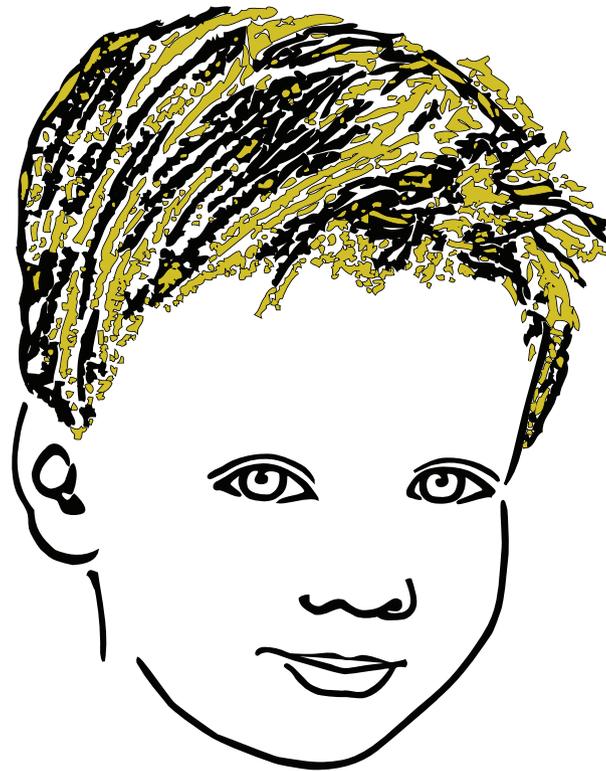


Building a Lasting Legacy
2008 Research Annual Report





Friends -

Our vision is simple, straightforward, and powerful: we will be the preeminent institution in the world dedicated to translational research for children. This vision drives everything we do on a daily basis at the Stokes Institute — from our cutting-edge research program to our focused administrative services.

But beyond our daily activities and fiscal year blinders, this compelling vision provides us with an opportunity to leave a lasting legacy for our patients and their families. What we do today will make a real difference tomorrow.

With those thoughts in mind, the theme of this year's report is legacy.

The legacy we leave extends far beyond state-of-the-art translational research and world-class care for children. Our legacy is evident in how we share our discoveries with the community at large and foster further scientific queries and collaboration. You can see it in our commitment to sharing our knowledge and skills with the next generation of investigators. And it's there when you look at our dedication to innovation, our way of always thinking "outside the box."

In essence, we strive to leave a legacy of vision, innovation, and promise for children in what we do every day. This is who we are, what we do. This is what inspires us and keeps us moving forward, even in the face of adversity.

This is our legacy. We are honored that you are part of it.

A handwritten signature in black ink that reads "Philip R. Johnson".

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

A handwritten signature in blue ink that reads "Tristram C. Colket Jr.".

Tristram C. Colket Jr.
Chair, Translational Medicine and
Science Committee

A handwritten signature in red ink that reads "Steven M. Altschuler".

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

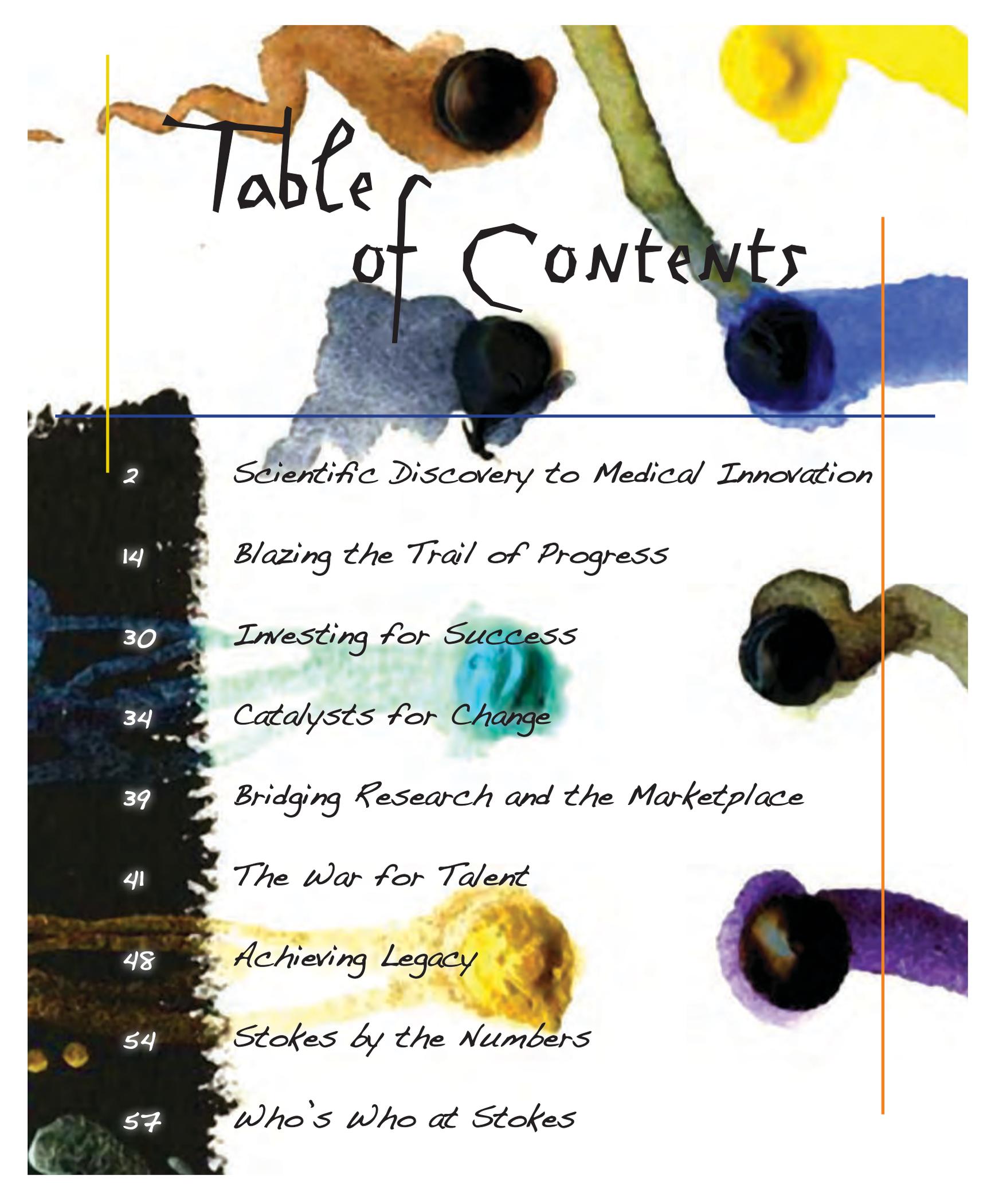


Table of Contents

2

Scientific Discovery to Medical Innovation

14

Blazing the Trail of Progress

30

Investing for Success

34

Catalysts for Change

39

Bridging Research and the Marketplace

41

The War for Talent

48

Achieving Legacy

54

Stokes by the Numbers

57

Who's Who at Stokes

Scientific Discovery to Medical Innovation

Causes and Care: Completing Autism's Complex Picture

Few events in life top the joy of welcoming a baby into the family. A tiny bundle comes with immense hopes, aspirations, questions, and worries for parents, many of whom celebrate a child's every developmental milestone: small hands grasping larger fingers, the endearing sound of a baby babbling and cooing, a child looking lovingly and innocently into a parent's eyes, first crawls, first steps, first words.

Parents' questions and worries mount when children fail to reach certain developmental milestones, or reach a mark as expected only to later regress. The developmental disabilities collectively referred to as autism spectrum disorders (ASDs) are characterized by lack of social play, diminished communication skills, and other unique, telltale behaviors.

ASDs have dozens of forms and affect an estimated 1 out of 150 children, making them among the most diagnosed developmental disorders in the United States. The prevalence of ASDs has led to many questions and increased attention and scrutiny from the scientific community and parents, as well as the media.

Questions For Our Doctor:
What causes autism? Is it purely genetic?
Why are some children more severely affected than others? Is it treatable?
Can anything be done to lessen the symptoms?
What services are available?
How can doctors and support staff help those with autism reach their potential?



Bob Schultz

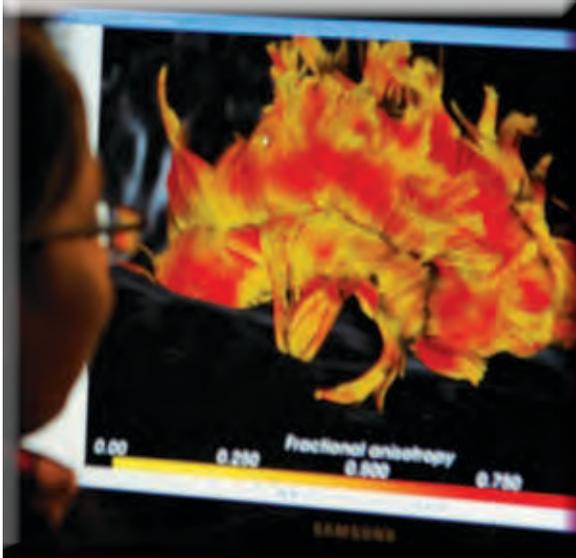
Led by Robert Schultz, Ph.D., the Center for Autism Research (CAR) studies the myriad of potential causes of ASDs, exploring them from every angle. CAR's programs and research stem from the belief that understanding the causal mechanisms — some of the pieces in autism's vast and complex puzzle — will lead to enhanced treatments for affected children and their families.

A new Center of Emphasis at the Stokes Institute, CAR has established a broad multidisciplinary research program to discover the causes of ASDs, spanning the bench to the bedside. At the heart of the center's efforts are research programs focused on the developmental, neurobiological, and genetic mechanisms of ASDs, with a particular emphasis on understanding the individual differences across the spectrum.

Investigators from Children's Hospital and the University of Pennsylvania collaborate to look into the current standard of care for patients with an ASD and test the effectiveness of promising new treatments.

Through such a multifaceted approach, a more concrete picture emerges of the spectrum disorders, their causes, and potential treatments and interventions.

Imaging the Early Features and Mechanics of Autism



Until very recently, autism investigators typically had a retrospective focus — looking at what an affected child was like at some point in the past and honing in on the earliest features of autism to determine how the disorder unfolds. Parents who have one child with autism have up to a 20 percent chance of having another child on the spectrum, making early detection and intervention key. Using imaging techniques to study brain development in autism is a primary research focus of Dr. Schultz, who holds the Hospital's Regional Autism Endowed Chair, and serves as president of the International Society for Autism Research.

Although research has begun to clarify what the brain looks like in children, adolescents, and adults with ASDs, few studies have been done in infants during the window of time when the disorder is emerging. By looking at the behaviors and developing brains of siblings of affected children during the siblings' risk period for developing an ASD — 6 to 24 months of age — Dr. Schultz and his colleagues clarify the earliest biological features, seeing how the brain develops and relating abnormal growth patterns that emerge over time to the gradual onset of behavioral symptoms.



"The earlier and more intensively we can intervene, the better the outcome," says Dr. Schultz. "So, for numerous reasons it's essential for the center to focus on infants. It would be phenomenal if, using something as simple as a brain scan, we could predict which children will need the most intensive interventions."

Dr. Schultz and Sarah Paterson, Ph.D., who directs several infant studies at CAR, are also systematically examining the brains and behaviors of newly diagnosed toddlers to further clarify the essential mechanisms that cause autism. This involves a longitudinal study, whereby investigators conduct detailed behavioral studies coupled with multiple neuroimaging studies during the preschool years to begin to untangle cause and effect and identify the developmental trajectories of the various forms of the disorder. Gaining more in-depth knowledge of the forms of ASDs will eventually lead to better-targeted treatments.



Related to the toddler study, CAR has established a regional service network that includes Children's Hospital, the University of Pennsylvania, Drexel University, intermediate units, and healthcare providers. This network allows investigators to disseminate information about ASDs quickly, coordinate services, identify children to study, and train the next generation of autism investigators.

Dr. Schultz's research also includes a cognitive neuroscience program that uses functional magnetic resonance imaging (fMRI) to look at brain-behavior relationships in children. At the heart of this program of research are studies on what is referred to as the "social brain" — processes that allow individuals to relate to each other in a reciprocal manner.

Because social deficits are at the core of what it means to have autism or an ASD, Dr. Schultz and his colleagues are studying intensively how children on the spectrum use and understand social signals. A significant aspect of this work involves using fMRI to measure the brain anatomy and function in a distributed network of areas that make up the social brain. Dr. Schultz is internationally renowned for this area of work, as he and his team have been able to characterize the brain networks responsible for the social problems that affect kids with ASDs.

New studies are looking at changes that may occur as children with autism develop and, in some cases, as their condition improves with age. One aspect of this work focuses on teaching children to read facial expressions — something that ordinarily is very difficult for those with an ASD.

Dr. Schultz also uses the newest MRI-based technologies to measure connections in the brain. He uses a process called diffusion tensor imaging to get a picture of the axonal connections, or the wires of the brain. New findings in genetics as well as MRI findings are pointing to ASDs as being fundamentally a problem of brain connectivity. Dr. Schultz finds that brain areas involved in social perception and social thinking are generally wired abnormally and function abnormally as a result.

"One of the most prevalent models of autism right now centers on connections — the fact that some parts of the brain are overconnected and some are underconnected," Dr. Schultz says. "Being able to look at the structure and the connections is a tremendous advantage to autism research and may lead to earlier and more effective treatments and interventions."

Creating Maps to Explain Language Deficits of Autism



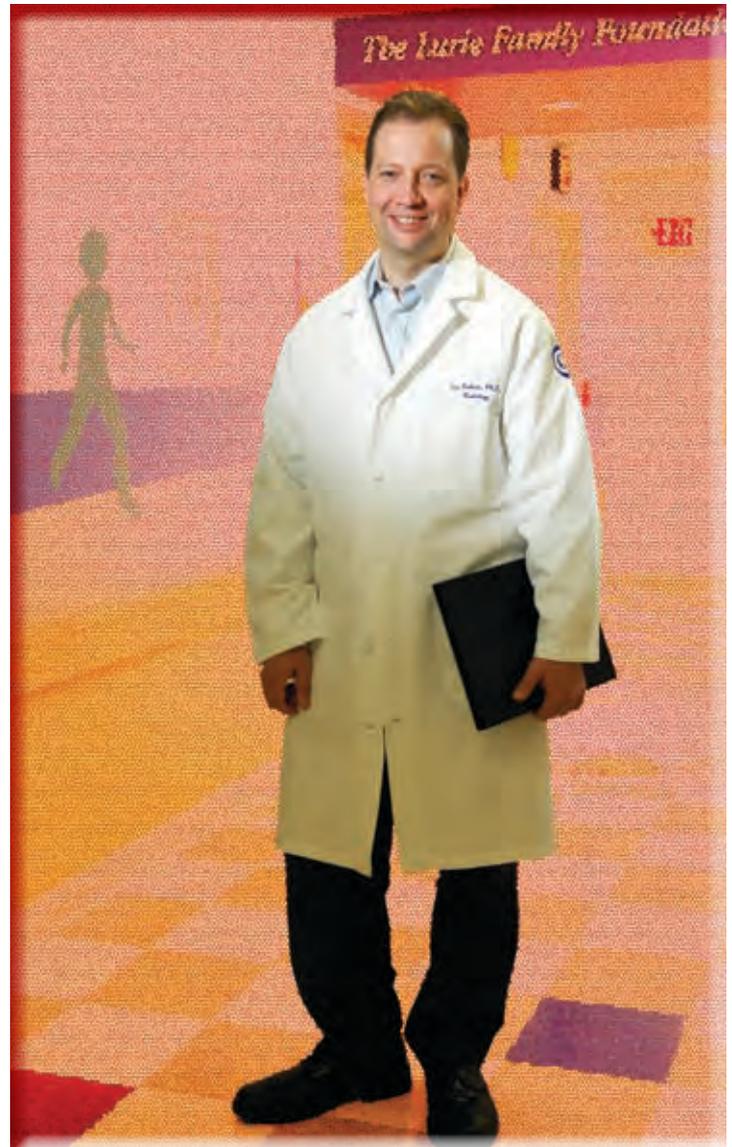
Language impairment is a common feature of autism and ASDs. Defined by a reduced cognitive capacity for speech and nonverbal communication, investigators believe language impairment may be the result of fundamental deficits within the brain's computational linguistic system.

Similar to Dr. Schultz, Timothy Roberts, Ph.D., vice-chair of research for the Department of Radiology and holder of the Oberkircher Family Endowed Chair in Pediatric Radiology, uses imaging to study children with autism. Dr. Roberts uses a state-of-the-art imaging technology — magnetoencephalography, or MEG — to focus on the communication deficits children with autism often experience.

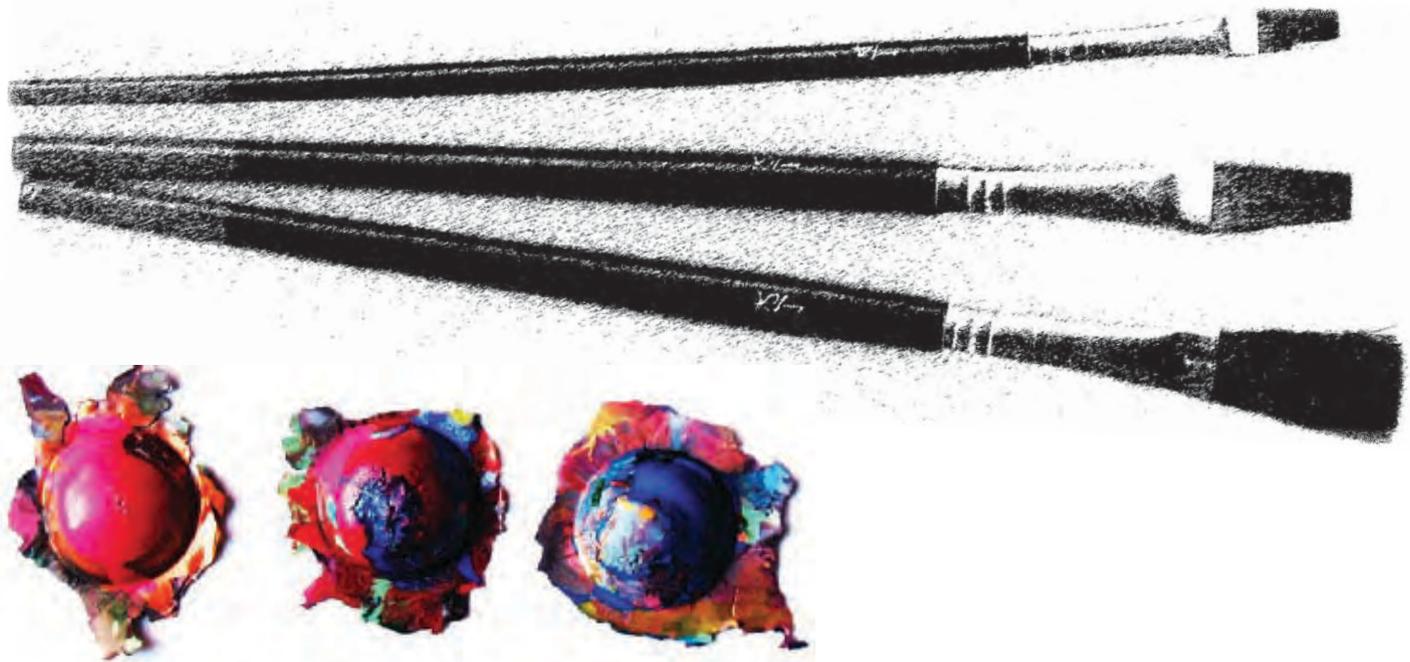
MEG provides real-time visualization and mapping of electrical activity in the brain with high temporal and spatial resolution. A generous donation from Jeffrey and Christina Lurie and Nancy Lurie Marks as part of the new Lurie Family Foundations MEG Imaging Center helps support Dr. Roberts' MEG research. In addition, their support has funded the commission of the first neonatal MEG to be used in a clinical setting. The Hospital will receive the new MEG in 2009.

As the severity of autism or ASDs can vary by child, so too can the severity of autism-associated language impairment, which can range from undetectable to speech-debilitating.

MEG imaging allows Dr. Roberts and his colleagues to identify and differentiate between the electrical "signatures" that underlie language impairment in the brains of autistic children and unaffected children.



"By comparing autistic and non-autistic children with normal speech we can gain more insight into the electrophysiological nature of language impairment," says Dr. Roberts, whose research is supported by a five-year, \$1.25 million grant from the National Institutes of Health as well as a gift from the Luries and Mrs. Marks.



Dr. Roberts' clinical studies involve monitoring the brain function of children with autism and unaffected children while they are exposed to a variety of auditory or speech stimuli. Changes in the electrical brain signatures in response to these stimuli allow for in-depth analyses of brain activity and a comparison between groups.

Language impairments seen in children with autism may stem, in part, from timing and communication difficulties among neurons in the brain; MEG provides a unique technology to track those signals within the brain, with real-time speed.

"Understanding the magnetoencephalographic responses of the autistic and non-autistic brain to auditory stimuli could provide a novel diagnostic tool for language impairment and greatly enhance our understanding of language cognition and physiology," says Dr. Roberts. "This understanding may also provide insight into the similarities and differences between the brains of children with autism spectrum disorders and other neurodevelopmental disorders."



Identifying Genetic Markers, Advancing Autism Research Worldwide

Hakon Hakonarson

The Center for Applied Genomics (CAG) at Children's Hospital continues its quest to find the genetic causes of common childhood diseases, including autism. Under the direction of Hakon Hakonarson, M.D., Ph.D., CAG recently used highly automated microarray technology to analyze 4,500 blood samples gathered by the Autism Genetic Resource Exchange (AGRE), the first collaborative gene bank for autism.

Dr. Hakonarson and his colleagues in CAG generated genotypes — based on a compilation of 550,000 genetic markers for each person — on the AGRE samples and contributed the genotyped data to the group so the scientific community worldwide can better study the genetic causes of autism.

By studying patterns of variation in those genotypes, researchers using the AGRE resources will be able to discover and investigate multiple genes that may contribute to autism. The high-density genotype data generated by CAG are expected to lead to novel insights into a genomic landscape of autism and other neurodevelopmental disorders.

Drawing on data from AGRE's open-access database, researchers from multiple institutions have previously published more than 120 scientific papers on the genetics of autism. The genotypes enhance AGRE's services to investigators across the globe by complementing and extending the genotype data made available by other research teams.

"The contribution will facilitate autism research at Children's Hospital as well," says Dr. Hakonarson.

"Investigations using AGRE's data repository will complement our own comprehensive research and clinical programs in autism, aimed at finding the causes and cure for this devastating disease."

Community Intervention,
Public Policy
Driven by Research

David Mandell



Research in the laboratory and clinic has dramatically increased the understanding of ASDs, and has led to promising treatments for these puzzling disorders. Some interventions aimed at improving socialization and communication and reducing problem behaviors have been found to be effective under controlled conditions. These interventions, however, are rarely used in the community-based education and behavioral health systems where most children with autism receive care.

It is not clear what types of policies, training, support, and other resources are needed to ensure that these programs are effective in real-world settings. A growing body of research points to large disparities in the availability of services within Pennsylvania and across the country.

CAR Associate Director David Mandell, Sc.D., aims to level the playing field and enhance the availability, consistency, and quality of services children with autism receive.

Dr. Mandell and his colleagues are conducting the largest study to date of an educational intervention for children with autism. Through a novel partnership with the School District of Philadelphia, the investigators are looking at applying approaches that have proven effective in more controlled settings.

Some of the teachers in the school district's more than 50 kindergarten through second grade autism-support classrooms will be trained to implement the Strategies for Teaching Based on Autism Research program; others will receive intensive training and coaching in the structured teaching method the school district typically uses. The investigators will then assess which program leads to better academic, social, and behavioral outcomes for children in these classrooms.

"This study comes at a critical time, since many states are developing autism intervention programs in schools despite the lack of evidence that the programs are effective," says Dr. Mandell. "Through this unique partnership with the school district, we can help educators implement proven-effective programs to change the quality of instruction children with autism receive. The most important questions this study answers will not be 'which program works better' but rather, 'what works best for which children under what circumstances,' and 'what kind of support must we provide to teachers and schools to make sure that children receive quality instruction?'"

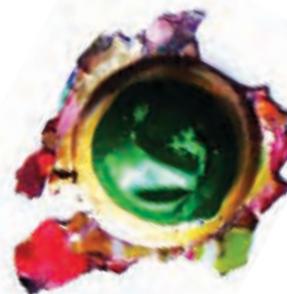
Dr. Mandell's efforts to enhance the services available to children with ASDs are not limited to the educational system. His work extends to improving services in the commonwealth of Pennsylvania, and policies and practices guiding autism-related services nationwide.

In Pennsylvania, Dr. Mandell and his colleagues in CAR recently received funding to support an Autism Services, Education, Research and Training (ASERT) Center. The center will act as a regional resource for families, diagnosticians, and interventionists working to improve the quality of care and quality of life for people with ASDs.

The ASERT grant allows investigators to assess the needs for and barriers to care; identify gaps between research findings and current practices; strengthen the service system for underserved groups; create a centralized resource for families and professionals; and train professionals to use evidence-based practices for diagnosing, assessing, and caring for those with ASDs.

At the national level, Dr. Mandell is looking at state policies and publicly funded healthcare use among children with autism, which can involve intensive, costly, and sometimes controversial approaches. Some estimates suggest that Medicaid-enrolled children with ASDs have nine times the healthcare expenditures of other children receiving Medicaid.

The quality and types of care children with ASDs receive often varies from state to state and from county to county. Dr. Mandell and his colleagues are analyzing state policies and publicly funded healthcare use among children with autism, with the aim of developing an exemplary set of state policies to guide autism practice.



"Children with autism vary tremendously in their needs, so we should expect differences in the care they receive. Problems arise, however, when that variability is driven by local policies, practices, and available resources, rather than the needs of children and their families," says Dr. Mandell. "We hope that this study will help local jurisdictions and states understand the consequences of their policies and practices, and offer them a template for improving the quality of care children receive."





Coordinating Clinical Care Supporting Research

Susan E. Levy

The Hospital's Regional Autism Clinic, which provides comprehensive, family-based care for children with ASDs, is now a member of the newly established CAR. In addition to its clinical services, the Regional Autism Clinic collaborates in numerous research studies at Children's Hospital and the University of Pennsylvania, including a large national multicenter study dedicated to examining risk factors and causes of autism.

Susan E. Levy, M.D., founded the clinic in 1999 after it became apparent that ASDs were more common and complex than previously thought, and that families of children with ASDs required more comprehensive care. In less than a decade, the Regional Autism Clinic has seen more than 3,000 children with some type of ASD and provided comprehensive evaluations and services from specialists in the fields of developmental and behavioral pediatrics, nursing, social work, psychology, occupational therapy, and speech therapy.

Following the establishment of CAR in 2007, all research activities regarding autism and ASDs fell under CAR's auspices. Dr. Levy and her colleagues work closely with other CAR investigators to facilitate their investigations. In return, the Regional Autism Clinic has established a formal and critical role within CAR, rapidly and efficiently unifying autism research at Children's Hospital.



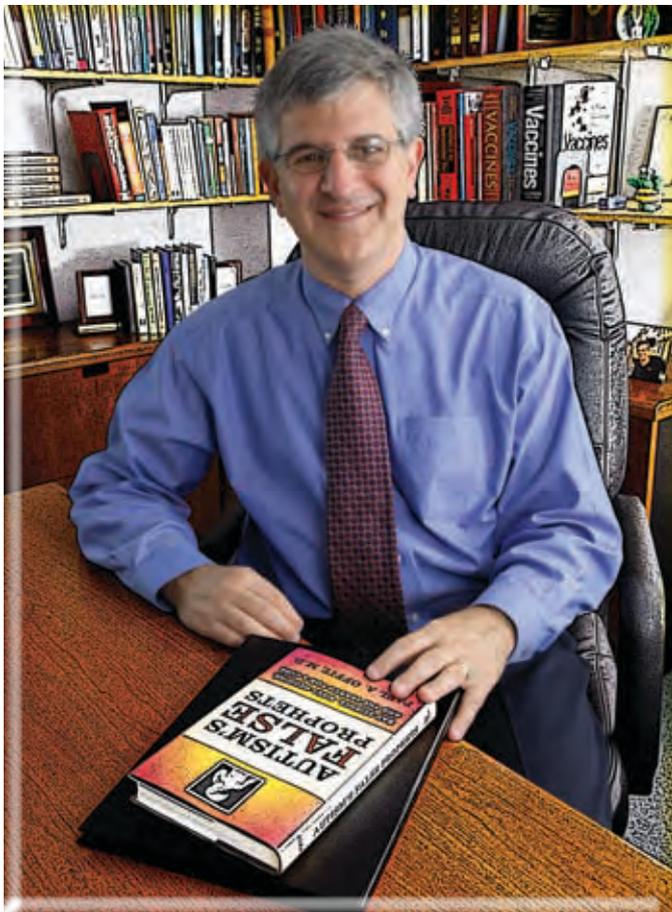
In 2001, the Regional Autism Clinic, with the University of Pennsylvania School of Nursing, received a grant from the Centers for Disease Control and Prevention (CDC) to establish a center for excellence for autism surveillance and research. This multicenter study looks at the prevalence, risk factors, and causes of autism in young children. Dr. Levy and her colleagues investigate risk factors and causes of autism in children 2 to 5 years of age. The six sites of the CDC study are investigating three groups of children, including children with autism, children with developmental delays, and a control group. After data collection, the investigators will have about 1,000 children in each group, making it the largest study of its kind looking at autism and its risk factors.

“Right now, we only know about 10 percent of the specific causes of autism, despite all the theories out there on potential causes. The speculation about causes sometimes results in unusual — and sometimes unorthodox — treatments that have not been adequately studied,” says Dr. Levy. “Understanding more about the causes and risk factors of autism will help us determine what might be done to prevent ASDs and what could be done to more effectively treat them.”



“Investigators at Children’s Hospital and the University of Pennsylvania who are interested in conducting autism research come through CAR for the support and coordination of their research,” says Dr. Levy.

“In addition, families of children on the autism spectrum use CAR as a resource, and receive state-of-the-art, comprehensive evaluations as part of the research effort. Pulling CAR and the Regional Autism Center together helps to rapidly advance research into the causes of autism while enhancing the comprehensive services available to children and their families.”



Autism and Vaccines: Connection or Conundrum?



Paul Offit, M.D., chief, Division of Infectious Diseases, Maurice R. Hilleman Endowed Chair in Vaccinology, and director of the Hospital's Vaccine Education Center, says the fear is misguided.

"The greatest risk from vaccines is driving to the pediatrician's office to get them," says Dr. Offit, co-inventor of Rotateq®, the rotavirus vaccine approved for use in more than 60 countries. Rotavirus is the single largest infectious disease killer of infants and young children worldwide.

Mention autism today and it's easy to focus on the controversy that seems to be swirling around the disorder. Autism has received widespread attention in the press, in the federal government and courtroom, and among celebrities and autism-related groups established by affected families.

Much of the autism controversy centers on what role vaccines — or the preservatives in them — may play in the disorder. Despite their role in preventing a variety of serious and potentially deadly conditions, vaccines have been criticized because of their suspected role in autism. As a result, some parents have opted to forego vaccination for their children out of fear.

Dr. Offit has written extensively on vaccines, and is the author of a new book delving into the controversy surrounding the alleged vaccine-autism connection.

Autism's False Prophets: Bad Science, Risky Medicine, and the Search for a Cure presents an unobstructed look at the history of autism research and how the results of some questionable and biased investigations have fueled the present controversy.

Extensive, peer-reviewed epidemiological studies consistently discredit the argument that vaccines or the preservative in them called thimerosal causes autism, Dr. Offit says.

"There may be a controversy raging in the media, in the legal system, and among groups supporting affected families," he adds. "But there is absolutely no controversy in the science."

Blazing the Trail of Progress

Drawing New Paths Toward a Brighter Future

Children's Hospital remains one of only a few academically based pediatric research institutions with the critical mass needed to conduct top-tier basic, translational, and clinical research on matters important and relevant to child health.

With more than 425 investigators and a research staff in the thousands, the Institute continues its groundbreaking research in all of the pediatric subspecialties. As a result, the Hospital is ranked as second in funding from the National Institutes of Health to pediatric hospitals, despite a flat federal budget for biomedical research in recent years.



As a testament to the impact of investigators' work, Stokes investigators received approximately 700 grant awards during the fiscal year and were featured in more than 525 publications, including many prestigious journals like the *New England Journal of Medicine*, *Nature*, *Pediatrics*, *Nature Medicine*, and the *Journal of the American Medical Association*.

The Stokes Institute's growing expertise in basic, clinical, and translational research, coupled with the clinical foundation at Children's Hospital, continue to allow for the rapid advancement of discoveries from the bench to the bedside.

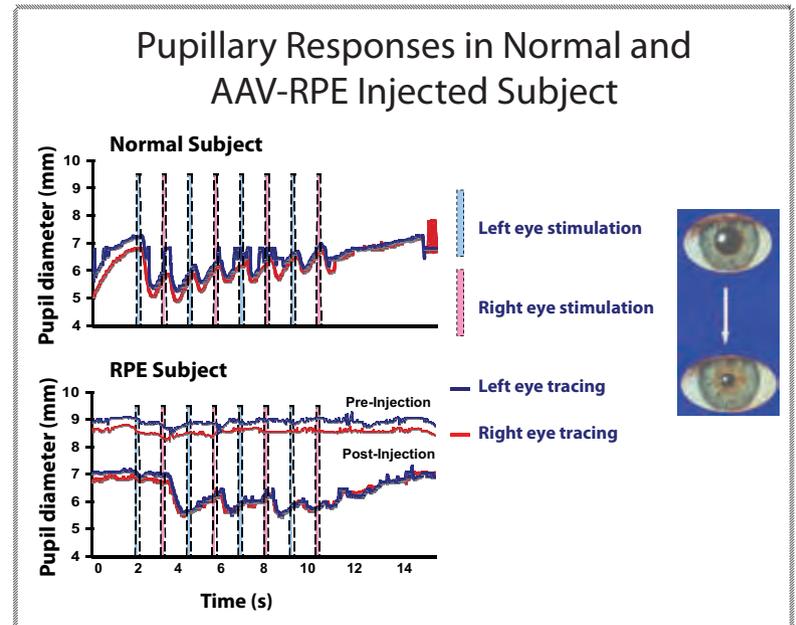
Katherine High, M.D., HHMI, Division of Hematology

My legacy: creating gene therapy treatments

Gene therapy has advanced significantly since I first began using it in my hemophilia clinical trials more than nine years ago. One of my most recent investigations, a collaboration with Albert Maguire, M.D., and Jean Bennett, M.D., Ph.D., at the University of Pennsylvania, used gene therapy to safely restore vision in three young adults with a rare form of congenital blindness, Leber's congenital amaurosis (LCA). The disorder usually begins stealing sight in early childhood and eventually causes total blindness.

We manufactured a vector at the Hospital's Center for Cellular and Molecular Therapeutics that carries a normal version of the gene mutated in one form of LCA. As we reported in the **New England Journal of Medicine**, all three patients had improved vision within a few weeks, and each injected eye had increased sensitivity to light and improved function compared to the uninjected, previously better functioning eye. Patients' vision improved from detecting hand movements to reading lines on an eye chart. Six months after the procedure, the patients also had less nystagmus, an involuntary movement of the eyes common in LCA.

Although the patients have not achieved normal eyesight, this finding offers hope to patients with the disorder, for which there is no current treatment, and lays the groundwork for future studies in this and other retinal disorders. This study was particularly groundbreaking as it was the first gene therapy trial for a nonlethal pediatric condition. We will continue to study this treatment, and expect improvements to be more pronounced if treatment occurs earlier in childhood, before the disease progresses.



Maguire AM, Simonelli F, Pierce EA, Pugh EN Jr, Mingozzi F, Bencicelli J, Banfi S, Marshall KA, Testa F, Surace EM, Rossi S, Lyubarsky A, Arruda VR, Konkle B, Stone E, Sun J, Jacobs J, Dell'Osso L, Hertle R, Ma JX, Redmond TM, Zhu X, Hauck B, Zelenia O, Shindler KS, Maguire MG, Wright JF, Volpe NJ, McDonnell JW, Auricchio A, High KA, Bennett J. Safety and efficacy of gene transfer for Leber's congenital amaurosis. *N Engl J Med.* 2008 May 22;358(21):2240-8.

**John Maris, M.D., Division of Oncology; and Hakon Hakonarson, M.D., Ph.D.,
Division of Human Genetics and Molecular Biology**

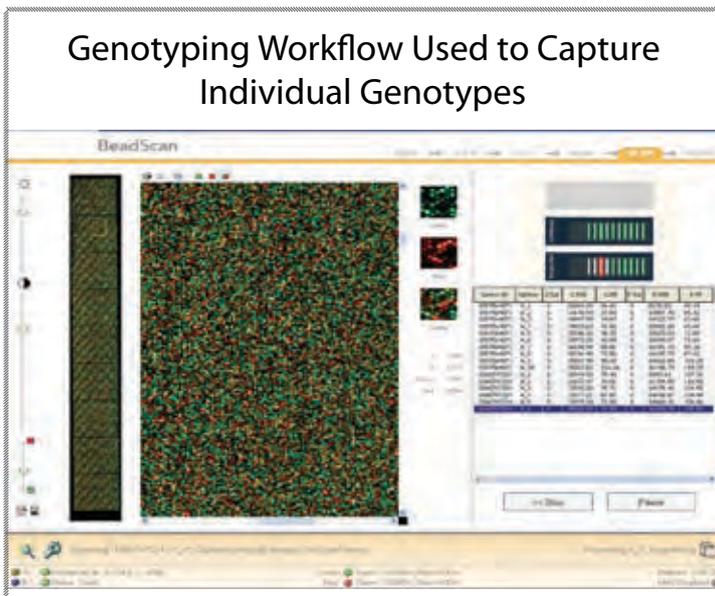
*Our legacies:
improving cures
and treatments for
pediatric cancer;
finding the genes
underlying complex
pediatric diseases*

By combining our expertise in childhood cancer and applied genomics, we found the gene location that is the source of genetic events that give rise to neuroblastoma, an often fatal childhood cancer. The most common solid cancer of early childhood, it accounts for 7 percent of all childhood cancers but causes 15 percent of all childhood cancer deaths. In roughly half of neuroblastoma cases, the cancer is not discovered until it has spread wildly in a patient's body, so understanding how it originates may enable us to design earlier and more successful interventions.

Our approach was to analyze blood samples from patients and healthy children and look for single nucleotide polymorphisms (SNPs) — changes in single bases on the DNA helix — using a DNA chip analysis. We found three SNPs that are much more common in patients with neuroblastoma. Patients with these at-risk SNPs, all of which are on chromosome 6, were more likely to develop aggressive forms of neuroblastoma. The initial changes seen on chromosome 6 eventually led to the genetic abnormalities seen in tumor cells in high-risk forms of the disease.

Our finding, published in the **New England Journal of Medicine**, is only the first step in a series of molecular events. We were awarded a \$4.3 million NIH grant to support our continued search for other gene changes that interact with the SNPs we identified in this study. However, this discovery lays the foundation for learning how these initial changes influence biological pathways that lead to neuroblastoma. Until now, the scientific community had very few clues about its cause, and understanding the origin of the disease provides a starting point for developing new and better therapies that precisely target its genetic cause.

Genotyping Workflow Used to Capture Individual Genotypes



Maris JM, Mosse YP, Bradfield JP, Hou C, Monni S, Scott RH, Asgharzadeh S, Attiyeh EF, Diskin SJ, Laudenslager M, Winter C, Cole KA, Glessner JT, Kim C, Frackelton EC, Casalunovo T, Eckert AW, Capasso M, Rappaport EF, McConville C, London WB, Seeger RC, Rahman N, Devoto M, Grant SF, Li H, Hakonarson H. Chromosome 6p22 locus associated with clinically aggressive neuroblastoma. *N Engl J Med.* 2008 Jun 12;358(24):2585-93.

Wayne W. Hancock, M.D., Ph.D., Division of Transplantation Immunology

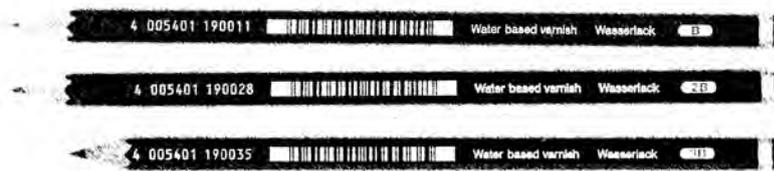
My legacy: creating treatments for problematic inflammatory and immune responses

A subset of immune cells, called regulatory T cells or Tregs, suppress activation of the immune system and close down immune responses that could potentially attack the body's own tissues. I have found a way to increase the number and function of these cells and to increase the gene expression of a protein called *Foxp3*, which regulates the development and function of Tregs and serves as a cellular marker.

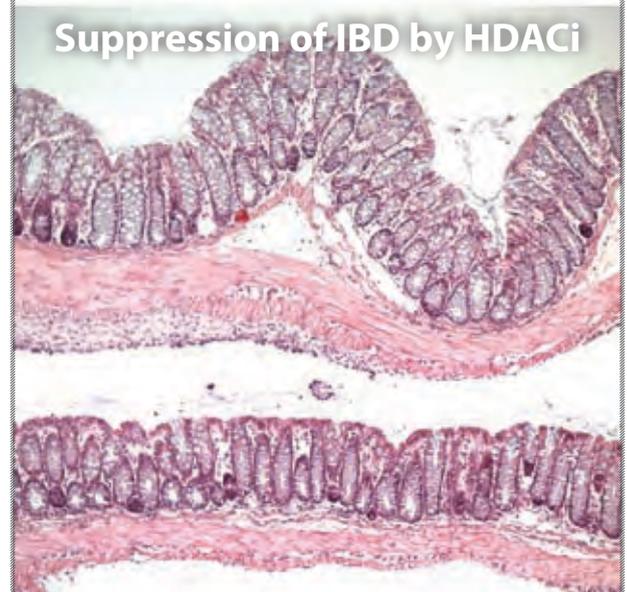
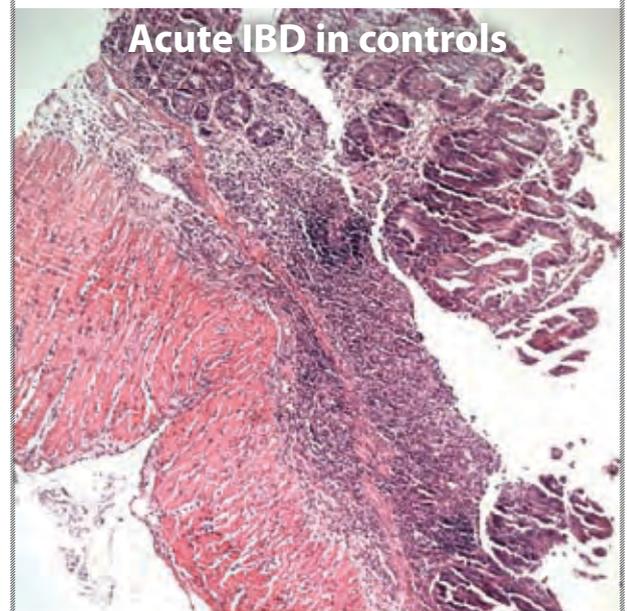
I examined optimal Treg function and found that *Foxp3* is regulated by activation of a region of *Foxp3* that was not previously thought to be involved in its function. My team found that this activation is essential for suppressing production of interleukin 2, a fundamental Treg activity. Using inhibitor molecules to present this aspect of biology in a new way, we showed the impact of altering the function of Tregs in autoimmune disorders.

Published in **Nature Medicine**, our results reveal therapeutically relevant mechanisms to alter inflammatory and immune responses that had never before been characterized. These findings may lead to a way to pharmacologically enhance the suppressive properties of naturally occurring Treg cells. One goal of this area of my research is developing therapies that improve the body's own cell production and may complement or replace therapies that depend on cellular transfer of Tregs.

Tao R, de Zoeten EF, Ozkaynak E, Chen C, Wang L, Porrett PM, Li B, Turka LA, Olson EN, Greene MI, Wells AD, Hancock WW. Deacetylase inhibition promotes the generation and function of regulatory T cells. *Nat Med.* 2007 Nov;13(11):1299-307.



Comparison of Gut Inflammation Associated With Control and HDACi Treatments



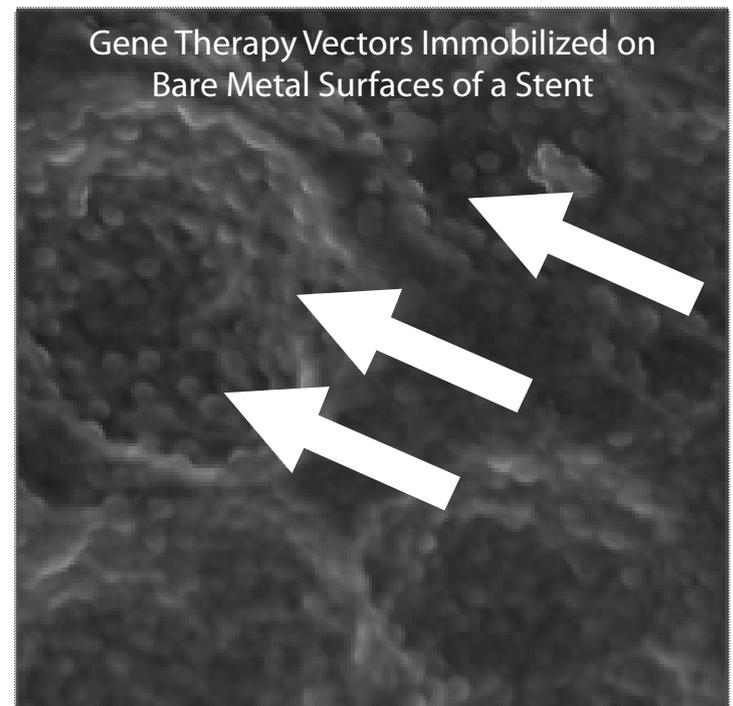
Robert J. Levy, M.D., Division of Cardiology

*My legacy: promoting and refining
site-specific therapy*

I am committed to bringing site-specific treatments to the forefront of clinical research. My research team and I launched an exploration into a magnetically driven gene therapy delivery system. We loaded endothelial cells with nanoparticles containing iron oxide and used magnetic force to increase the attraction between the particles and their target. This system, published in the **Proceedings of the National Academy of Sciences**, allowed us to steer the particles into arterial smooth muscle cells for a therapeutic effect.

Until now, targeting cell therapy has been a challenge. In previous studies, researchers haven't been as successful in their approaches to introduce normal endothelial cells to diseased blood vessels. Our magnetic nanoparticle system is ideal for delivering cells to target organs because the materials composing the nanoparticles are biodegradable, so they break down into simpler, nontoxic chemicals that can be carried away in the blood. The nanoparticles are also nonviral; therefore, this method avoids the unwanted immune system responses that have occurred when viruses are used to deliver therapy.

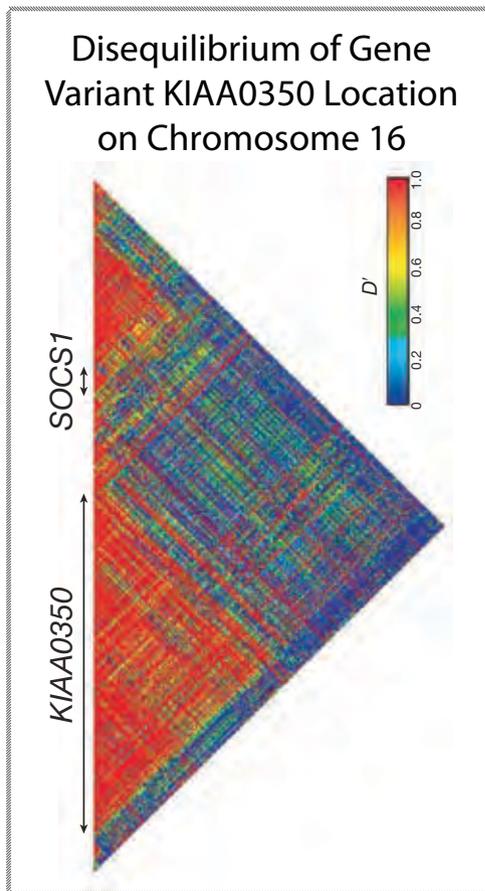
This innovative treatment also has the ability to deliver gene therapy to tumors and could be useful to physicians who implant steel stents to deliver medication to organs like the esophagus, bile ducts, and lungs. This strategy might also be useful in orthopedic procedures in which surgeons implant steel nails to stabilize fractured bones or use steel screws to correct spinal abnormalities. In future studies, I will use this approach to deliver magnetic nanoparticles to peripheral arteries.



Polyak B, Fishbein I, Chorny M, Alferiev I, Williams D, Yellen B, Friedman G, Levy RJ. High field gradient targeting of magnetic nanoparticle-loaded endothelial cells to the surfaces of steel stents. *Proc Natl Acad Sci U S A.* 2008 Jan 15;105(2):698-703.

Hakon Hakonarson, M.D., Ph.D., Division of Human Genetics and Molecular Biology

My legacy: discovering genes responsible for common childhood diseases



Hakonarson H, Grant SF, Bradfield JP, Marchand L, Kim CE, Glessner JT, Grabs R, Casalunovo T, Taback SP, Frackelton EC, Lawson ML, Robinson LJ, Skraban R, Lu Y, Chiavacci RM, Stanley CA, Kirsch SE, Rappaport EF, Orange JS, Monos DS, Devoto M, Qu HQ, Polychronakos C. A genome-wide association study identifies KIAA0350 as a type 1 diabetes gene. *Nature*. 2007 Aug 2;448(7153):591-4.

Over the past several years, I have focused my research efforts on genome-wide mapping and association studies for complex medical disorders. Recently, I used a new genotyping technology to identify a gene variant that raises a child's risk of type 1 diabetes. The study, published in **Nature**, was conducted at the Center for Applied Genomics (CAG), a Children's Hospital center dedicated to identifying the genes responsible for common childhood diseases.

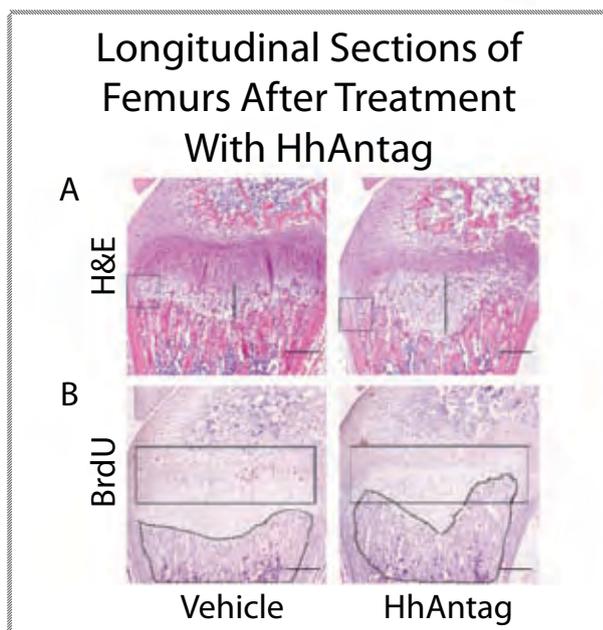
My team of investigators and I compared the genomes of more than 1,000 patients with type 1 diabetes to those of 1,146 matched control subjects. Almost 500 of these diabetic cases included family trios, in which the genomes of a child with the disease and both parents were examined. We also validated this discovery in another family-based cohort of approximately 1,000 patients with type 1 diabetes. I anticipate that further investigation may yield as many as 15 or 20 additional genes that may interact with each other in the disease. Indeed, since this discovery, we have found four additional genes that are also major players in type 1 diabetes.

By pinpointing the genes contributing to diabetes, we aim to provide a scientific basis for designing better treatments and preventative measures. Now that we know more about the gene pathways that give rise to diabetes, we may be able to screen newborns for these genes and prevent the disease from developing by intervening early. It is our goal at CAG to translate the discovery of major disease-causing variants into successful treatments.



Tom Curran, Ph.D., Division of Developmental Biology

My legacy: investigating the promise and problems of signal transduction inhibitors in pediatric cancer

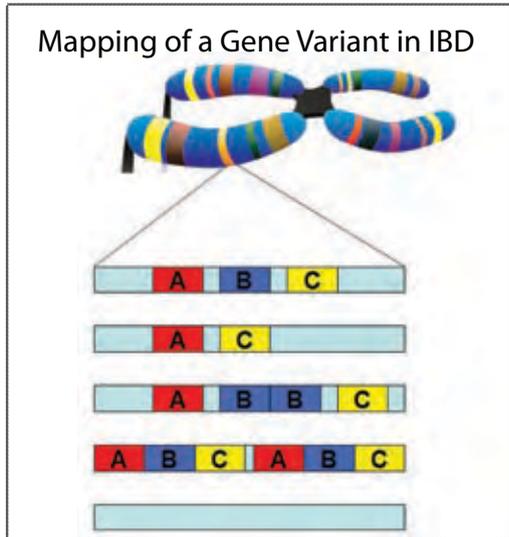


Kimura H, Ng JM, Curran T. Transient inhibition of the Hedgehog pathway in young mice causes permanent defects in bone structure. *Cancer Cell*. 2008 Mar;13(3):249-60.

Signal transduction inhibitors (STIs) have received a great deal of attention as potential anti-cancer therapies, in part because of their exquisite specificity and reduced toxicity compared to standard chemotherapeutic agents. Previously, we conducted proof-of-concept studies of an STI that blocks the hedgehog pathway (HhAntag) and dramatically eliminates large tumors in a model of medulloblastoma. However, in a study published in **Cancer Cell**, my investigators and I found that HhAntag may also damage growing bones, a finding that shows a potential dark side of the use of STIs in children.

In a 2004 study, we found that HhAntag caused tumors to shrink and even disappear. In models of disease, HhAntag administration led to much longer survival and no serious side effects. Despite these promising results, we recently discovered serious impairments to developing bones in young models of disease that were administered the drug. The effects were irreversible; as few as four doses of the drug permanently led to stunted growth. Because of the potential effect of this drug, these findings raise a strong caution that HhAntag should be used with careful monitoring in children.

The hedgehog pathway plays multiple roles during a child's development, and the genes along that pathway lead to different cancers, including medulloblastoma, the most common cancerous brain tumor in children. Although this study's results are disappointing, we have not ruled out the use of HhAntag for treatment of medulloblastoma. The effects we observed in model systems may be less severe in children and could depend on the age of the child. In the future, we hope it will be possible to protect growing bones or to deliver the drug selectively to tumor cells to avoid these problems.



**Robert Baldassano, M.D.,
Division of Gastroenterology,
Hepatology, and Nutrition**

My legacy: **advancing the knowledge
and care of inflammatory bowel disease**

The current treatments for Crohn's disease are based on a poor understanding of the causes of the disease and lead to serious side effects. My colleagues and I, including Drs. Hakon Hakonarson and Struan Grant, identified a gene variant of ATG16L1 that raises a child's risk of Crohn's disease by 62 percent, the same variant identified in a separate study of adults conducted by German researchers. Our findings, published in **Gut**, lead us to think that a mutation in this gene might weaken a cell's ability to degrade waste products, which could stimulate the inflammatory response characterizing Crohn's disease. We plan to continue investigating gene influences to gain a better understanding of the disease mechanism and eventually develop improved, targeted treatments.

Baldassano RN, Bradfield JP, Monos DS, Kim CE, Glessner JT, Casalunovo T, Frackelton EC, Otieno FG, Kanterakis S, Shaner JL, Smith RM, Eckert AW, Robinson LJ, Onyiah CC, Abrams DJ, Chiavacci RM, Skraban R, Devoto M, Grant SF, Hakonarson H. Association of the T300A non-synonymous variant of the ATG16L1 gene with susceptibility to paediatric Crohn's disease. *Gut*. 2007 Aug;56(8):1171-3.

**Ron Keren, M.D., M.P.H.,
Division of General Pediatrics**

My legacy: **establishing evidence-based treatments for common pediatric problems**

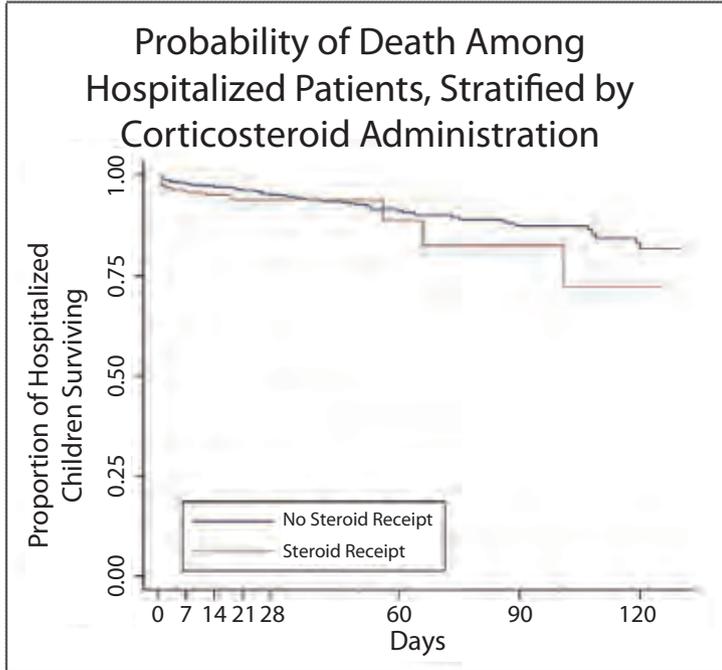
Most newborns get some jaundice (yellowing of the skin) in the first few days of life. Occasionally the bilirubin that causes jaundice can rise to levels that cause brain damage. The American Academy of Pediatrics currently recommends two options to assess an infant's risk of developing dangerous levels of bilirubin. I found that one of these methods, a predischarge measurement of the bilirubin level, combined with the baby's gestational age, is the most accurate method for predicting which newborns are at risk. This screening method, published in **Pediatrics**, allows pediatricians to determine if a newborn should stay in the hospital, go home but return for additional bilirubin tests, or go home without additional testing.

Keren R, Luan X, Friedman S, Saddlemire S, Cnaan A, Bhutani VK. A comparison of alternative risk-assessment strategies for predicting significant neonatal hyperbilirubinemia in term and near-term infants. *Pediatrics*. 2008 Jan;121(1):e170-9.

**Risk of Significant Hyperbilirubinemia
According to Predischarge Bilirubin
Percentile and GA**

		Predischarge bilirubin percentile		
		≤75th	76th-95th	>95th
Gestational age, wk	<38	L	H	H
	38-39 ^{6/7}	VL	L	H
	≥38	VL	VL	H

LEGEND	Risk Category	No. (%) in Risk Category	No. Developed Significant Hyperbilirubinemia	Probability of Significant Hyperbilirubinemia, % (95% CI)	LR
VL	Very low	523 (70)	1	0.2 (0.005-1.000)	0.028
L	Low	127 (17)	5	4 (1-9)	0.600
H	High	100 (13)	42	42 (32-52)	10.600



**Samir Shah, M.D., M.S.C.E.,
Division of Infectious Diseases**

My legacy: improving the diagnostic evaluation and treatment of children with infectious diseases

Corticosteroids given to children who are hospitalized for bacterial meningitis do not provide a benefit in survival or in reduced hospital stays according to my study published in the **Journal of the American Medical Association**. Because there are demonstrated benefits of these drugs in adults, physicians have increasingly been using corticosteroids in children. My results demonstrate the need for further studies in children to determine whether the problems associated with corticosteroid use, such as diminished penetration of antibiotics into the spinal fluid or gastrointestinal bleeding, outweigh any potential benefits.

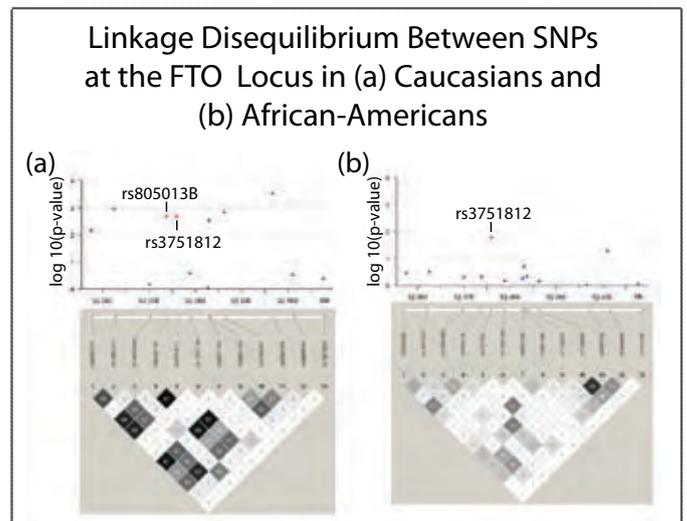
Mongelluzzo J, Mohamad Z, Ten Have TR, Shah SS. Corticosteroids and mortality in children with bacterial meningitis. *JAMA*. 2008 May 7;299(17):2048-55.

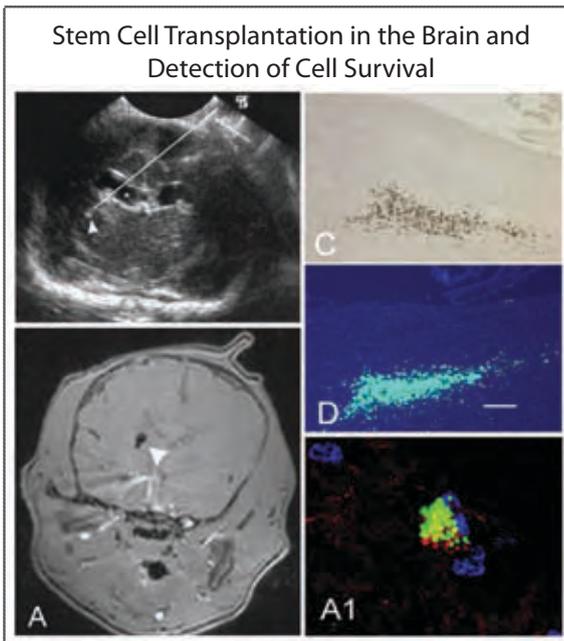
**Struan Grant, Ph.D.,
Division of Human Genetics
and Molecular Biology**

My legacy: isolating genes involved in metabolic diseases

I used a genetic screening technique in order to seek replication of a finding made by a British group who discovered that a variant in the *FTO* gene was associated with obesity. I found that the same variant was operating among Caucasian children, but not among African-American children. As published in **Public Library of Science ONE**, I figured out that there is a second variant in the gene that equally impacts pre-disposition to obesity in both Caucasians and African-Americans, and that this was the only marker significantly linked to obesity among the African-American children. This second gene variant, which may have deep roots in evolutionary history, should be considered in future studies that are aimed at thoroughly assessing the influence of this gene on obesity worldwide.

Grant SF, Li M, Bradfield JP, Kim CE, Annaiah K, Santa E, Glessner JT, Casalunovo T, Frackelton EC, Otieno FG, Shaner JL, Smith RM, Imielinski M, Eckert AW, Chiavacci RM, Berkowitz RI, Hakonarson H. Association analysis of the *FTO* gene with obesity in children of Caucasian and African ancestry reveals a common tagging SNP. *PLoS ONE*. 2008 Mar 12;3(3):e1746.





**John Wolfe, V.M.D., Ph.D.,
Division of Neurology**

My legacy: developing treatments for genetic diseases that affect the brain

My lab successfully delivered a beneficial gene to the entire brain using only one injection of gene therapy. We targeted a region of the brain that is well connected to other areas with a gene that corrected problems associated with Sly syndrome, a lysosomal storage disease. The level of correction resulting from this small injection was unprecedented. The technique corrected diseased areas throughout the brain, and the diseased areas were corrected to the point that they were indistinguishable from non-diseased brain tissue. Published in the **Journal of Neuroscience**, this result may have potential for developing gene therapy to treat a host of rare but devastating congenital neurological disorders.

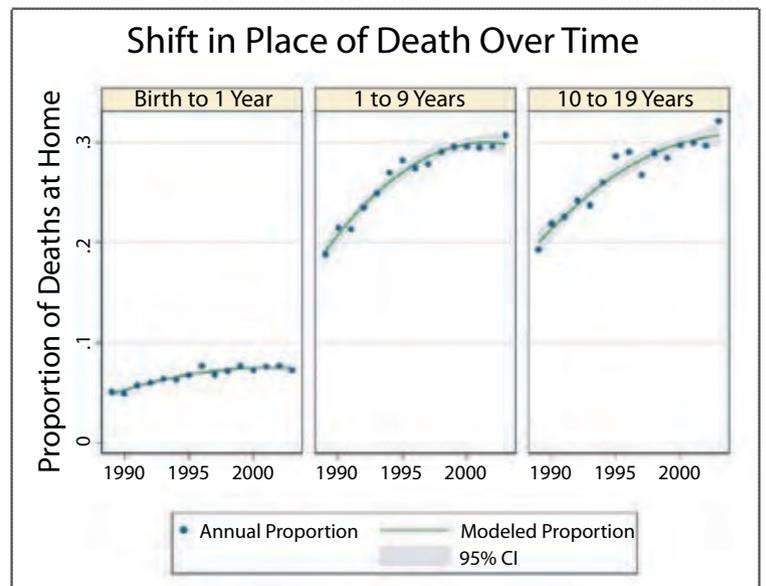
Cearley CN, Wolfe JH. A single injection of an adeno-associated virus vector into nuclei with divergent connections results in widespread vector distribution in the brain and global correction of a neurogenetic disease. *J Neurosci.* 2007 Sep 12;27(37):9928-40.

**Chris Feudtner, M.D., Ph.D., M.P.H.,
Division of General Pediatrics**

My legacy: improving the quality of life for children with complex chronic conditions

Advances in medicine and shifts in attitude toward end-of-life care are allowing medically fragile children to live at home and affecting the choices given to them and their families. I have found that children who die of a chronic illness are more likely to spend their final days at home instead of in the hospital, when compared with children who died two decades ago. While my study, published in the **Journal of the American Medical Association**, shows that a majority of chronically ill children still die in hospitals, the shifting trend in place of death suggests each family should make care decisions based on their own preferences, and medical professionals should help families make decisions in an atmosphere of mutual trust and respect.

Feudtner C, Feinstein JA, Satchell M, Zhao H, Kang TI. Shifting place of death among children with complex chronic conditions in the United States, 1989-2003. *JAMA.* 2007 Jun 27;297(24):2725-32.

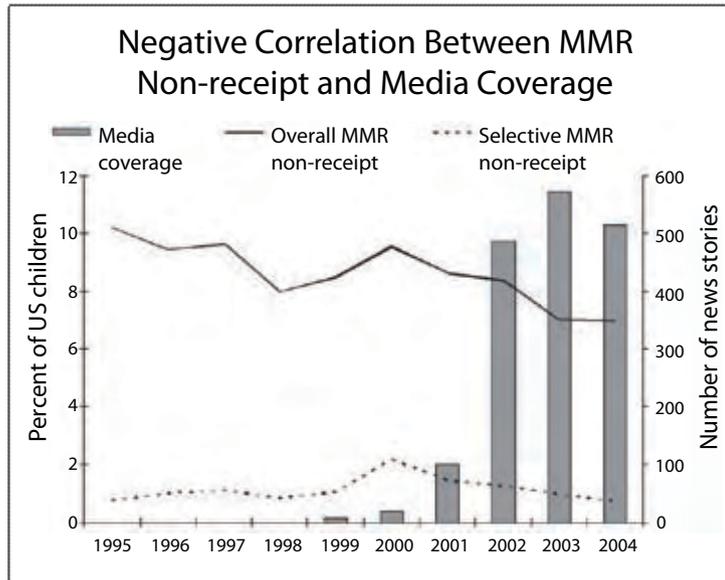
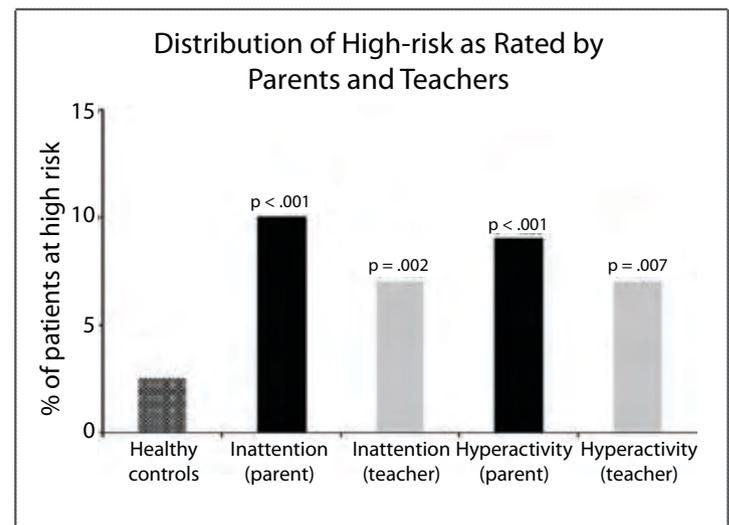


**Gil Wernovsky, M.D., F.A.C.C., F.A.A.P.,
Division of Cardiology**

My legacy: improving the long-term outcomes in children with congenital heart disease

As a pediatric cardiac intensivist and outpatient cardiologist, I am devoted to improving the quality of life of children with complex congenital heart disease (CHD). My colleagues and I have found that children who had surgery for CHD as infants may develop inattention and hyperactivity problems and require remedial services in school, as was published in **Pediatrics**. Our findings reinforce the need for children with CHD to have ongoing follow-up and neurodevelopmental screenings. These results are raising awareness among parents, children, and physicians about the possibility of neurodevelopmental problems and the need for early detection of such problems. In future studies, I plan to develop formalized follow-up protocols for children with CHD, as well as treatment strategies in the intensive care unit to reduce the risks in the future.

Shillingford AJ, Glanzman MM, Ittenbach RF, Clancy RR, Gaynor JW, Wernovsky G. Inattention, hyperactivity, and school performance in a population of school-age children with complex congenital heart disease. *Pediatrics*. 2008 Apr;121(4):e759-67.



**Michael Smith, M.D., M.S.C.E.,
Division of Infectious Diseases**

My legacy: promoting immunization education

Many parents struggle with the critical decision of whether to allow their children to receive the mumps, measles, and rubella (MMR) vaccination. This decision hasn't been made any easier with the recent onslaught of news stories alleging a harmful link between autism and the MMR vaccine. I found that despite negative press, parents follow their pediatrician's advice when the time comes to make such a critical decision. These results, published in **Pediatrics**, suggest that physicians may buffer negative media coverage of immunization controversies, and decisions relating to immunization are made during private conversations between a family and its doctor. Ensuring doctors have up-to-date, accurate information may be the most efficient way to guarantee successful immunization practices.

Smith MJ, Ellenberg SS, Bell LM, Rubin DM. Media coverage of the measles-mumps-rubella vaccine and autism controversy and its relationship to MMR immunization rates in the United States. *Pediatrics*. 2008 Apr;121(4):e836-43.



Nelangi M. Pinto, M.D.,
Division of Cardiology

My legacy: **improving the outcomes of pediatric congenital heart disease**

As a pediatric cardiologist, I want my patients to live healthy and full lives after the diagnosis and treatment of disease. My colleagues and I found that more than 25 percent of children with congenital and acquired heart disease are overweight or obese, which shows that healthy-lifestyle counseling may be underemphasized in pediatric cardiology visits. The long-term impact of obesity in children with heart disease is unknown, but likely to increase morbidity and mortality, as it does in adults. Our study results, published in **Pediatrics**, indicate that in order to prevent additional cardiovascular risks, it is imperative that weight control and exercise counseling become an important part of pediatric cardiology visits.

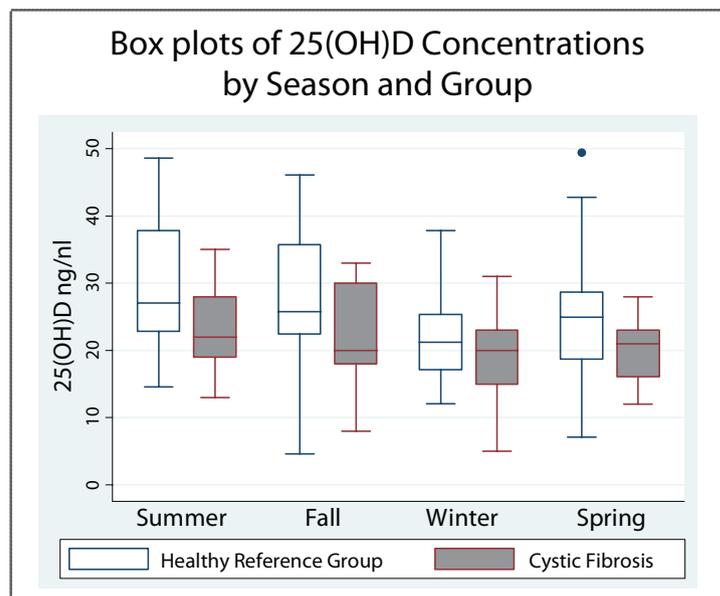
Pinto NM, Marino BS, Wernovsky G, de Ferranti SD, Walsh AZ, Laronde M, Hyland K, Dunn SO Jr, Cohen MS. Obesity is a common comorbidity in children with congenital and acquired heart disease. *Pediatrics*. 2007 Nov;120(5):e1157-64.

Babette Zemel, Ph.D.,
Division of Gastroenterology,
Hepatology, and Nutrition

My legacy: **optimizing dietary health in healthy and chronically ill children**

My research has contributed extensively to the understanding of growth and nutrition in healthy and chronically ill children and adolescents. In one of my latest studies, published in the **American Journal of Clinical Nutrition**, I found that low vitamin D levels are common in healthy children and vary according to season. In addition, children with cystic fibrosis — a common genetic disease that affects absorption — had even lower vitamin D levels. Nearly all children with cystic fibrosis take vitamin D supplements, but these findings indicate that they need a higher dose. Bringing light to an under-recognized problem that is not well studied emphasizes the need for physicians to speak to families about being aware of the prevalence of the deficiency and the ways it can be prevented.

Rovner AJ, Stallings VA, Schall JI, Leonard MB, Zemel BS. Vitamin D insufficiency in children, adolescents, and young adults with cystic fibrosis despite routine oral supplementation. *Am J Clin Nutr*. 2007 Dec;86(6):1694-9.



Grant Awards

National Children's Study

Jennifer Culhane, Ph.D., Division of Adolescent Medicine

My legacy: uncovering the relationship between genes and environment on children's health

Some childhood health problems such as obesity, autism, and asthma are becoming more common, but the reasons for the increase are unclear. The National Children's Study (NCS), the first and largest long-term study of children's health ever conducted in the United States, was developed to answer this question. By examining the complicated interplay between the environment and genes in more than 100,000 children, the NCS hopes to explain the increase in disease as well as other pediatric health problems. Children's Hospital was chosen to have a significant role in the NCS.

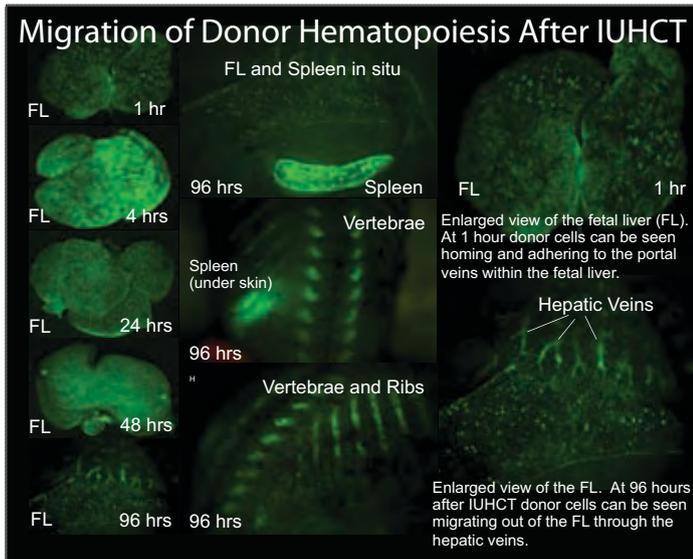
Children's Hospital was selected as one of the first seven centers to implement the National Children's Study protocol. This Vanguard activity is being conducted in Montgomery County, Pa. Last year, Children's Hospital was also awarded three additional sites where the NCS will be conducted, Schuylkill County, Pa.; Philadelphia County, Pa.; and New Castle County, Del. We anticipate that approximately 1,000 families from each location will take part in the study, which will follow children from before birth until age 21. The Vanguard award from 2005 and the more recent contracts equal approximately \$57 million in funding over five years to Children's Hospital.



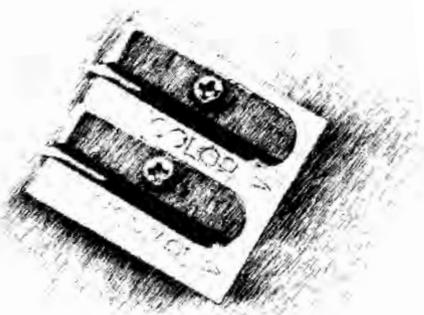
The children enrolled from these sites represent a snapshot of America's children and will help us improve the health of children locally and across the nation for generations to come. The sites were selected as part of 105 locations that are representative of the nation's population based on factors such as race and ethnicity, income, and education level.

Prenatal Sickle Cell Disease Therapy

Alan Flake, M.D., Division of General, Thoracic, and Fetal Surgery



Transplanting hematopoietic cells — cells that give rise to all blood cell types — to a fetus in utero is a potential therapeutic approach for treating many genetic disorders. Engraftment, a process where the transplanted cells start to grow and make new blood cells, is essential for treatment but is often thwarted by immune responses to donor cells. Because of the immunological conditions during gestation, the fetal environment offers a unique opportunity to engraft cells without removing bone marrow or suppressing the immune system.



*My legacy:
improving fetal therapy,
specifically in utero
transplantation of
stem cells to treat
genetic disease*

I received a \$2.1 million four-year Commonwealth Universal Research Enhancement Award from the commonwealth of Pennsylvania to study in utero hematopoietic cell transplantation (IUHCT) as a potential therapy for sickle cell disease. Sickle cell disease is the most common genetic disorder in African-American children and affects more than 50,000 people in the United States. Postnatal hematopoietic stem cell transplantation (HSCT) for sickle cell disease is uncommon, as matched sibling donors are rare and there are too many risks associated with other donors. Recent studies have demonstrated that IUHCT results in tolerance of the donor cells, leading to successful transplantation from the same donor after birth using non-toxic methods of HSCT.

My goals are to perform preclinical studies designed to optimize the safety of IUHCT followed by HSCT, establish new ways to enhance engraftment using this method, and lay the groundwork for a future clinical trial of this treatment. If we are able to develop a safe and successful application of IUHCT to treat sickle cell disease, it may be used for prenatal treatment of a large number of genetic disorders that are currently only treated by postnatal HSCT.

Ring 20 Chromosome

Nancy Spinner, Ph.D., Division of Human Genetics and Molecular Biology

My legacy: identifying and understanding genes that contribute to congenital disease

Ring 20 chromosome syndrome is a rare but potentially devastating disorder characterized by chromosomes that take a ring shape rather than the typical rod-shaped form. The ring shape makes it difficult for a patient's cells to copy the chromosomes and may lead to impaired growth and viability. Almost all patients with this chromosome abnormality have severe seizures that do not respond well to medication. Some patients have additional symptoms, such as mental retardation, growth disturbances, a smaller-than-average head circumference due to improper brain development, and other abnormalities.

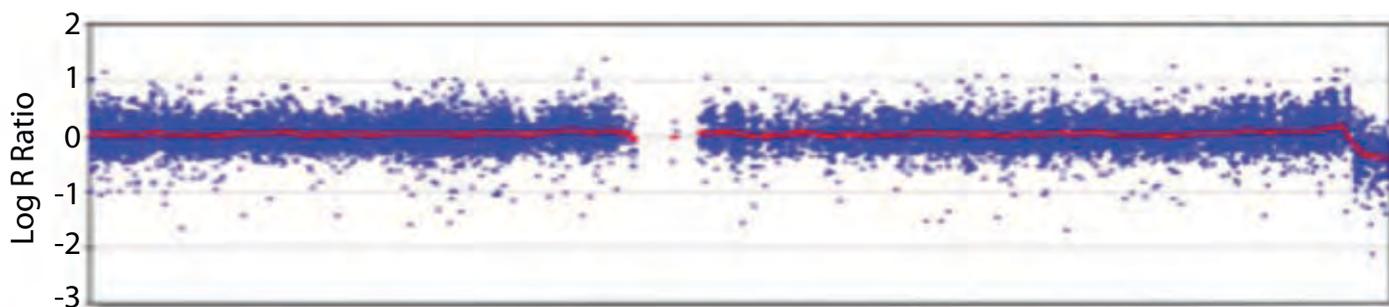
I suspect that the abnormal ring shape of the chromosome leads to the deregulation of genes that cause the specific pattern of abnormalities seen in patients with the disorder. I was awarded \$126,000 from the Ring Chromosome 20 Foundation for a two-year study of the ring 20 chromosome.

My colleagues and I are working with the Center for Applied Genomics to identify the genetic and genomic basis of the disease. We will define the underlying defects at the molecular level and draw upon our wealth of experience to investigate how the ring chromosome affects gene expression and function.

Understanding the genes involved in ring chromosome 20 abnormalities will pave the way for future research to study these genes and understand how they lead to seizures and other symptoms seen in affected patients. We hope to use this understanding to eventually form the basis of new therapies for seizure management.



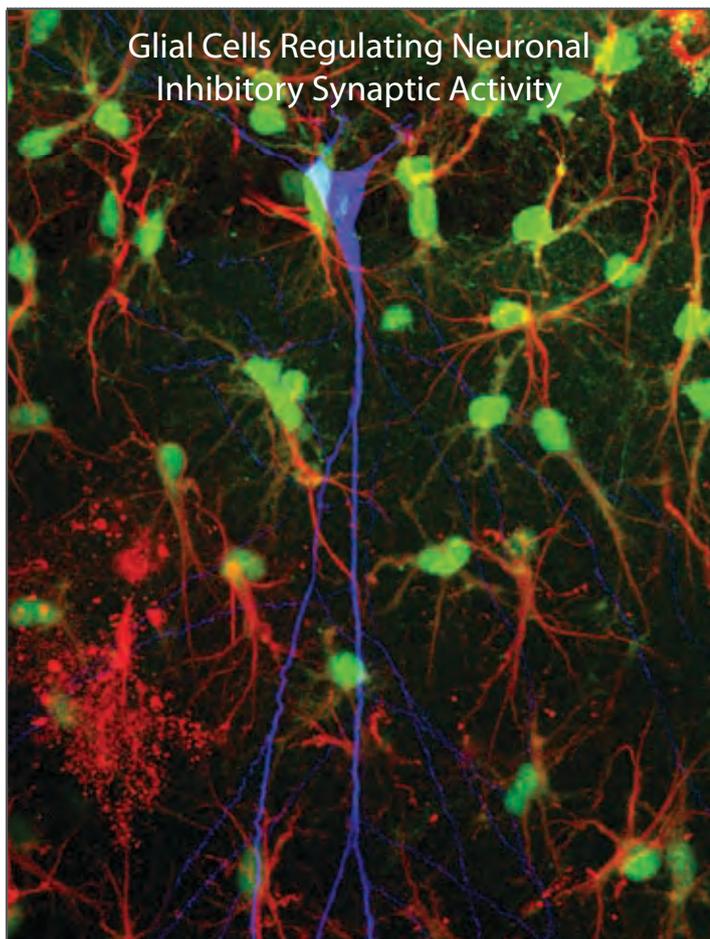
Portion of Chromosome 20 Deleted From Ring Chromosome



Delineating the Epilepsy Pathway

Douglas A. Coulter, Ph.D., Division of Neurology

*My legacy:
understanding the
cellular and molecular
mechanisms underlying
the development
of epilepsy*



Temporal lobe epilepsy (TLE) is among the most prevalent and least medically responsive forms of epilepsy. Current therapies for TLE are either drastic or purely symptomatic, ranging from removing parts of the brain to using drugs to control seizures. There are currently no therapies that target the disease process. To address this therapeutic need, I was awarded a \$6.6 million, five-year project grant from the National Institute of Neurological Disorders and Stroke to study epileptogenesis, the process in which a normal brain becomes epileptic.

Working with my fellow investigators, I will focus on gamma-aminobutyric acid (GABA), a neurotransmitter that acts at inhibitory synapses in the brain. In previous studies, we found evidence that GABA recycling mechanisms are compromised in inhibitory synapses in the brains of experimental models of TLE, and this alteration develops very soon after the injury that later leads to TLE. Restoration of normal GABA production soon after an epileptogenic injury may be a viable therapeutic intervention, capable of blunting the severity of, or completely blocking, the subsequent development of epilepsy.

Using a combination of electrophysiological, molecular, and disease model approaches, we will examine the mechanisms mediating GABA production and recycling and determine the timing of altered GABA recycling during epileptogenesis. Understanding how changes in metabolic processes within inhibitory synapses influence seizure generation in TLE may lead to early interventions in these processes and alter disease progression, ultimately resulting in new therapeutic strategies to better treat and perhaps cure this devastating disorder.



Investing for Success

Programs Simplify Research, Improve Care

The rich sources of data available to researchers today present incredible opportunities, but they also present challenges. Stokes Institute recognizes these challenges and, through a commitment to providing services to investigators, establishes effective solutions.

Last year the Institute made several investments — in both funding and knowledge — to augment the data resources available to investigators, and to move completed research closer to impacting clinical care. These new contributions to research at the Stokes Institute have already resulted in positive feedback and impressive results.

Shifting Support to Meet Evolving Needs



The Hospital's electronic health record captures a vast amount of clinical data, but the data cannot be efficiently harvested and accurately interpreted without a precise understanding of what it represents relative to the care delivery process.

Sorting through this data to find the information crucial to answering clinical, research, and managerial questions is the specialty of the Clinical Reporting Unit (CRU). With an intimate knowledge of the tools that capture the data and clinical practice standards and procedures, the CRU's staff provides efficient and highly relevant data extraction for research purposes.



This year, Stokes Institute established the CRU as a research core facility, allowing the group to provide a highly visible and accessible service under the direction of core facility administration. The chargeback mechanism associated with core facilities will allow the CRU to grow its services based on demand over time and ensure that investigators continue to have access to a high-quality, sustainable service.

"The facility, under the direction of the Center for Biomedical Informatics, continues its close associations with other Hospital information-based groups, including the Institute to Transform and Advance Children's Healthcare, the Pediatric Research Consortium, and Research Information Systems, relationships that have strengthened the CRU and contributed to its accomplishments," says Robert Grundmeier, M.D., F.A.A.P., CRU director.



Creating a Standard of Evidence-based Care



Despite the numerous guidelines and recommendations guiding pediatric clinical care, many clinical practices for managing pediatric illnesses are not strongly based on direct evidence. Children's Hospital is devoted to making sure that the care given to children is grounded in proven clinical results. Stokes Institute launched the Center for Pediatric Clinical Effectiveness (CPCE) to discover and disseminate knowledge about best practices in the management of pediatric disease.

A new Center of Emphasis at Children's Hospital, CPCE builds on existing research expertise and infrastructure to facilitate research aimed at understanding the best ways to prevent, diagnose, and treat diseases in children. The center creates opportunities for the exchange of ideas among clinical effectiveness researchers, facilitates the performance of clinical effectiveness research, trains researchers in clinical effectiveness research methods, and disseminates best practices.

A handwritten signature in black ink that reads "Ron Keren". To the right of the signature is a small graphic consisting of several green cubes of varying sizes, some overlapping, with a soft, glowing effect around them.

To achieve these goals, CPCE uses a variety of strategies including a lecture series for visiting scholars and one for members seeking feedback on ongoing research, training programs for fellows and residents that focus on using evidence to answer clinical questions, and podcasts covering common topics on using clinical effectiveness research to manage care.

CPCE also strives to lessen the administrative burdens of clinical effectiveness research, and to that end the center provides a database of successful grant applications to assist investigators with the grant writing process, is working toward umbrella Institutional Review Board review for studies that use deidentified data sets, and is developing a data services unit that will provide statistical expertise and data analysis services to all of Children's Hospital.

"We invite all faculty across the Hospital to join the critical mass of highly trained and experienced investigators seeking to improve the health of children through clinical effectiveness research," says Ron Keren, M.D., M.P.H., director of CPCE. "Our collaborations and the benefits of our data services unit distinguish Children's Hospital as a leader in this field of research."

Providing Critical Support, Generating Outstanding Results

The Center for Applied Genomics (CAG), a Center of Emphasis created at Children's Hospital to lay the foundation for personalized pediatric medicine, has provided an extensive set of control samples to the worldwide research community, significantly reducing the time and expense needed for genotypic studies.

The company that supports CAG's advanced automated technology created iControlDB as a genotypic control repository available for immediate use by researchers conducting genetic case-control association studies. This type of study compares groups of patients who have a disease with healthy individuals to identify genetic risk factors. Having iControlDB available to researchers significantly reduces the time and expense of genotypic studies, and will hopefully advance CAG's goal of building scientific foundations that will lead to successful treatments for childhood diseases.

CAG contributed 4,000 control samples from healthy individuals to iControlDB, the largest genotype donation by a single institute. Putting this in perspective, it includes more than 2.5 times the number of genotypes released by the International HapMap Project, which took several years to generate with the help of dozens of investigator sites.

"We are extremely pleased to provide these genotypes to the public domain," says Hakon Hakonarson, M.D., Ph.D., director of CAG. "Scientific work using these data repositories will complement our own comprehensive research and clinical programs aimed at finding the causes and cures for devastating diseases."



The center also contributed a large genotype dataset to the Autism Genetic Resource Exchange, a scientific program of the organization Autism Speaks, dedicated to advancing genetic research in autism. The dataset was constructed from 4,500 blood samples from 1,250 children with autism spectrum disorders, their parents, and their unaffected siblings. A compilation of 550,000 genetic markers for each person, the patterns of genetic variation in this dataset will enable investigators to discover and investigate multiple genes that may contribute to autism.



Catalysts for Change

Seizing Opportunities to Accelerate Discovery

Science is constantly evolving — expectations and practices shift in response to new information, new ideas, new ways of doing things. Stokes investigators are innovators; content not to just discover ways to anticipate and embrace change, they take the bold steps needed to challenge convention and make profound discoveries.

The findings at Stokes frequently change the landscape of science and have a lasting impact on the future of children's health. By taking risks, embracing challenges, and seeking support for ambitious ideas, Stokes investigators have established a legacy of innovation that continues to flourish.



Pieces of Immunity Puzzle fitted to a 'T'

Terri A. Finkel



The immune system is the first line of defense against infection, bacteria, viruses, and disease, responding instantaneously to perceived threats to a person's health. A malfunctioning immune system, however, can lead to immunodeficiency, leaving a person susceptible to infection, or causing the body to turn on its own tissues as part of an autoimmune or autoinflammatory attack.

A specific white-blood cell called a T cell plays a critical role in the delicate functioning of the body's immune system. Too few or too many of the immunity-mediating T cells can lead to a variety of diseases and disorders.

Terri Finkel, M.D., Ph.D., chief, Division of Rheumatology, and Joseph Lee Hollander Endowed Chair in Pediatric Rheumatology, investigates the critical role T cells play in immunity. She explores how the cells participate in both immunodeficiency and autoimmune responses and what triggers T cells in the first place.

On one end of the spectrum, Dr. Finkel continues her efforts to unravel the T cell's life cycle and develop new therapies to combat those cells that attack the body's own tissues and lead to diseases like juvenile idiopathic arthritis (JIA), formerly called juvenile rheumatoid arthritis.

Along with her colleagues and with the assistance of the Center for Applied Genomics, Dr. Finkel recently discovered that a genetic region that plays a role in some adult forms of arthritis is also present in all types of childhood arthritis. She anticipates that the discovery of this "master switch" for regulating autoimmune disease will result in greater insight and understanding about the pathways leading to arthritis. This is especially important since there is no singularly effective treatment for JIA. Many children develop severe allergic reactions and side effects to current therapies, and there is no cure for childhood arthritis.

On the other end of the T-cell spectrum, Dr. Finkel investigates what happens to the immune system when T cells aren't working properly or are too few in number, which is commonly seen in HIV infection. The dogma about HIV infection had been that it killed T cells, but Dr. Finkel and her colleagues discovered that the virus protects some T cells from being killed during the initial phase of infection by turning on certain survival proteins. The T cells will eventually die but not until they send out a viral burst.

The complex role of T cells in HIV infection is also evident in their ability to maintain infection in a latent state, apparently protected from apoptosis or cell suicide. Dr. Finkel and her team are working to identify which proteins turned on by the virus provide these survival signals. One survival protein they recently discovered is called HALP, or HIV-Associated Life Preserver, which appears to protect T cells from suicide until the cells have produced their viral bursts. After these bursts, the levels of HALP decrease and the cells die.

Dr. Finkel and her colleagues developed a mirror image of HALP that remains in hiding until it sees HIV infection. After delivery through gene transfer, the vector called siHALP knocks down the level of the HALP protein, eliminates it from the cell, and causes the HIV-infected cell to die. The investigators received two patents and a Small Technology Transfer Research Award from NIH for their work on this siHALP technique.

"This is similar to a chemotherapy approach to ridding the body of infected cells," says Dr. Finkel. "This could be a way to not only kill infected cells but also put good, healthy T cells back into a patient's blood that can repopulate the immune system."



In addition to exploring what happens in conditions of too few or too many T cells in the body, Dr. Finkel is investigating the mechanisms that initially trigger T cells. It is well understood that these cells are activated after the T cell's antigen receptor binds to an antigen presenting cell's peptide-loaded major histocompatibility complex, or pMHC. The baffling piece of the puzzle — critical to understanding how the immune system works — rested with how the very first steps of activation occurred.

Dr. Finkel and her team developed a model showing how an activating signal from the T-cell receptor is triggered by the engagement of pMHC. This receptor deformation model is an entirely new explanation for how T-cell triggering works. This finding may lead to further understanding of a key step in the immune system's recognition of foreign antigens, as well as identifying potential targets for manipulating T-cell activation for vaccines and anti-cancer therapy.

CytoGenomics - Expanding the Realm of Diagnosing Genetic Abnormalities

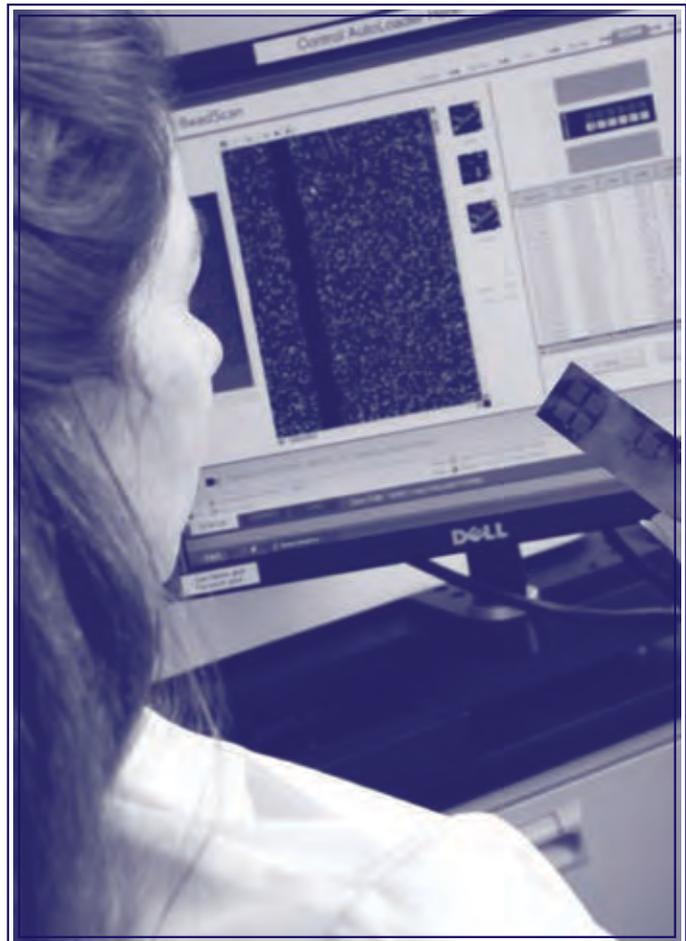


For decades, investigators have looked at chromosomes in a cell to unravel the genetic causes of various diseases. Called cytogenetics, the process involves looking at a person's karyotype — a relatively low-resolution picture of the chromosomes in a cell — to determine if any parts of the chromosomes are missing and may lead to disease.

The Human Genome Project and recent breakthroughs in array technology have refined the process, allowing investigators to look at the genome in finer, more precise resolution. As a result, the field of genetic diagnostics has shifted from one of cytogenetics to the emerging field of cytogenomics.

The Hospital's Clinical CytoGenomics Lab, directed by **Nancy Spinner, Ph.D.**, recently completed the transition from cytogenetic to cytogenomic testing. This was accomplished by a multidisciplinary team including members of the Center for Applied Genomics, directed by Hakon Hakonarson, M.D., Ph.D.; the Center for Biomedical Informatics and the Bioinformatics Core, directed by Peter White, Ph.D., and Xiaowu Gai, Ph.D.; and Tamim Shaikh, Ph.D., from the Division of Human Genetics and Molecular Biology; and with support from Bryan Wolf, M.D., Ph.D., from the Department of Pathology and Laboratory Medicine.

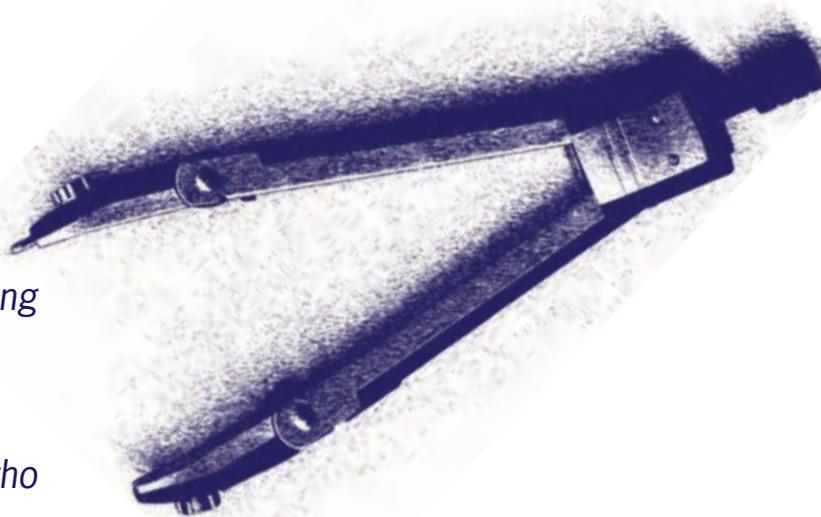
Nancy Spinner



Dr. Spinner and her colleagues in the Clinical CytoGenomics Lab used the Illumina® BeadArray platform to validate the results of traditional cytogenetic testing of more than 200 patients with known genetic abnormalities. The investigators confirmed all of the known abnormalities. They next analyzed a group of patients who had normal chromosomes to see if the array was more sensitive and, in fact, they identified additional abnormalities by array diagnostics in a significant percent of them.

After reviewing samples, the lab team taps into public and in-house databases that plot the areas where there are chromosomal duplications or deletions. "This process allows us to see the exact location of potential abnormalities," says Dr. Spinner. "From there, we explore the potential clinical consequences of the abnormalities based on previous studies."

Since its launch on May 1, the Clinical CytoGenomics Lab has reviewed hundreds of samples. Of those samples that were determined to be abnormal, approximately 80 percent would not have been found using conventional cytogenetics. A similar undertaking is in process for the Cancer Cytogenetics Laboratory directed by Jaclyn Biegel, Ph.D.



"The Stokes Institute's continued investment in state-of-the-art technology, coupled with the extensive expertise of investigators and support staff, continues to fuel breakthrough research and clinical diagnostics at Children's Hospital that makes an impact on children's health every day," says Dr. Spinner.

A young child with dark hair, wearing a bright yellow jacket and blue jeans with colorful patches, stands on a grey playground structure. The child is holding onto a yellow handrail. The background shows a blurred outdoor setting with greenery and a black metal fence. The entire page is framed by a decorative orange border with a repeating pattern.

Bridging Research and the Marketplace

Improving Child Health Through Partnership

New programs and resources, talented and dedicated investigators, grant awards, and scientific publications are some of the results of the preeminent research program at the Stokes Institute. Despite these benefits, every effort and investment at Stokes is made with a singular purpose in mind — eradicating disease and improving the lives of children through rigorous scientific study.

A concerted and specialized effort is required to bring the fruits of Children's Hospital discoveries to the next level, where a partnership with industry can bring a discovery to the marketplace and ultimately have an impact on the health of children across the globe.

The Office of Technology Transfer bridges research and the marketplace by serving as the conduit for intellectual property and the disclosure of new inventions. This effort involves tracking inventors, patents, agreements, documents, and correspondence, as well as funds for expenses and royalties. Technology Transfer's critical role at the Stokes Institute extends to protecting patents, copyrights, trademarks, and trade secrets.

The following patents were issued in the United States and Australia during fiscal year 2008 for technologies developed by Stokes investigators.

US Patent 7,288,644 and 7,405,292

Terri Finkel, M.D., Ph.D., chief, Division of Rheumatology, identified a cellular protein called HALP involved in the progression of HIV infection. The virus may use the cellular HALP gene to help protect HIV-infected cells from being targeted for destruction by a patient's immune system. The technology may ultimately lead to a therapeutic treatment to counteract HIV's stimulation of the HALP protein, allowing a patient's immune system to properly eliminate HIV-infected cells from the body.

US Patent 7,282,489

A technology developed by Robert Levy, M.D., Division of Cardiology, focuses on a "reverse gene therapy" concept, a term coined by Dr. Levy to emphasize the counter-intuitive approach that involves using a disease associated gene abnormality for therapeutic benefit. For example, Dr. Levy's group has shown that some of the gene abnormalities that can cause cardiac rhythm abnormalities, if incorporated into gene vectors, can be locally delivered to specific sites in the heart, where they can block the progression of other non-genetic, abnormal heart rhythms. The invention has wide applications in many diseases in addition to heart disease.

US Patent 7,244,571

Michael Grunstein, M.D., Ph.D., Division of Pulmonary Medicine, along with Hakon Hakonarson, M.D., Ph.D., developed a method to screen for drugs that may prove to be of use for asthma and other inflammatory diseases. The invention may also ultimately identify novel genes involved in causing asthma or an inflammatory state.

Australia Patent 2005201735.0

A patent issued to the Division of Hematology focuses on a recombinant adeno-associated viral vector that may be very effective in treating hemophilia patients, including children, via gene therapy. The vector delivers a gene for a clotting factor, and forms the basis for a clinical trial underway at Children's Hospital and other medical centers.

Patent Awards

Technology Transfer Stats

Active Licenses:

31

Patents Issued:

3 U.S.

Patent Applications Filed:

19 U.S.

Invention Disclosures Received:

56

License Revenues:

\$190,787,567

Revenues Not Including Rotateq® Monetization:

\$13,299,124

A young child with light brown hair and striking blue eyes is climbing a rope structure outdoors. The child is wearing a red jacket with grey accents and blue jeans. The background shows green trees and a clear sky. The entire image is framed by a decorative border of yellow dots.

The War for Talent

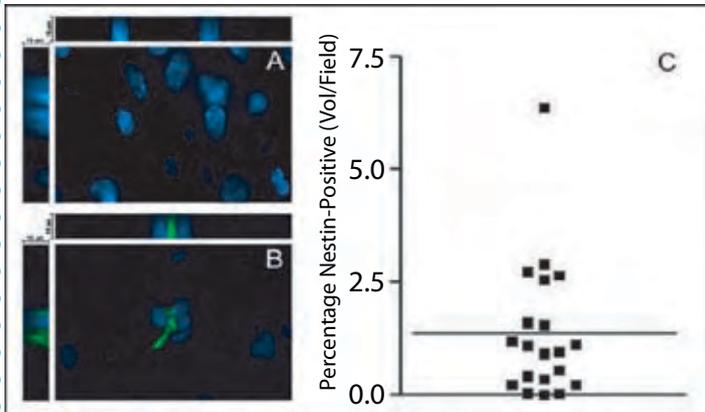
New Faces, Fresh Ideas, Consistent Success

Achieving our mission would be impossible without the team of talented people who conduct Stokes' preeminent pediatric research. Maintaining this team is an enormous challenge, but it results in our greatest asset — a community of investigators who create a better future for children.

Stokes aims not only to bring new investigators into the Institute, but also to retain investigators with flourishing research programs. Commingling the expertise of renowned investigators with the enthusiasm of new ones creates an electrified environment where anything is possible.

The following pages feature Stokes investigators at every stage: starting a first lab, solidifying a career path, continuing established research, becoming a mentor, and ending a lifelong passion.

Nestin Expression in Neonatal Hippocampus



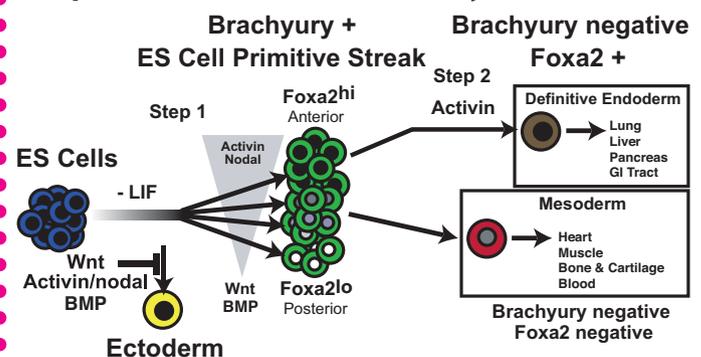
Lynnae Schwartz, M.D.
 Division of Research Anesthesiology

Children who have experienced neuroinflammation early in life as a result of HIV-1 infection often experience developmental problems. In collaboration with the National Institutes of Health, I study the development of children and adolescents who were infected by HIV-1 in utero or soon after birth. Because many of my patients have problems with learning and memory, I am focusing on how HIV-1 affects neural progenitor cells and neurogenesis in developing brains. These results may help practitioners and caregivers address the mental health needs of children and adolescents infected with HIV-1.

Paul Gadue, Ph.D.
 Division of Hematology

I am exploring the prospect of using embryonic stem (ES) cells — cells that have the ability to generate all cell types present in the body — to generate tissue that will treat a wide variety of diseases. Working in the Center for Cellular and Molecular Therapeutics, I am focusing on the molecular mechanisms that regulate endoderm development using the in vitro differentiation of ES cells. Endoderm, one of three primary germ layers formed in embryonic development, gives rise to the liver, pancreas, and lungs, which are important targets for the development of cell-based therapies.

Stepwise Differentiation of Embryonic Stem Cells



Tropical Rickets: Mutation in the *CYP2R1* Gene Encoding the 25-hydroxylase



Genu Varum



Genu Valgum



Windswept Deformity

*Michael Levine, M.D.,
F.A.A.P., F.A.C.P.
Division of Endocrinology*

I investigate genetic disorders of bone and mineral metabolism using a translational approach. To address disorders that affect the growing skeleton, I focus on the molecular pathophysiology of parathyroid hormone and vitamin D, both of which play essential roles in vertebrate physiology and development. Building on my previous findings, I am identifying the targets of a gene that controls parathyroid development, examining mechanisms of parathyroid hormone signaling in the skeleton, and isolating genetic mutations that influence vitamin D metabolism.

*James Kreindler, M.D.
Division of Pulmonary Medicine*

I am a pediatric pulmonologist who focuses on the effects of secondhand smoke (SHS) and the mechanisms of ion transport in human airways. Exposure to SHS often results in significant respiratory problems associated with poor mucus clearance from the respiratory tract.

My research has unveiled that the extracts of cigarette smoke impair chloride secretion in human airway cells, which may impair mucus clearance. I am now focusing on the exact way that SHS inhibits this secretion, as an understanding of how SHS causes cells to malfunction is critical to developing new therapies.

Normal Human Bronchial Epithelial Cells

HHMI Selects Stokes Investigator as New Member

Following a nationwide competition, **Vivian Cheung, M.D.**, Division of Neurology, was named a Howard Hughes Medical Institute (HHMI) investigator. She was 1 of 15 physician-scientists selected by the prestigious research organization.

HHMI is a nonprofit medical research organization that supports hundreds of investigators throughout the United States by providing them with a research budget and laboratory space. The institute conducts medical research and supports science education in the United States and biomedical scientists in other countries.

Dr. Cheung's goal is to help physicians predict how a patient will respond to a given drug or treatment based on the patient's particular genetic profile. Specifically, she investigates how the sequence of DNA units in a person's chromosomes affects that person's susceptibility to disease. By determining how gene expression changes in response to drugs and other treatments, she discovers how each patient's genetic tools are associated with the effectiveness of their disease treatments. This process removes some of the guess work in making therapeutic decisions and providing the best preventive and therapeutic care.



As a pediatric neurologist, Dr. Cheung continues to work at Children's Hospital and remains an associate professor of pediatrics and genetics at the University of Pennsylvania School of Medicine.





Investigator Honored With IOM Membership

Katherine High, M.D., HHMI, was elected as a member of the Institute of Medicine (IOM), one of 65 new members recognized last year for their major contributions to the advancement of medical sciences, healthcare, and public health. She is the seventh Children's Hospital investigator to be granted this prestigious honor.

Established in 1970 by the National Academy of Sciences, the IOM honors professional achievement in the health sciences and serves as a national resource for independent analysis and recommendations on issues related to medicine, biomedical sciences, and health.

Dr. High was selected in honor of her leading research in hematology and gene therapy. An internationally prominent hematologist and researcher, her investigations and position as the director of the Center for Cellular and Molecular Therapeutics at Children's Hospital have led to clinical trials exploring gene therapy for hemophilia and other disorders.

She leads a National Institutes of Health-funded laboratory and has contributed scores of papers to the scientific literature. In addition, she is the William H. Bennett Professor of Pediatrics at the University of Pennsylvania School of Medicine, a Howard Hughes Medical Institute Investigator, and a past president of the American Society of Gene Therapy.



From Hand to Hand, Passing the Torch of Discovery

Tom Moshang, M.D., a senior physician in the Division of Endocrinology, dedicated the last 25 years of his career to Children's Hospital, where he conducted world-renowned research in the areas of growth failure and endocrine complications in long-term survivors of childhood cancer.

A distinguished clinician, investigator, and educator, Dr. Moshang was an emeritus professor of pediatrics at the University of Pennsylvania School of Medicine and the founding director of the Diagnostic and Research Growth Center at the Hospital, a center nationally recognized for expertise in the clinical evaluation, diagnosis, and treatment of children with disorders of growth and puberty.

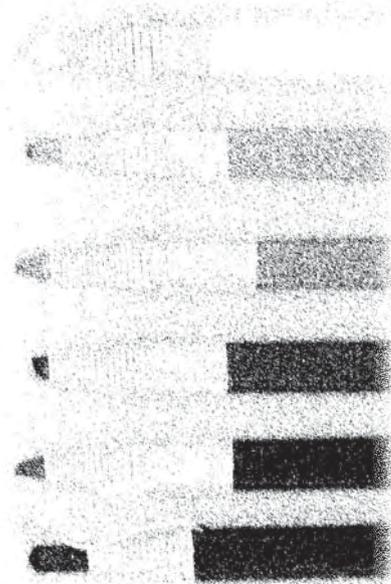
Dr. Moshang dedicated his research to improving the quality of life of children who survived cancer. He had a special interest in disordered growth and sexual development related to pediatric cancer and the therapies for treating cancer.

Dr. Moshang's contributions to pediatric endocrinology earned him the title of president-elect of the Lawson Wilkins Pediatric Endocrine Society, the major scientific organization in his discipline. The Department of Pediatrics and Children's Hospital recently honored Dr. Moshang with the establishment of the Thomas Moshang Jr., M.D., Endowed Chair in Pediatric Endocrinology.

An outstanding and resourceful mentor to pediatric endocrinology fellows, Dr. Moshang developed lasting relationships with his mentees and continued to counsel students until the time of his death on February 24 at age 70.



An Opportunity to 'Discover Stokes'

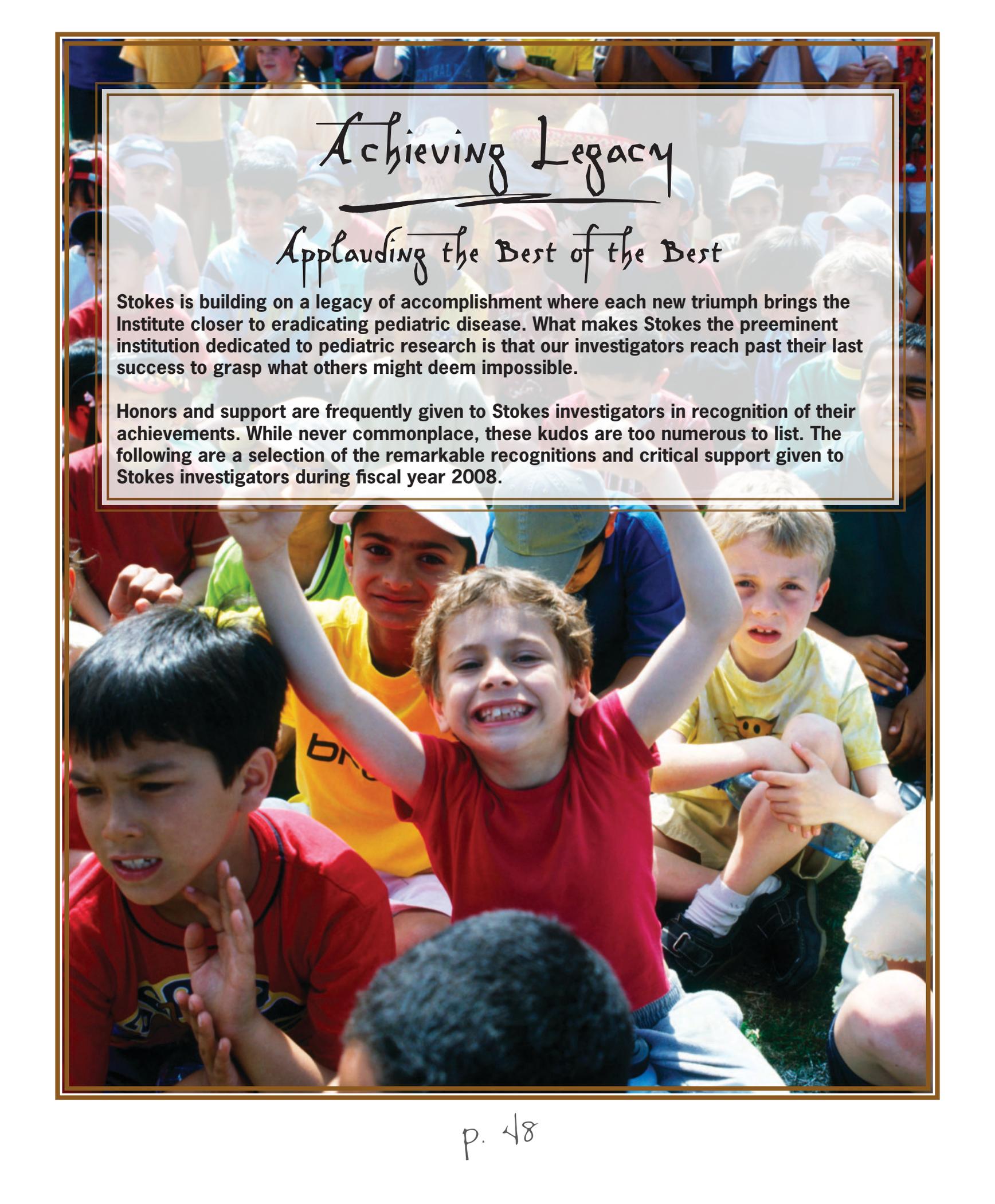


When investigators make decisions about their careers they are concerned with finding a place where they will flourish, their research has the potential to make a direct impact, and they will be supported by an institutional commitment to the success of research programs.

“Discover Stokes,” a highly visual, Web-based tool, shows investigators — those who have recently joined the Institute and those considering it — that the Stokes Institute is the world-class center of pediatric research and teaching.

Developed by the Department of Research Education, “Discover Stokes” includes short videos of facilities, resources, researchers, leadership, and patients and showcases the commitment of the Stokes Institute to turn scientific discovery into medical innovation.

Discover how you can be a part of where pediatric medicine is going by accessing “Discover Stokes” on this report’s multimedia CD or the Stokes Web site.

A group of children sitting on the grass, some with their arms raised in celebration. The children are wearing various colored shirts and caps. The scene is outdoors and appears to be a group activity or event.

Achieving Legacy

Applauding the Best of the Best

Stokes is building on a legacy of accomplishment where each new triumph brings the Institute closer to eradicating pediatric disease. What makes Stokes the preeminent institution dedicated to pediatric research is that our investigators reach past their last success to grasp what others might deem impossible.

Honors and support are frequently given to Stokes investigators in recognition of their achievements. While never commonplace, these kudos are too numerous to list. The following are a selection of the remarkable recognitions and critical support given to Stokes investigators during fiscal year 2008.

Endowed Chairs: Philanthropy Supporting Research



Children's Hospital established its endowed chair program 20 years ago in honor of C. Everett Koop, M.D., a former surgeon-in-chief at the Hospital who went on to become the U.S. surgeon general.

Since its inception, the endowed chair program has become a driving force in the continued success of the institution.

A chair is one of the highest honors a physician-scientist can hold and an invaluable resource for supporting research and promoting superior education. A chair also represents one of the most meaningful and permanent forms of philanthropy.

In fiscal year 2008, the Board of Trustees at Children's Hospital approved the establishment of several new endowed chairs, the support of which allows chairholders to continue their pursuit of new research programs and initiatives aimed at improving the health and well-being of children.

The **Buck Family Endowed Chair in Hematology** honors the memory of Anne Garrett Buck, who suffered from a rare blood disorder called aplastic anemia. The endowed chair will focus on advancing treatments and cures in bone marrow failure and aplastic anemia.

Advancing diabetes research is at the heart of the **Daniel B. Burke Endowed Chair in Diabetes Research**, established to honor the father of Stephen Burke. Daniel Burke has served as a distinguished member of the joint Board of Trustees of The Children's Hospital of Philadelphia and Children's Hospital Foundation for nearly a decade and is currently the chairman of the Board.

The **Children's Hospital of Philadelphia Endowed Chair in Critical Care Medicine** supports the clinical, research, educational, and other charitable endeavors in the area of pediatric intensive care medicine. The endowed chair was established from the proceeds of the 2007 Carousel Ball and with the support of Children's Anesthesiology Associates and the Children's Hospital Foundation.

The **Jane Fishman Grinberg Endowed Chair in Stem Cell Research** honors the sister of Mark Fishman, who has held numerous leadership responsibilities at Children's Hospital over more than 20 years. Jane Fishman Grinberg was a philanthropist who lost her life to breast cancer. Mr. Fishman continues to serve on the joint Board of Trustees of The Children's Hospital of Philadelphia and the Children's Hospital Foundation.

In honor of his life and 25 years of service, the Hospital established the **Thomas Moshang Jr., M.D., Endowed Chair in Pediatric Endocrinology**. The late Dr. Moshang distinguished himself as a clinician, investigator, scholar, teacher, and mentor who also served in a variety of administrative positions at the Hospital, including chief of the Division of Endocrinology. He was a member of several honorary and professional societies and shared his research findings with the scientific community through more than 150 peer-reviewed articles, book chapters, and reviews.

During his tenure as director of the Division of Hematology, Elias Schwartz, M.D., fostered the division's growth substantially so that it now serves hundreds of children and has become a major center for research in blood disorders. A pioneer in his own right, Dr. Schwartz combined innovative clinical research and meticulous patient care to implement treatment programs that improved the outlook for many children with blood disorders. The **Elias Schwartz Endowed Chair in Pediatric Hematology** was recently awarded to current division chief Catherine Manno, M.D.

Deputy Scientific Director Tom Curran, Ph.D., furthers his research into the molecular and neoplastic growth of the developing nervous system with assistance from the **Mai and Harry F. West Endowed Chair in Pediatric Research**. The chair honors the close friends of the late Evelyn Willing Bromley, who was inspired to support Children's Hospital by Mr. West's four decades of service as a Hospital trustee.

The **Evelyn and George Willing Endowed Chair in Pathology Research** was established in honor of the parents of the late Evelyn Willing Bromley. The chair supports the research efforts of Janis Burkhardt, Ph.D., Department of Pathology and Laboratory Medicine. Dr. Burkhardt's investigations center on understanding the regulation of T lymphocyte function. In particular, her research asks how changes in cell structure control the ability of these cells to move within body tissues and interact with other cells during an immune response. Dr. Burkhardt plans to use the chair funds to study two important proteins that control cell structure, HS1 and c-Abl. Normal function of these proteins is important for the T cell response to infectious agents and cancers, but mutations in these proteins result in autoimmune disease and leukemia.



Awards Recognize Achievements, Potential



Stokes investigators are fueled not only by the groundbreaking outcomes of their research but also by continuous support and recognition from the scientific community. Their many accomplishments are encouraging to both their patients and their peers. The following list represents only a fraction of the many awards that Children's Hospital investigators received during the past year.

Robert Levy, M.D., and Ilia Fishbein, M.D., Ph.D., Division of Cardiology, developed a technology for using magnetism to guide nanoparticles into stents that Forbes magazine called one of the "Promising Disruptive Technologies" for 2008.

Alan Flake, M.D., Division of General, Thoracic, and Fetal Surgery, received the Sheen Award of the American College of Surgeons, an award honoring individuals that have made important contributions to medicine.

Journal Watch, a physician-targeted newsletter published by the New England Journal of Medicine, selected a study led by Ron Keren, M.D., M.P.H., Division of General Pediatrics as one of the Top Ten Pediatric Stories of 2007. The study, published in the Journal of the American Medical Association, found that prophylactic antibiotic therapy was not associated with a reduction in recurrent urinary tract infections in children.

A study led by Jeffrey H. Silber, M.D., Ph.D., Center for Outcomes Research, titled "Hospital Teaching Intensity, Patient Race and Surgical Outcomes," was selected as the 2008 Most Outstanding Abstract on Racial Disparities by AcademyHealth, a professional society for health service researchers.

Joshua Friedman, M.D., Ph.D., Division of Gastroenterology, Hepatology, and Nutrition, was awarded the Young Faculty Investigator Award from the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition.

Mary Leonard, M.D., M.S.C.E., Division of Nephrology, was elected to the American Society for Clinical Investigation, an honor society of physicians who excel in translational research.

Kathleen Sullivan, M.D., Ph.D., Division of Allergy and Immunology, was elected as the 2007-2008 president of the Clinical Immunology Society and named to the NIH Board of Scientific Counselors.

Robert "Skip" Nelson, M.D., Ph.D., Division of Critical Care Medicine, received the Commissioner's Award of Excellence from the FDA's Office of the Commissioner for his work in pediatric research ethics.

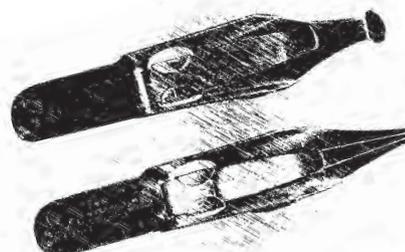
Vinay Nadkarni, M.D., Division of Critical Care Medicine, was elected as the chair of the International Liaison Committee on Resuscitation, the highest honor for a resuscitation scientist.

Michael Bennett, Ph.D., Division of Laboratory Medicine, received the 2007 Award for Outstanding Contributions in a Selected Area of Research from the American Association for Clinical Chemistry. This award recognizes Dr. Bennett as one of the world's foremost experts in inborn errors of mitochondrial energy metabolism.

Jeffrey Golden, M.D., Division of Developmental Biology, was elected president of the American Association of Neuropathologists and received honorable mention for the 2007 Weil Award for the Best Paper on Experimental Neuropathology from the American Association of Neuropathologists.

Joseph Zorc, M.D., Division of Emergency Medicine, received the Best Abstract Award in Pediatric Emergency Medicine at the Annual Meeting of the Pediatric Academic Societies for his work on improving primary care follow-up after an emergency department visit for asthma.

Flaura Winston, M.D., Ph.D., Division of General Pediatrics, and Dennis Durbin, M.D., M.S.C.E., Division of Emergency Medicine, received the Fellow Achievement Award from the American Academy of Pediatrics section on injury, violence, and poison. Co-scientific directors of the Center for Injury Research and Prevention, both Dr. Winston and Dr. Durbin were awarded for their impressive body of work in health sciences research.



Nancy Kassam-Adams, Ph.D., Division of General Pediatrics, was chosen to serve on the American Psychological Association Presidential Task Force on Child Trauma and Posttraumatic Stress Disorder (PTSD). The task force will identify the key contributions of psychological science to understanding PTSD in youth.

Paul Offit, M.D., Division of Infectious Diseases, received the Stanley A. Plotkin Award for Outstanding Achievement in Vaccines from the Pediatric Infectious Disease Society.

John Maris, M.D., Division of Oncology, received the Oski Award from the American Society of Pediatric Hematology/Oncology, given to an outstanding clinical or laboratory investigator. In addition, he was elected to the American Society for Clinical Investigation, and was awarded the Best Paper in Basic Science at the Advances in Neuroblastoma Research 2008 Conference for his paper titled, "A genome-wide association study (GWAS) identifies susceptibility loci to high-risk neuroblastoma," which was subsequently published in the New England Journal of Medicine.

Larissa T. Bilaniuk, M.D., Division of Neuroradiology, received the 2008 Gold Medal Award from the American Society of Pediatric Neuroradiology for her outstanding contributions, especially in the fields of head and neck and fetal neuroimaging, and her dedication to teaching.

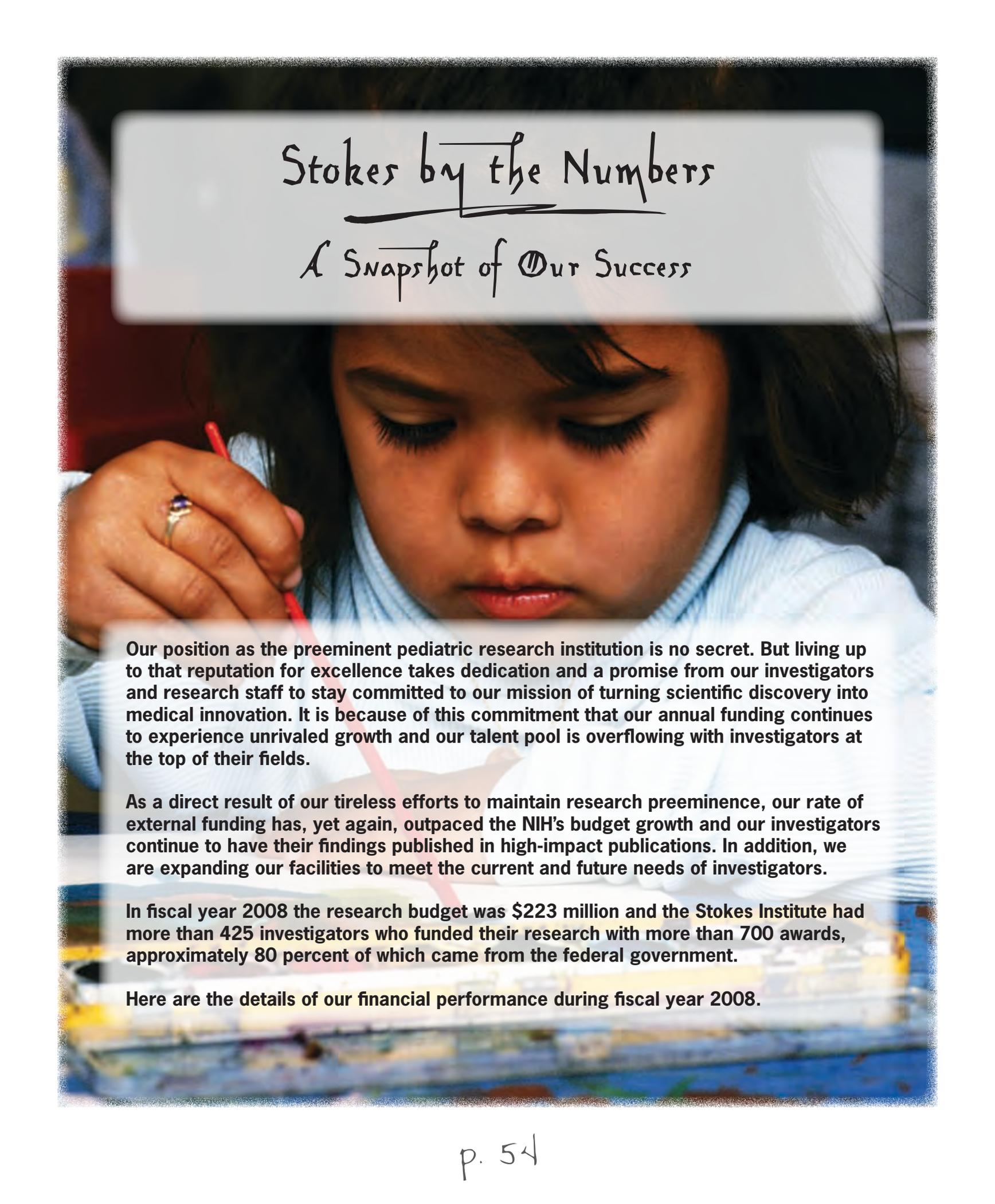
J. Nadine Gracia, M.D., M.S.C.E., a general research fellow in the Division of General Pediatrics, was one of 14 individuals selected as a White House Fellow for 2008-09.

Jinglan Liu, Ph.D., Division of Human Genetics and Molecular Biology, was awarded a two-year Cornelia de Lange Syndrome Foundation fellowship — the first for the nonprofit.

Barbara Schmidt, M.D., M.Sc., Division of Neonatology, received the SCT/ImpACT Trial of the Year Award from the Society for Clinical Trials and Project Impact. The award recognizes Dr. Schmidt's study on caffeine for apnea of prematurity published in the New England Journal of Medicine.

Tammy Kang, M.D., Division of Oncology, was named to the 75 Greatest Living Philadelphians list. The list, sponsored in part by the Philadelphia Eagles, acknowledges people who "motivate, inspire, and improve others and give back to the community."





Stokes by the Numbers

A Snapshot of Our Success

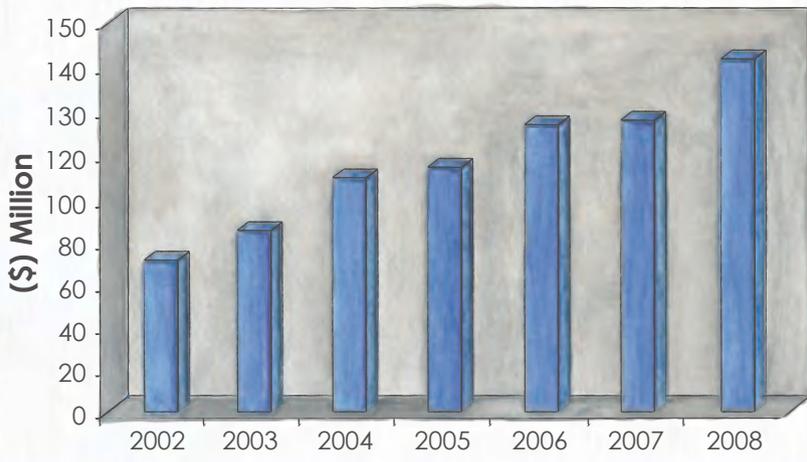
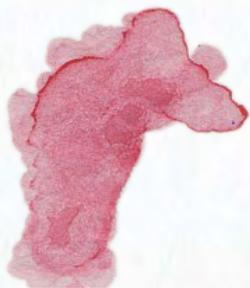
Our position as the preeminent pediatric research institution is no secret. But living up to that reputation for excellence takes dedication and a promise from our investigators and research staff to stay committed to our mission of turning scientific discovery into medical innovation. It is because of this commitment that our annual funding continues to experience unrivaled growth and our talent pool is overflowing with investigators at the top of their fields.

As a direct result of our tireless efforts to maintain research preeminence, our rate of external funding has, yet again, outpaced the NIH's budget growth and our investigators continue to have their findings published in high-impact publications. In addition, we are expanding our facilities to meet the current and future needs of investigators.

In fiscal year 2008 the research budget was \$223 million and the Stokes Institute had more than 425 investigators who funded their research with more than 700 awards, approximately 80 percent of which came from the federal government.

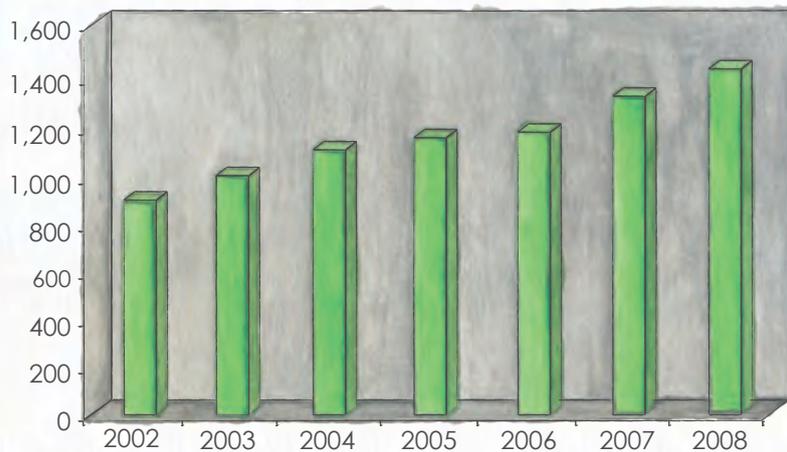
Here are the details of our financial performance during fiscal year 2008.

External Grants and Contracts*

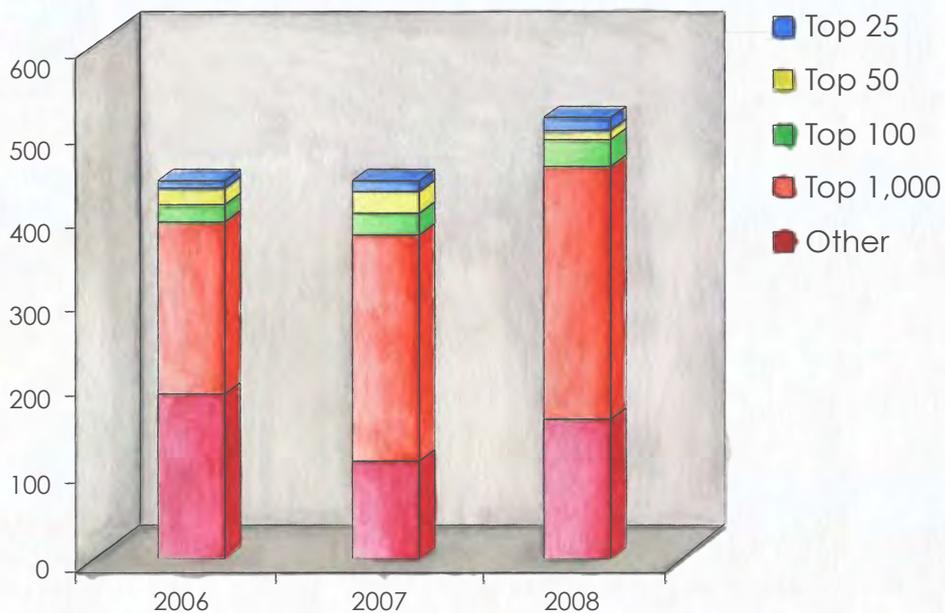


*Total Costs (direct and indirect)

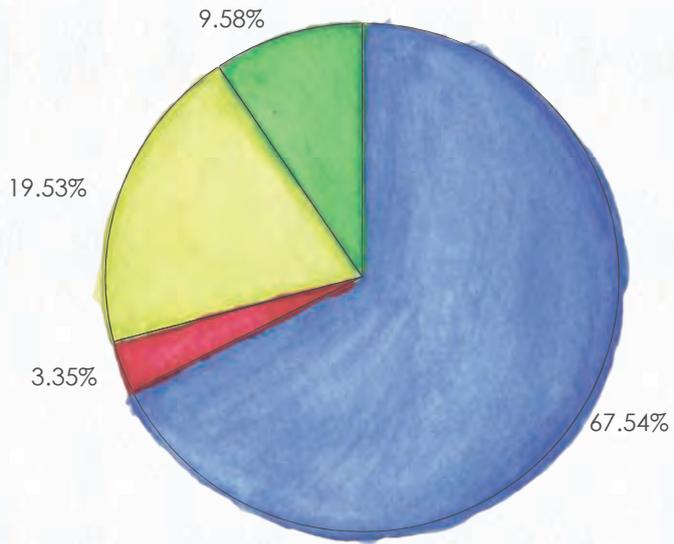
Number of Research Staff



Publications

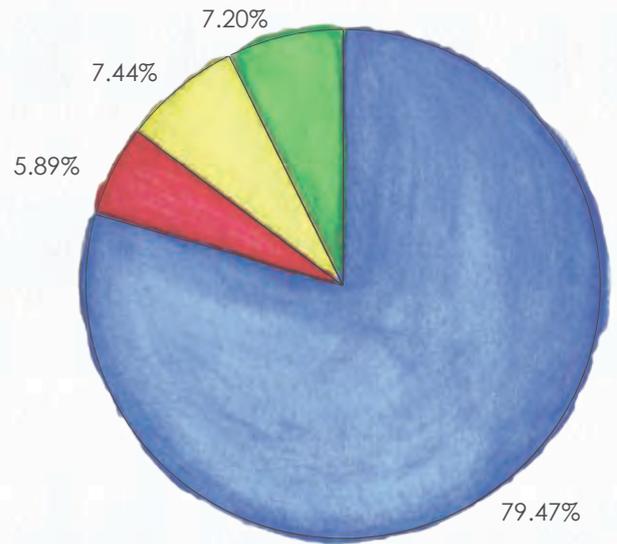


All Sources of Funding



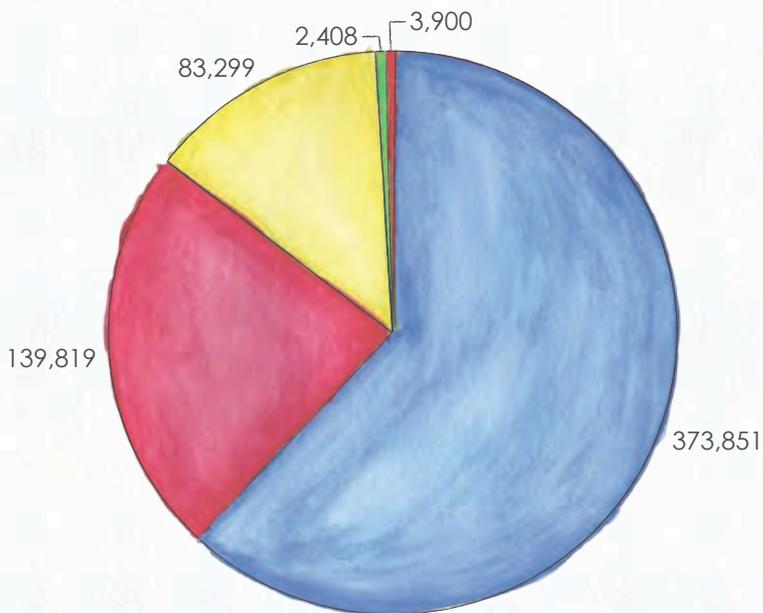
- External
- Hospital
- Endowment
- Other

All Sources of External Funding



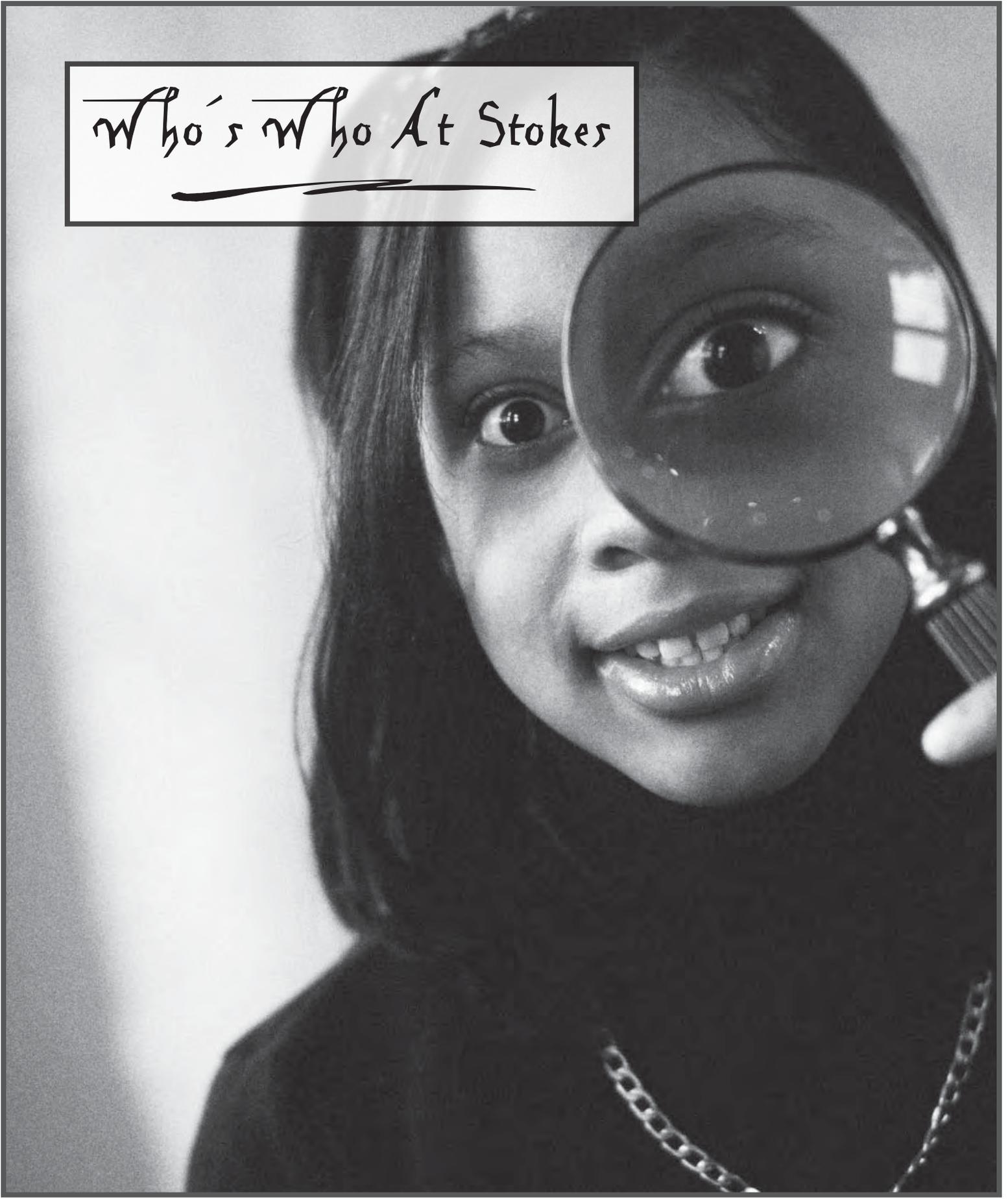
- Federal
- Industrial
- Foundation
- Other

Total Research Space



- Abramson Research Center
- 3535 Market Street
- Colket Translational Research Building
- 3550 Market Street
- Main Building

Who's Who At Stokes



**The Joseph Stokes Jr. Research Institute
Leadership**

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

*Tom Curran, Ph.D.
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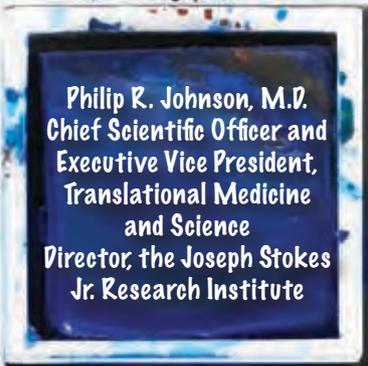
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