drug disposition and action in pediatric patients, and address the lack of pharmacological information about drugs used in children.

Leading the Way in an Emerging Field

Katherine High, M.D., a leading hematology researcher at Children's Hospital and a Howard Hughes Medical Institute investigator, served as the president of the American Society of Gene Therapy (ASGT).

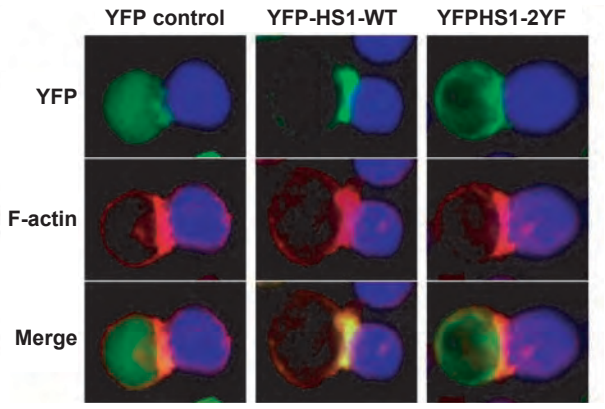
The ASGT is the largest medical professional organization representing researchers and scientists dedicated to discovering new gene therapies, an approach focusing on treating disease by delivering therapeutic genes directly into a patient's cells.

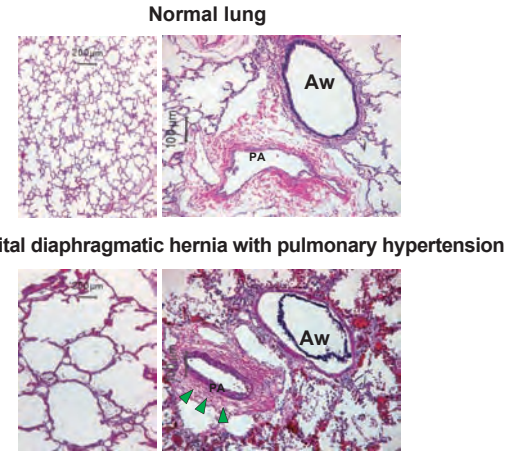
Dr. High began serving her yearlong term on June 2, 2004, at ASGT's annual meeting in Minneapolis. During the meeting, Dr. High also reported the preliminary results of a detailed study of immune responses in a clinical study of a gene therapy approach for treating hemophilia B.

Internal Awards

Through its internal awards programs, the Stokes Institute provides support and recognition to investigators with innovative research ideas and to new investigators embarking on their research careers.

Among these internal awards are the Ethel Brown Foerderer Fund for Excellence and the Florence R.C. Murray Awards, each of which provide one year of support for basic or clinical research projects.





Stokes Institute awarded one of the project grants to **Janis Burkhardt, Ph.D.**, Department of Pathology and Laboratory Medicine, who is investigating how phosphorylation, or adding a phosphate and oxygen group to a protein, affects the protein HS1 — a protein linked to immunodeficiency and autoimmunity — and the structure and function of a closely related protein called cortactin. The researchers are focusing on how this regulation relates to the role of these proteins in cancer and autoimmune disease. In the long run, understanding how HS1 and cortactin are regulated may allow investigators to use them as drug targets for the treatment of autoimmune disease and cancer.

Marcus Davey, Ph.D., Department of Surgery, received a new investigator grant for his project on treatment strategies of pulmonary hypertension in severe lung hypoplasia. The project examines the effects of different drugs on lung blood flow in congenital diaphragmatic hernia, a devastating disease in which the diaphragm fails to form completely and allows abdominal organs to invade the chest cavity and compress the developing lungs. Dr. Davey hopes the research will identify optimal drug therapies for patients with CDH.

Knee cartilage replacement using triglycidylamine (TGA)-Treated Prosthesis

Robert Levy, M.D., Division of Cardiology, received the Foerderer-Murray Innovation Award for his project on cartilage prepared with triglycidyl amine. Dr. Levy hopes to create an artificial cartilage implant to treat knee injuries in children and adults. The key to this strategy involves a novel reagent called TGA, which Dr. Levy and investigators in his laboratory discovered and patented

Dr. Levy and his colleagues originally created TGA for preparing artificial heart valves and are still investigating the use of the reagent for that purpose. If beneficial for preparing artificial knee cartilage, the chemical compound may aid in the development of implants that will restore function and last longer than the therapies currently used to treat knee injuries.

2001

Dr. Beverly Lange and associates devise a strategy that has about a 70 percent salvage rate for recurring acute lymphoblastic leukemia. This has been successful in getting children into remission until another therapy (e.g., bone marrow transplant) is available.

2001

Dr. Scott Adzick, in collaboration with Drs. Charles Stanley and Robin Kaye, performs a partial pancreatectomy, a procedure to cure newborns of focal congenital hyperinsulinism without causing diabetes.

2005 Foerderer-Murray Awardees

Project Grants

Terri Finkel, M.D., Ph.D., Division of Rheumatology, "Lentiviral therapy for acquired and congenital immunodeficiency disease."

Wenzhe Ho, M.D., Division of Allergy and Immunology, "Establishment of infectious hepatitis C virus cell model."

Michael Hogarty, M.D., Division of Oncology, "Global tumor proteomics-applied neuroblastoma."

Weidong Xiao, Ph.D., Division of Hematology, "Gene therapy of hemophilia using split Factor VIII gene."

X. Long Zheng, M.D., Ph.D., Department of Pathology, "ADAMTS13 protease and liver fibrosis."

New Investigator Awards

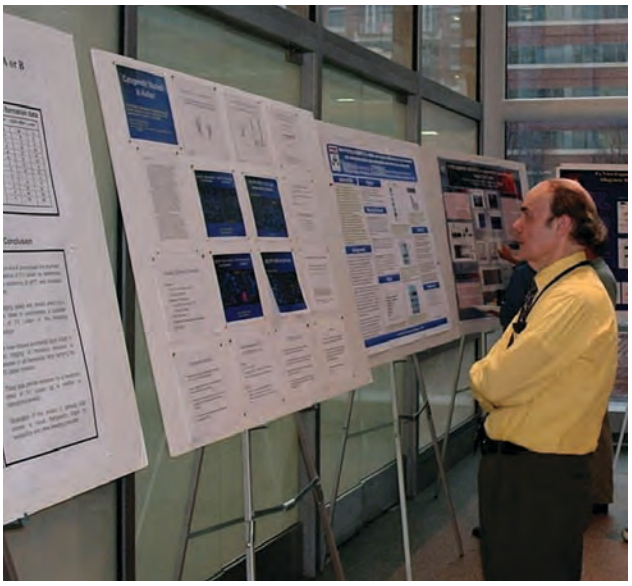
Craig Bassing, Ph.D., Department of Pathology, "The consequences of combined H2AX and ATM inactivation."

Ilia Fishbein, M.D., Ph.D., Division of Cardiology, "Chemically modified adenoviral vectors to bypass receptor-mediated cell uptake for cardiovascular gene therapy."

Stefania Gallucci, M.D., Division of Rheumatology, "Function of CD40 in lupus dendritic cells."

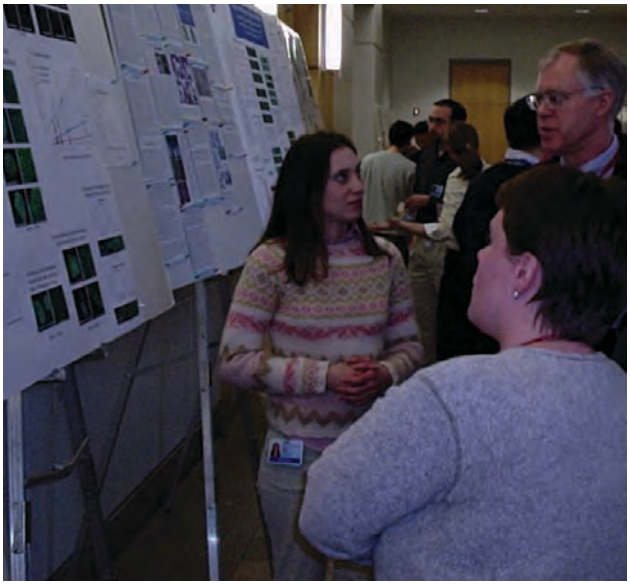
John Germiller, M.D., Ph.D., Department of Surgery, "Analyzing the neurotrophic activity of the early embryonic inner ear."

Adda Grimberg, M.D., Division of Endocrinology, "Factors influencing short stature referrals."



Celebrating Postdoctoral Fellows and Students

As part of its continuous support for training young scientists, Children's Hospital held its 15th annual Children's Hospital/Stokes Institute Fellows' Research Poster Day in February. During the daylong event, graduate students and postdoctoral and clinical fellows showcased their basic, translational and clinical research.



Poster Day attendees review fellows' presentations.

More than 130 abstracts were presented during the event, which was organized by William Fox, M.D., Division of Neonatology, Helen Korchak, Ph.D., Division of Allergy and Immunology, and Roger Wood, director of Research Operations.

The Stokes Institute recognized 19 posters as particularly outstanding. These posters received an award in one of nine categories — clinical, translational and basic research by clinical staff, postdoctoral fellows and predoctoral candidates.

These awards were made possible thanks to an endowment created by Mrs. Mary Hummeler, wife of the late Dr. Klaus Hummeler, the first director of the Stokes Institute.

Fellows' Poster Day Awardees

The awardees and their poster topics were:

Obinna Adibe, M.D., Department of Surgery, "Retrospective comparison of outcomes following open versus laproscopic pyloromyotomy."

Majed Aljamali, Ph.D., Division of Hematology, "Hemostatic effects of long-term expression of activated murine FVII in normal and hemophilic mice."

Pinaki Banerjee, Ph.D., Division of Allergy and Immunology, "Cdc42 interacting protein 4 is a potential link between actin and microtubules at the natural killer cell immunological synapse."

Elsa Bianchini, Ph.D., Division of Hematology, "Ratcheting between two distinct conformations of substrate drives the sequential cleavage of prothrombin by prothrombinase."

Angela Breidenstine, Ph.D., Department of Psychology, "Protective factors in the lives of children experiencing the risks of poverty and maternal depression."

Jin-Wen Chen, Ph.D., Division of Infectious Diseases, "Normal heart development requires cardiomyocyte-specific expression of coxsackievirus and adenovirus receptor."

Michael Chorny, Ph.D., Division of Cardiology, "Injectable adenovirus-polylactide nanoparticle composites for efficient gene transfer to smooth muscle cells (A10) and cardiomyocytes (HL-1)."

Julie Davis, M.D., Division of Cardiology, "Longitudinal assessment of cardiovascular exercise performance after pediatric heart transplantation."

Daniel Delaney, M.S., Division of Urology, "Molecular analysis of the HOX!9 gene in cryptorchidism."

Marco Gonzalez, Ph.D., Division of Child Development and Rehabilitation Medicine, "Regulation of the neuronal glutamate transporter, Eaac1/Eaat3, by caveolae/lipid rafts."

Lisa Meltzer, Ph.D., Department of Psychology, "Sleep and functioning in caregivers of ventilator-dependent children."

Karna Murthy, M.D., Division of Neonatology, "Cathepsin H (CTSH) and Napsin A (NapA) expression during human lung development."

Emily Rowell, B.A., Department of Pathology and Laboratory Medicine, "Opposing roles for the cyclin-depenent kinase inhibitors p18ink4c and p27kip1 in allograft tolerance induced by costimulatory blockade."

Diana Shellmer, Ph.D., Department of Psychology, "Pediatric HIV: effects of adjustment, social support, and disclosure on cognitive and psychosocial functioning."

Amanda Shillingford, M.D., Division of Cardiology, "Inattention and hyperactivity are common 6-11 years after neonatal cardiac surgery."

Jason Stoller, M.D., Division of Neonatology, "Mechanisms of DiGeorge syndrome: characterization of human TBX1 mutations."

David Teachey, M.D., Divisions of Hematology and Oncology, "Unmasking Evans syndrome: T cell phenotype and apoptotic response reveal autoimmune lymphoproliferative syndrome (ALPS)."

Zhi Wang, Ph.D., Division of Neonatology, "Zinc protophophyrin IX inhibits cell proliferation via suppression of cyclin D1 protein synthesis in hepatoma cells."

Mingce Zhang, Ph.D., Division of Rheumatology, "C-maf cooperates with NFAT1 to augment HIV-1 transcription in T-helper-2 CD4 T cells."

Addressing the Needs of Faculty, Trainees and Staff

Whether working in the laboratory or clinic or crunching data in an office, conducting research is a complicated matter, extending far beyond generating a research question, developing a plan to answer that question or mastering a specific technique.

For example, a project like targeting gene therapy to the fetus to treat genetic disorders involves complex regulatory, legal and ethical issues surrounding the conduct of research. Those issues include laboratory safety, confidentiality of specimens and data, the safety of human subjects, publication practices, collaboration, authorship, mentoring and intellectual property.

Success, therefore, means not only getting interesting research results through experimental dexterity, but also managing a research group, mentoring, maintaining relationships with colleagues, and understanding and abiding by the rules for handling data and publishing study results.

Few young investigators receive training in these types of "survival skills," yet failure to understand and comply with government requirements and the expectations of the scientific community can ultimately jeopardize an investigator's career as well as an institution's entire research program. Highly trained, responsible investigators and research staff are imperative to the long-term success of individual investigators and the research institution as a whole.

Rather than pursuing information or training on an individual basis, investigators and clinical and postdoctoral fellows can now participate in a comprehensive program aimed at fortifying their knowledge and understanding of the ethical issues accompanying research.

The Responsible Conduct of Research (RCR) training program teaches and promotes ethical research practices based on regulatory standards. A program for training grant-supported trainees and career award recipients, the RCR program fulfills an NIH training requirement and is offered to all postdoctoral and medical fellows at Children's Hospital.

The RCR program, administered by the Department of Research Education, aims to prevent outright research misconduct, like fabrication of data and plagiarism, as well as questionable behaviors — like the refusal to collaborate — and authorship issues. The Hospital's RCR program, encompassing 10 areas of instruction, is tailored to the Stokes Institute's environment and pediatric research.

2002

The first tandem transplantation of peripheral stem cells performed in a pediatric oncology center.

Page 74 Jodi Leckrone, M.Ed., assistant director, Research Education
Page 75 Research Education Director Wendy Williams, Ph.D.

Initiative Takes Aim at Study-Coordinator Certification

Conducting clinical research is a complex endeavor that involves more than recruiting subjects or administering a questionnaire or experimental treatment. After principal investigators, study coordinators bear the brunt of responsibility for the proper handling of projects that involve human subjects and may be regulated by the FDA. Study coordinators' duties include project initiation, administration responsibilities and budgeting, among others.

However, despite the wide range of responsibilities, formal training for clinical study coordinators has been historically limited to that received on the job or through one-on-one mentoring. Although the federal government does not require training and certification, many institutions — including Children's Hospital — are implementing formal training programs for employees working in clinical research.

The Hospital's Research Compliance Oversight Committee instituted a policy requiring training for all clinical research staff. As a result, the Hospital developed a training and certification program through the Department of Research Education.

Those working on clinical studies now complete the seven-module Clinical Research Coordinator Certification Program, which addresses the regulatory and ethical issues governing research involving human subjects; how to prepare for an audit or monitor a visit; how to initiate and close a study; how to budget a study and how to address regulatory issues that may arise during the course of a study.

The Web-based, interactive program covers institutional policies and procedures and federal regulations. More specifically, the modules — developed by a team of leading study coordinators in conjunction with Research Education, faculty and other staff — address topics such as pre-study activities, clinical and administrative responsibility, and working with the Hospital's Institutional Review Board.

Advanced training modules address Investigational New Drugs and Investigational Device Exemptions, with future modules covering topics such as research ethics and budget development.

Completion of the program ensures that study coordinators successfully manage the many facets of clinical research while protecting the Hospital's most cherished resource — its patients and their families.

2002
Dr. Katherine High is named the Hospital's first Howard Hughes Medical Institute Investigator based on her leadership of research in the area of gene therapy for hemophilia.

Stokes is home to a large number of trainees, among them, undergraduates conducting independent research studies or graduate students conducting thesis research with Hospital investigators. Others are clinical fellows who are receiving training in research as part of their subspecialty programs and are the physician-scientists of the future.

Another important group of trainees is the Hospital's postdoctoral fellows. These trainees, who have completed their Ph.D.s, will spend as long as five years conducting mentored research with investigators at the Stokes Institute before taking permanent positions as faculty or researchers at Children's Hospital or elsewhere. Postdoctoral fellows do not apply for admission to a program; rather, they apply directly to investigators conducting research or using techniques of particular interest to them. This puts postdoctoral fellows in a unique position that requires specialized attention.

The particular needs of the Hospital's expansive postdoctoral fellow community are addressed through the **Office of Postdoctoral Affairs**. Here, mentors receive specialized support for the Hospital's more than 100 postdoctoral fellows, most of whom are from outside the U.S. and encounter immigration-related issues and other hurdles because of their international status.

Enhancing Collegiality, Building a Community

With the rapid growth of the Stokes Institute, flourishing research programs and the continuous recruitment of new investigators, it can be difficult for researchers to stay informed about the work of their colleagues. To remedy this situation, Stokes provides special events to give researchers the opportunity to interact and learn about each other's research.

Nobel Prize winner Michael Brown, M.D., delivers the keynote address at the 2005 Scientific Symposium.

The annual Stokes Scientific Symposium highlights the breadth of the research programs at the Stokes Institute and continues to strengthen the Institute's sense of community. The daylong, off-campus event included 13 presentations from investigators in basic, translational and clinical research, and featured a keynote address by Nobel Prize winner Michael Brown, M.D. In cooperation with Joseph L. Goldstein, M.D., Dr. Brown discovered the low-density lipoprotein (LDL) receptor that controls the level of cholesterol in blood and cells.

The presentations were chosen to stimulate dialogue among investigators. The event also included extended breaks, a group luncheon and a reception to encourage investigators to learn about one another's research and to open the door to greater cross-collaboration.

In addition to the scientific presentations, the Stokes Core Facilities provided displays and presentations to promote their services, new technologies and capabilities available to support and enhance the research efforts of Stokes investigators.

Celebrating Clinical Research

Thanks to the efforts of dedicated volunteers, Clinical Research Week in 2005 recognized the efforts of those involved in clinical research and their many achievements. The week served as an opportunity for all members of the clinical research community — study coordinators, physicians, nurses and psychologists — to share their research and its potential impact on clinical care.

Participants discuss clinical research during the Hospital's first Clinical Research Week.

Richard Behrman, M.D., chair of the Institute of Medicine's Committee on Clinical Research Involving Children, gave the week's keynote address, titled "The Threat to Clinical Research from the Cult of Irrationality."

Events during the week were designed to encourage clinical research, promote careers in the field, and educate the community on topics such as privacy regulations, the essentials to successfully launching a clinical research study, and nursing research. Poster presentations highlighted the results of clinical interventions, changes to standard of care based on research, and descriptions or evaluations of research programs.

The success of both the Stokes Scientific Symposium and the Clinical Research Week ensures that the Stokes Institute will continue to hold such events to enhance the experience of its investigators and to provide a sense of community among its researchers.

Administrative Enhancements

Changes to Support Our Growing Research Enterprise

The Hospital embarked on a new initiative aimed at streamlining procedures for research subjects participating in research studies.

The Clinical Research Processes and Systems Improvement Project aims to ensure all clinical research business processes comply with "best practices," to improve the experiences of principal investigators working in clinical research, and to enhance the quality of service to research subjects and their families.

Improvements made under this pilot project center on several clinical trial elements: correct budget preparation, proper registration of subjects in Hospital systems, appropriate identification of procedures as "research" rather than standard of care, and billing of procedures and account reconciliation.

When fully implemented, streamlining and coordinating clinical research business will enable the responsibility for administrative aspects of studies to be placed on the appropriate Hospital departments. This, in turn, will enhance the experience of patients and allow investigators to conduct research rather than manage administrative steps.

2004

Dr. Ian Krantz leads a team that identifies the gene that causes Cornelia de Lange syndrome, (CdLs) which leads to a genetic test. CdLs symptoms include mental retardation, growth failure, hearing loss, and physical defects affecting the limbs, face, heart, intestines and other structures.

Above: Judith Argon, vice president of Research Administration.

Administrative Changes Lead to Heightened Services

To enhance efficiency and customer service for investigators and research staff, the Stokes Institute consolidated all sponsored projects under a single point of leadership and created a new administrative position to manage these tasks.

As a result, Mary Tomlinson, who distinguished herself as the director of Research Finance, was named as the first vice president of Research Finance and Sponsored Projects.

In her new position, Mary is responsible for pre- and post-award grant management functions, electronic research administration and business management functions related to research accounts.

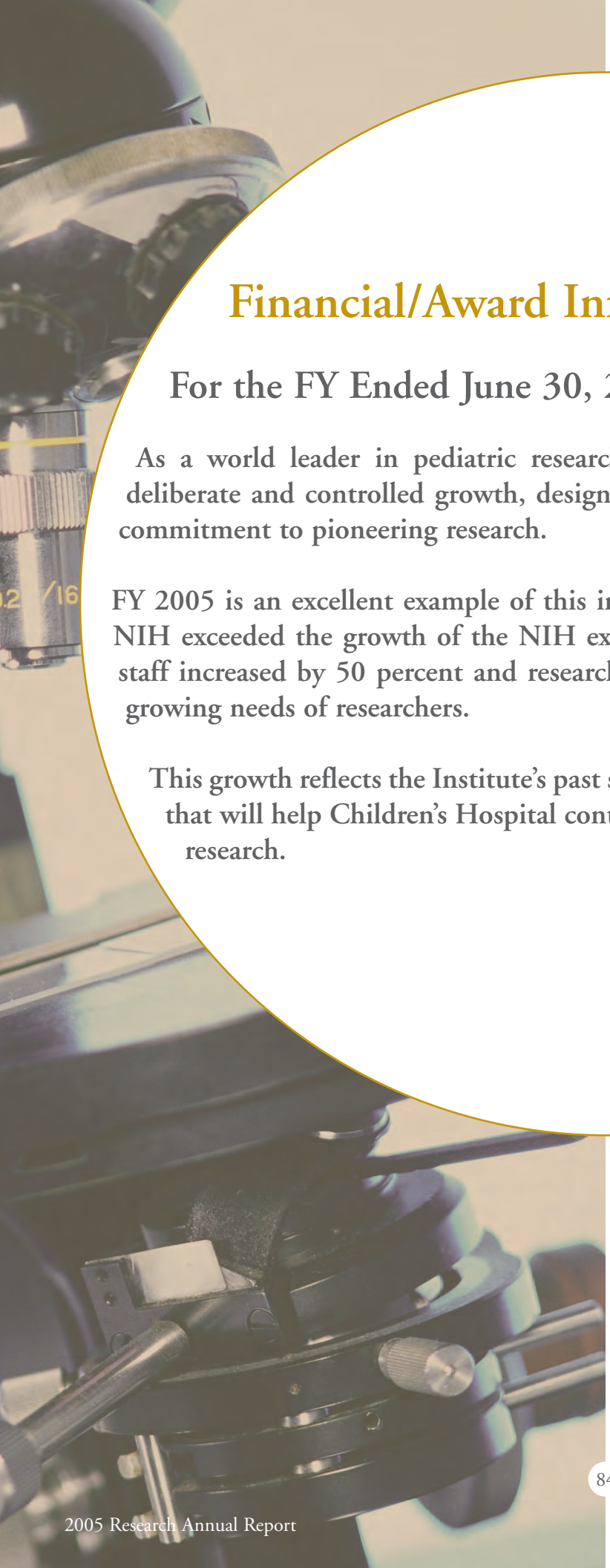
Stokes also united Research Services, including the offices of Grants Preparation and Grants Management, and Research Finance, which includes the Research Business Office, into a single administrative unit.

Steven Wiley, who served as the manager for Research Accounting for 11 years, now serves as the director of Research Finance. Sara Dubberly, who previously served as the manager of the Research Business Office, serves as director of Sponsored Programs.

Above: Director of Research Finance Steve Wiley.
Page 83 (left to right): Director of Sponsored Projects Sara Dubberly and Mary Tomlinson, vice president of Research Finance and Sponsored Projects.

2005

Supernumerary der(22) syndrome (or Partial Trisomy 11/22) — a genetic condition characterized by an extra chromosome made up of parts of chromosome 22 and a part of chromosome 11 — is renamed Emanuel Syndrome in honor of Beverly Emanuel, Ph.D., chief, Division of Human Genetics and Molecular Biology, who spearheaded research efforts into the syndrome.



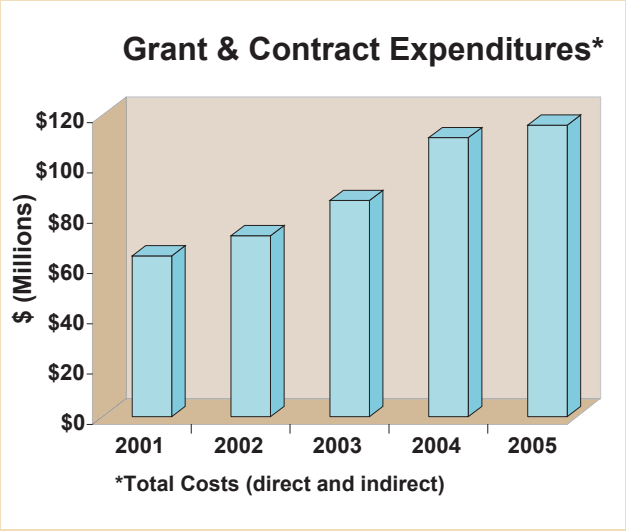
Financial/Award Information

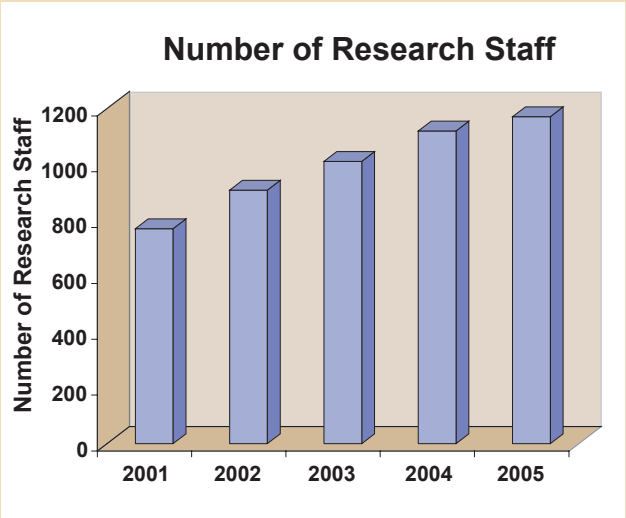
For the FY Ended June 30, 2005

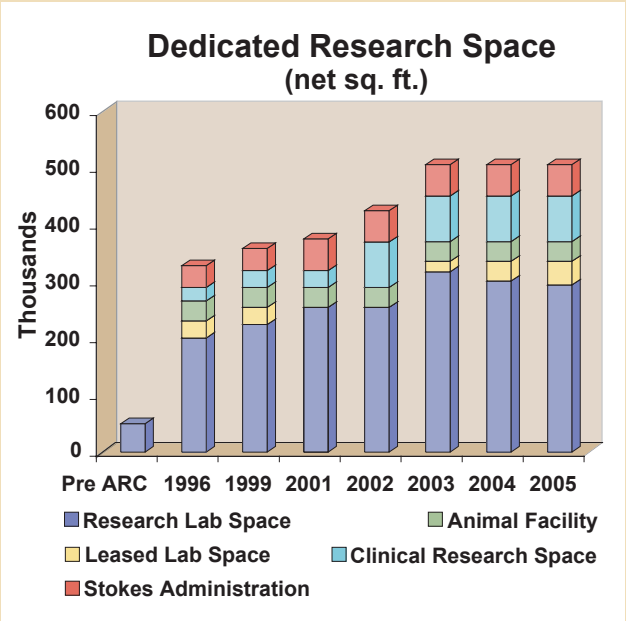
As a world leader in pediatric research, Children's Hospital is dedicated to deliberate and controlled growth, designed to strategically expand the Institute's commitment to pioneering research.

FY 2005 is an excellent example of this impressive growth. Grant awards from the NIH exceeded the growth of the NIH extramural budget, the number of research staff increased by 50 percent and research space continues to expand to meet the growing needs of researchers.

This growth reflects the Institute's past successes and fuels the pioneering spirit that will help Children's Hospital continue to be a world leader in pediatric research.







2005

Dr. Vivian Cheung identifies genomic regions that contain the transcriptional regulators for about 1,000 genes. These results provide a better understanding of transcriptional regulation in human cells and may be applicable for discovering the genetic basis of other complex human traits and diseases.

Gifts and Awards for Research from Private Sources

$1,000,000 or more

Anonymous (1)
State Farm Insurance Companies

$100,000 — $999,999

Anonymous (2)
The W. W. Smith Charitable Trust
The Pew Charitable Trusts
Friends of Trisomy 21 Center
Muscular Dystrophy Association, Inc.
The Philadelphia Foundation
Craig-Dalsimer Fund
Alex's Lemonade Stand Fund of
The Philadelphia Foundation
Genzyme Corporation
Juvenile Diabetes Research Foundation
Foundation for Anesthesia
American Society of Clinical Oncology
American Heart Association
Amylotrophic Lateral Sclerosis Association
Epilepsy Foundation
National Multiple Sclerosis Society
Mr. and Mrs. Robert J. Edmunds

$25,000 — $99,999

American Cancer Society, Inc.
Child Neurology Foundation
Eastern States Hyundai
Philadelphia Insurance Companies
Heineman Foundation
The Valerie Fund
Madelyn Bucksbaum Adamson and Allen Adamson
American Diabetes Association
American Epilepsy Society
American Liver Foundation
Lola Ervien Douglass Fund of
The Philadelphia Foundation
Louis Callmann Goldschmidt
The Childhood Brain Tumor Foundation
PhRMA Foundation
American College of Surgeons
National Sleep Foundation
Comprehensive Consulting Solutions
Cooley's Anemia Foundation
First Hospital Foundation
Hope Street Kids
Mr. and Mrs. John C. Haas
Caesars Atlantic City
Caitlin Robb Foundation
Citizens United for Reseach in Epilepsy
Daniel Patrick Sullivan Foundation at Fidelity
Charitable Gift Fund
Mr. Duane D. Deaner
F. and B. Berman Family Foundation Inc.
Goldman Philanthropic Partnerships
R & B Inc.
The Schulman Foundation

$10,000 — $24,999

Lincoln Financial Group
Kayla's Hope for Kids
National Neurofibromatosis Foundation Inc.
Friedreich's Ataxia Research Alliance
Wawa Inc.
Eagles Fly for Leukemia Inc.
Safe Kids Coalition of Southeastern PA
The Evan T.J. Dunbar Neuro-Blastoma Foundation
University of Pennsylvania
Merck Partnership for Giving Campaign
Alexander Graham Bell Association
Capita Foundation
Goerlich Family Foundation Inc.
L.I. Maternal Fetal Medicine P.C.
National Organization for
Hearing Research Foundation
Cornelia de Lange Syndrome Foundation Inc.
Philadelphia Chapter of Credit Unions
The William Penn Foundation
United Way of Kitsap County
To Our Children's Future With Health
Davis Cup Golf Tournament
United Way of Tri-State Inc.
Indian Valley Middle School
A.L.M. Lubrications Inc.
Advanta Foundation
American Academy of Otolaryngology
Dr. and Mrs. Toshio Asakura
Commerce Bank
Mr. and Mrs. Harry G. Hayman III
Irwin Homer Breslow, M.D.
Nursing Scholarship Fund
Ms. Judy Jamison
Pediatric Endocrinology Nursing Society
The Starner Spitalny Memorial

$5,000 — $9,999

H & R Auto Radio Service, Inc.
Ballard Spahr Andrews & Ingersoll, LLP
National Hemophilia Foundation
Prudential Fox & Roach Realtors
Friends of Vinnie
JulieDance Inc.
Orthopaedic Research and Education Foundation
Phoebe W. Haas Charitable Trust "A"
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Order of the Golden Chain Charity Foundation
Build A Bear Workshop Foundation, Inc.
Mr. and Mrs. Kevin D. Scarborough
Bayer Healthcare
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Blank Rome Comisky & McCaule, LLP
American Society for Parenteral
Mr. and Mrs. Daniel Austin
Mr. and Mrs. Louis Bucksbaum
Mr. and Mrs. Dominic J. Caruso
Greatworld Inc.
Mr. and Mrs. Thomas J. Hughes
Kristin & William Loomis Foundation
Ms. Carol Levitt
March of Dimes Philadelphia Chapter
Rosario's Restaurant
The Harold Wetterberg Foundation
WPVI-TV
Ms. Ellen C. Wolf and Mr. Richard A. Harris

$1,000 — $4,999

Ms. Elaine Breslow
United Way Miami-Dade Inc
Christine's Kids
Kane Builder's Inc.
RBC Dain Rauscher
Ventiv Health U.S. Sales
Philadelphia Main Line Alumnae Chapter
Mrs. Herbert Sarvetnick
Mr. and Mrs. John M. Strotbeck
Carlson Shared Services
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D'Ignazio's Towne House
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Philadelphia Coca Cola Bottling Co.
Q.E.D. Communications Inc.
Sol Goldman Charitable Trust
Mr. and Mrs. Robert Tallon
TargetRx Inc.
Mr. and Mrs. Thomas J. Conroy
Springfield Township Hockey League
Kanoski & Associates
Public Financial Management, Inc.
Callan, Koster, Brady & Brennan, LLP
Dr. and Mrs. Timothy K. Hart
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Pretzel & Stouffer Chartered
Subaru of America Foundation Inc.
Atlantic City Hockey, LLC
Penn's Town Properties
Mr. and Mrs. John W. Pollard
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Mr. Duncan A. Haas
Interboro High School
Mr. Edward D. Ohlbaum
Phillies Charities
Radian Guaranty Inc.
SHS North America
The Craigmyle Foundation
The Ryan Foundation Inc.
US Airways Pilots Union and Families
The Philadelphia Flyers
Dance for the Kids
Montgomery County Intermediate Unit
The Prudential Foundation Matching Gifts Program
Hamilton High School West
United Way of Camden County
Bessie Garber - Philadelphia Link 33
Mr. Robert J. Blink
Cross Atlantic Capital Partner
Dr. Jeffrey A. Fine Associates, P.C.
Embassy Suites Hotel and Employees
Franklin Homeowners Assurance Company
Merrill Lynch Pierce Fenner & Smith Inc.
Orleans Corporation
Pepper Hamilton, LLP
Premiere Conferencing
Ross Family Fund
The Coca-Cola Bottlers' Foundation
Mr. and Mrs. William C. Davis

Gifts and Awards for Research from Private Sources

$1,000 — $4,999

Physicians Pharmaceuticals Inc.
American Academy of Pediatrics
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Delta Delta Delta Sorority, Psi Chapter
Mr. and Mrs. Paul K. Brantley
The Baldwin School
21 Down
Mr. and Mrs. David Altman
BJNB Foundation
Ms. Cathleen M. Bannigan
Ms. Laura B. Barness
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Ms. Melissa Bhatnagar
Ms. Kathryn I. Buckley
Burns Pontiac/GMC
Callahan, McCune & Willis
Carousel Toyota/Hyundai/Suzuki
Castle Dealerships
Colonial Cadillac/Sterling
Colonial Hyundai
Dodge Chrysler City
Fred Beans Ford/Lincoln/Mercury/Isuzu
Hyundai of Springfield
Hyundai of Turnersville
Mr. and Mrs. Ronald S. Kierpa
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Mr. And Mrs. James J. Maguire Sr.
Marshall, Conway & Wright, P.C.
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Mr. and Mrs. Jay Ochroch
Pacifico Hyundai
Mr. and Mrs. J. G. Popper Jr.
Porter Chevrolet/Hyundai
Quality Mercury/Hyundai, Inc.
Raymond James Charitable Endowment Fund
Mr. and Mrs. Peter A. Rohr
Mr. Carlo Rondina
Saul & Eleanor Lerner Foundation Inc.
Savage Hyundai Inc.
Secrest, Wardle, Lynch, Hampton
Shaddox, Compere, Walraven
Mr. Henry D. Smith
Sport Hyundai/Dodge
Susanna Delaurentis Charitable Foundation
Sussman Honda
Mr. and Mrs. Joseph Tarditi
The Citizens National Bank
The William J. & Dorothy K. O'Neill Foundation
William Guy Forbeck Research Foundation
Wilmington Trust of Pennsylvania
Winner Hyundai

Who's Who at Stokes in 2005

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Chief Scientific Officer and Senior Vice President, Director of The Joseph Stokes Jr. Research Institute

Virginia A. Stallings, M.D.
Deputy Director, Clinical Research

Judith Argon
Vice President, Research Administration

Mary Tomlinson
Vice President, Research Finance and Sponsored Projects

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R. Anderson Pew
Phillip S. Schein, M.D.
Salem D. Schuchman
James M. Steven, M.D.
Frank E. Weise III

Research Operations

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N. Scott Adzick, M.D.
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Judith Argon
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Bryan Wolf, M.D., Ph.D.

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Yair Argon, Ph.D.
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Who's Who at Stokes in 2005

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Laureen Kotzer, Pharm.D.
Stephen Leff, Ph.D.
Jennifer Long, M.S, M.J.
Roger Marsh, Ph.D.
Oscar Mayer, M.D.
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Chuck Scott, Ph.D.
Jennifer Smith, M.D.
Tyra Bryant-Stephens, M.D.
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Leonard S. Buchoff, Ph.D.
Shirley Bonnem
Avital Cnaan, Ph.D.
Kim Davis, M.A.
Jacquelyn Evans, M.D.
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