CINCINNATI
CHILDREN'S

RESEARCH FOUNDATION

2010 ANNUAL REPORT

Cincinnati Children's

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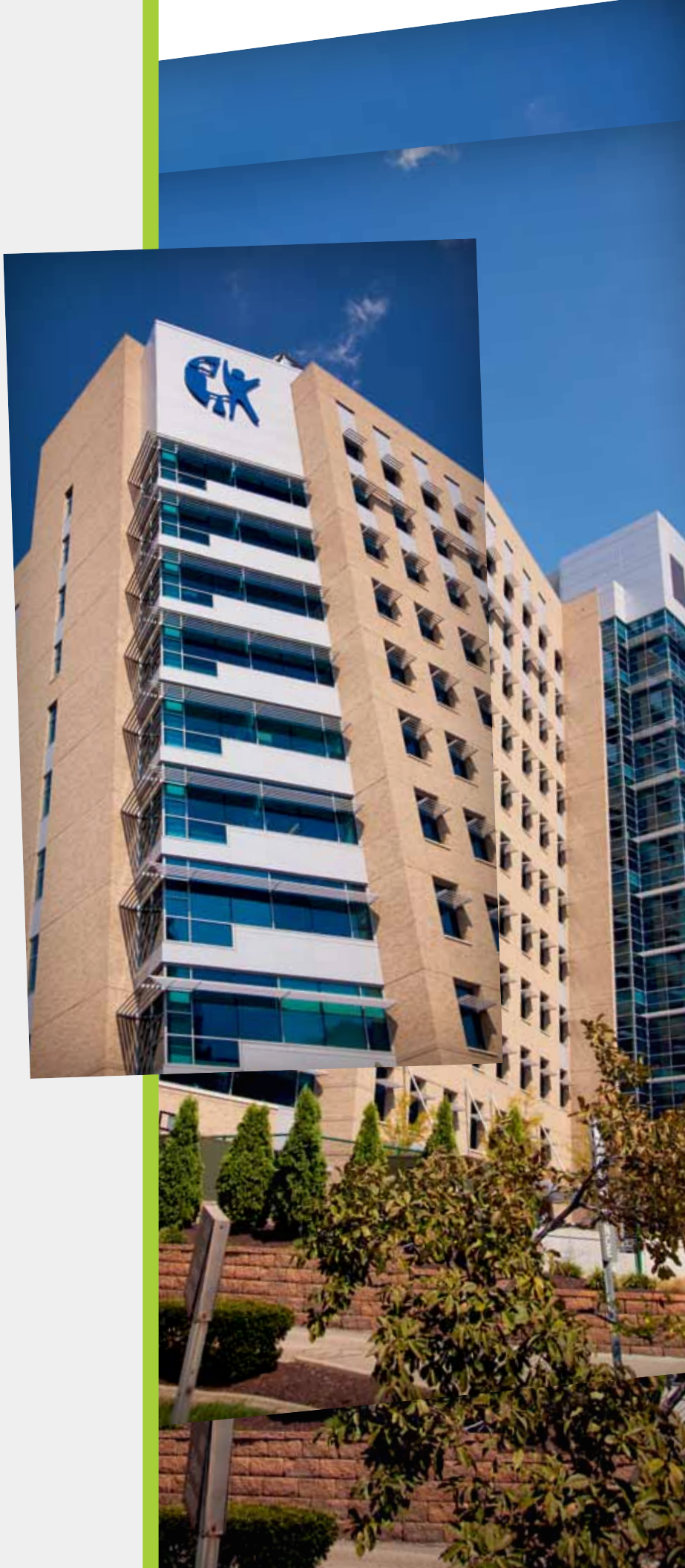

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This report features highlights of our research activities of the past year. For a detailed look at our research, publications and faculty, go to **www.cincinnatichildrens.org/research10**.

Arnold W. Strauss, MD, is director of the Cincinnati Children's Research Foundation and Rachford professor and chair of the Department of Pediatrics, University of Cincinnati College of Medicine.

Changing the World for Children

Dear Colleagues,

Our mission is to improve child health in our Cincinnati community and globally, literally by changing the world through the spectrum of biomedical research.

In this 2010 Annual Report, you will learn how that change occurs. You will see how our talented faculty and staff discover the underlying biologic and disease mechanisms, translate those discoveries to new therapies, test those treatments in patients, and assess the outcomes. And while the focus of this report is on our creative and talented investigators, you will also read about the unique infrastructure we have created that is required for this work.

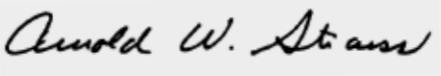
In laboratory discovery, the stem cell core, for example, provides investigators with well-characterized pluripotent cells to investigate organogenesis, lineage development and differentiation. In translational research, the vector and cell manipulation cores use sophisticated production facilities in a tightly controlled environment to generate viral vectors and genetically altered cells for gene and cell-based therapies in humans.

For clinical and outcomes research, our research nurses and data management specialists provide the machinery to recruit patients and to accumulate and analyze data for multi-site, multi-investigator trials of drug therapies. This allows us to assess outcomes much more quickly than would be possible with single investigator, single-site studies, accelerating the application of novel therapeutics to wide-based use. Similarly, we have developed approaches to gather clinical information for all patients evaluated at Cincinnati Children's into a data warehouse that provides a complete, rich source of information for clinical investigation. Through these critical infrastructural components, the Cincinnati Children's Research Foundation is able to integrate research across the spectrum and take advantage of our collaborative attitude. We can move quickly to improve discovery and patient outcomes.

Our 2010 accomplishments are many and the stories about our discoveries are compelling. Each division provides a description of its clinical care, research and educational efforts, with more detail available on-line. In aggregate, the results demonstrate why Cincinnati Children's is a leader in pediatrics nationally and internationally, with more than 1100 publications, $170 million in sponsored research programs, 600 faculty and highly ranked programs in all pediatric and surgical subspecialties.

Wherever I travel, whether to China, Philadelphia, Los Angeles or Vancouver, I hear of the impact and reputation that Cincinnati Children's caregivers, investigators, educators and advocates are having in the world. Together, we are changing the world for children, every day.

Sincerely,



Arnold W. Strauss, MD
Rachford Professor and Chair
Director, Cincinnati Children's Research Foundation

Thomas G. Cody
Chairman
Cincinnati Children's Board of Trustees

Nancy Eddy, PhD
Research Chair
Cincinnati Children's Board of Trustees

The collaborative spirit, intellectual strength and clinical expertise of our scientists and physicians are producing answers to some of the most persistent, challenging health problems of our time.

From the Board

Cincinnati Children's has a long, proud legacy of using scientific inquiry and exploration to understand and overcome the health problems that beset children not just within our walls and our community, but around the world.

The oral polio vaccine. The vaccine for rotavirus, the most common cause of severe diarrhea in infants and children worldwide. A rapid test to detect kidney injury before irreparable harm can occur. A gene chip that quickly and less invasively identifies jaundice in patients with liver disease.

These discoveries were all made here at Cincinnati Children's – and all of them are being used to prevent and treat devastating illnesses in children worldwide.

This year's annual report showcases the global impact of our researchers. You will read about the diverse and exciting research our scientists are conducting with colleagues in every part of the world – work that is already making a difference in children's health.

In the spirit of "the more good minds, the better," you will learn about our prominent role as a lead institution in the growing trend of multicenter studies, where collaboration accelerates and enhances the exchange of information, the pace of discovery and the ability to deliver effective treatments.

In the story about our remarkable core laboratories, you will see how breakthroughs in gene and stem cell therapy made over years of basic research are being transformed into treatments with the potential to change the lives of patients with rare and troubling diseases.

The pace of scientific discovery has accelerated exponentially in the last decade. As you will read in these pages, Cincinnati Children's is well positioned to keep up. We have planned for it; we have invested in it; we are now reaping the rewards of that investment.

When we opened our new research facility nearly three years ago, our vision was for a physical space where basic science and patient care would come together. We are proud to see how that vision has not only taken hold, but exceeded our expectations. The collaborative spirit, intellectual strength and clinical expertise of our scientists and physicians are producing answers to some of the most persistent, challenging health problems of our time. We are attracting worldwide attention for our work, and world-renowned physicians and scientists to our ranks.

As members of the Cincinnati Children's Board of Trustees, we are proud to help support the work of our researchers and physicians as they change the future of medicine and of children around the world.

BRINGING GENE THERAPY TO LIFE

Translational core labs turn years of research into treatments with the potential to cure

Clad head to toe in bright white clean suits, Han van der Loo, PhD, and his colleagues at Cincinnati Children's Hospital Medical Center are working to transform a long-pursued scientific quest into medical reality.

Here, in high-tech facilities kept cleaner than most hospital operating rooms, these scientists combine re-engineered human cells with carefully modified viruses that will deliver bold new gene therapies to patients.

These treatments – entering human clinical trials after years of lab-based research – offer new hope for devastating conditions ranging from brain tumors to sickle cell anemia to X-SCID, the rare condition also known as "bubble boy syndrome."

These gene therapy trials, along with others still in the planning stages, reflect the leading edge of a new age of medical innovation, and the Translational Core Services at Cincinnati Children's are helping pave the way.

"This is the pipeline for translating gene therapy research from the bench to the bedside," says Punam Malik, MD, *(at right)* molecular and gene therapy program leader at Cincinnati Children's. "It's a huge endeavor that requires carefully controlled environments and highly skilled staff. Very few medical centers have facilities as comprehensive as these."

From viral vectors to engineered cells, the translational core labs at Cincinnati Children's provide scientists with the latest gene therapy tools.

"This is the pipeline for translating gene therapy research from the bench to the bedside."

Trials mark new chapter

Three projects mark Cincinnati Children's emerging role in human testing of gene therapy.

In May 2010, a team led by Timothy Cripe, MD, PhD, began a clinical trial of a gene therapy for rhabdomyosarcoma and other solid tumor cancers that have not been controlled by other treatments. This trial, which follows years of pre-clinical testing, marks the first gene therapy attempted in patients at Cincinnati Children's. The viral vector for this trial was developed in Scotland, but was processed and prepared for administration here. Cripe, a specialist in pediatric hematology/oncology, also serves as co-medical director for the Office for Clinical and Translational Research.

Experts at Cincinnati Children's also developed the viral vector being used for an X-SCID gene therapy trial started in 2010. This Phase I clinical study will involve up to 20 boys to be treated in Boston, Cincinnati, Los Angeles, London and Paris. At Cincinnati Children's, a team led by Alexandra Filipovich, MD, director of the Immune Deficiency and Histiocytosis Program, is collaborating with Children's Hospital Boston, which leads this study.

Meanwhile, the FDA has approved plans for Cincinnati Children's to begin a clinical trial for a potential breakthrough gene therapy for sickle cell anemia. Patients are expected to receive treatment beginning in Spring 2011. This study is led by Malik, who also serves as deputy director of the Comprehensive Sickle Cell Program.

More clinical trials involving other conditions are likely to begin in the year to come, pending review and approval from the FDA and the medical center's Institutional Review Board, Malik says.

Dr. Timothy Cripe leads a clinical trial of a gene therapy to treat cancer, one of three gene therapy projects approved for human testing. Others include sickle cell anemia and X-SCID.

Years of planning bear fruit

Together, the Translational Core Laboratories are a one-stop-shop for translating research in genetic and cellular therapies into patients. The laboratories include more than 20 people who conduct and support work occurring in 11,000 square feet of controlled-access laboratory space. The labs and their staff occupy most of the top floor of the medical center's newest research tower.

The Cell Processing and Manipulations Lab, co-directed by Diana Nordling and Carolyn Lutzko, PhD, has processed 350 bone marrow aspirates, 700 umbilical cord blood products from normal deliveries, and 60 mobilized peripheral blood products for stem cells and have released nearly 3 billion blood stem cells to 53 different investigators at Cincinnati Children's and 12 external investigators in the last five years.

Dr. Han van der Loo oversees viral vector production in labs where every action is scripted and witnessed by an observer.

Air quality in these labs is up to 100 times cleaner than a surgical suite.

A day in the labs

Production of gene therapy test materials occurs in the nine cleanroom suites of the Aseptic Processing Labs. Services conducted here include production of research-grade and clinical-grade viral vectors, generation of cell lines, transduction for gene transfer, cryopreservation, transportation and thawing in preparation for infusion.

The work to maintain a highly-controlled environment is intense.

Van der Loo opens a freezer chilled by liquid nitrogen to a negative 196 degrees Celsius to briefly display a frosty tray containing nearly 200 tiny vials. Each vial represents a dose of gene therapy for an upcoming clinical trial.

"This is more than $650,000 worth of product," he says. "The materials stored in these freezers can be worth millions."

During production, people cannot enter the labs without completing special training to work in a clean room setting. Just putting on a clean suit requires following proper procedure. Pant legs, for example, cannot touch the floor while donning the suit. Hoods and masks cover everything but the eyes. Hands require double gloves plus sleeve protectors.

Staffers get tested on clean suit procedures every six months. Those who make a mistake must get it right three times in a row before re-entering the labs.

Production work occurs under highly sensitive hoods that prevent fumes and particles from escaping. While the air in the lab room is kept as clean as a surgical suite, the air under the hoods is maintained at levels 100 times cleaner.

The work tasks themselves are scripted, step-by-step. Each action is not only documented, it is witnessed by an observer who initials every step for the official record.

A typical clean-room session, be it transferring product to stacked dishes of growth media or breaking down a batch of finished product into dose-sized vials for shipping, can last four hours or more – with no snacks, drinks or restroom breaks.

When the day's tasks are complete, the cleaning begins. Every surface gets wiped down with powerful disinfectants. The hood. The floors. The walls. Everything. Staffers' clean suits also get swabbed for contamination testing.

Through it all, air sampling devices under the hood and in the lab room sniff for particles. Computers monitor every door, including incubators and freezers. Leave a door open too long, an alarm triggers.

The facility also features a dedicated, redundant HEPA-filtered air handling system, with its own emergency back-up power. The system uses positive and negative pressure to strategically manage air flow in the labs and hallways, with airlocks controlling human traffic with green and red lights.

The Pluripotent Stem Cell Facility already has produced pancreatic, retinal, intestinal, liver and cardiac cells for use in research and perhaps ultimately for therapy.

Testing and monitoring

In addition to the cleanrooms, the facility includes teams that closely monitor the various stages of production.

The Translational Trial Development and Support Lab (TTDSL) conducts the custom medical tests needed to analyze the performance of the test product. Work here includes analyzing blood and tissue samples with custom-tailored molecular assays to track protein and cell function. This lab also maintains a repository of normal donor cells for research use.

All the production work must comply with regulatory standards. Making sure that happens is the task of the Quality Assurance Group.

Meeting GMP and GTP manufacturing standards can require documentation for everything from production records to lab test results to equipment calibration data. Even in the digital age, research record-keeping still requires rooms filled with file cabinets and floor-to-ceiling shelves of three-ring binders. In fact, the paperwork for a single gene therapy project can stand more than seven feet high.

The standards are strict because the stakes are high.

"Materials produced in these labs will go from here to an operating suite to be injected into a patient. We want to avoid even the slightest contamination," van der Loo says.

The cell manipulation process often includes separating stem cells from blood products.

Drs. James Wells *(far left)* and Chris Mayhew direct Ohio's first Pluripotent Stem Cell Facility at Cincinnati Children's.

Stem Cell Facility: Pioneering Approach to Frontline Research

Some of the therapeutic agents manufactured in the clean-rooms of the Translational Services Laboratories ultimately will trace their roots to another important facility launched in 2010 at Cincinnati Children's.

The Pluripotent Stem Cell Facility is the first of its kind in Ohio, Kentucky or Indiana. Here, scientists can generate induced pluripotent stem cells (iPSCs) by reprogramming mature human cells into embryonic-like stem cells that can become any cell type in the body.

The ability to produce iPSCs gives researchers at Cincinnati Children's, the University of Cincinnati College of Medicine, and other laboratories in the region a powerful new tool to study the causes of disease and to grow replacement tissues for future therapies, says James Wells, PhD, director of the facility and a researcher in the Division of Developmental Biology at Cincinnati Children's.

"This technology is a bit like the internal combustion engine in terms of how it will drive future advances in stem cell biology," Wells says. "It allows us to use cells from patients to study what goes wrong at the genetic and cellular level to cause their disease – whether it's muscular dystrophy, diabetes or any number of degenerative diseases. This technology could allow us to fix genetic defects and use these cells to generate healthy cells and tissues to treat or cure the patient."

Pluripotent stem cells have the theoretical ability to become any of the more than 200 cell types found in the human body. The stem cell team already has coaxed iPSCs into forming pancreatic cells that make insulin, retinal cells of the eye, nerve cells of the brain, intestinal cells, liver cells and cardiomyocytes that can be seen beating under a microscope.

To generate induced pluripotent stem cells, researchers grow cells from healthy people or patients with specific diseases in a Petri dish. Scientists begin the reprogramming process by inserting specific genes into a cell's nucleus, which instruct the mature cells to essentially reverse their life cycle and become unspecialized "embryonic-like" cells. It takes about two months in a Petri dish to make a single batch of iPSCs, says Chris Mayhew, PhD, co-director of the facility.

The viral vector core at Cincinnati Children's has produced some of the vectors involved in the induction process, Mayhew says.

"We also are investigating viral delivery methods to modify gene expression in pluripotent stem cells as well as in cell types differentiated from these cells. These viruses have also been obtained through the viral vector core," Mayhew says.

The stem cell facility opened in January 2010, offering a full range of pluripotent stem cell services, including access to human pluripotent stem cell lines, generating iPSC lines, cell line maintenance, and training for scientists wanting to use cell lines in their own laboratories.

So far, Cincinnati Children's has made a significant investment in opening the facility, and is discussing plans to expand it as demand for stem cell lines grows.

The Development Lab makes sure that gene therapy products function as intended when produced in larger quantities.

Scaling up the Process

The Development Lab, co-directed by Punam Malik, MD, and Carolyn Lutzko, PhD, coordinates the scaling-up process to a clinical level.

This typically requires using larger pumps, wider tubes and bigger bioreactors. Instead of growing virus-infused cells in a single plastic dish, scaled up production may call for "cell factories," which involve entire trays of product stacked 10 layers high.

Genetic manipulation of the cells needs to be scaled up in large bags. Complex biological assays to support vector production, cell manipulation or clinical trial monitoring need to be validated to meet preclinical or clinical standards.

The Development Lab works with the Vector Production Facility, or the Cell Manipulations Lab or the TTDSL, depending on whether virus, cells or assays need to be developed to a clinical level.

Such changes must be tested to assure that the new production process works as intended.

"It's not as simple as baking a cake and then multiplying the ingredients to bake a bigger cake," says Scott Cross, manager of the Translational Cores' Vector Production Facility. "Scale-up is a process that requires testing, re-testing and refining of every single step. It takes a lot of time but guarantees that when the clinical product is made the results are as expected."

"It's not as simple as baking a cake and then multiplying the ingredients."

The Translational Trial Development and Support lab tests the performance of gene therapies.

Unique resource

Few other pediatric medical centers worldwide possess the full spectrum of gene therapy production offered by Cincinnati Children's.

Before the Translational Core Services were fully up and running, Cripe recalls the difficulty he faced convincing for-profit companies to make their lab facilities available for his study. "I worked with one company for almost two years, but after they were bought out, our project was no longer part of their strategic plans."

Now, Cripe works with the Translational Core on pre-clinical testing of a handful of potential cancer therapies involving viral vectors. Should any of them make it to human testing, Cincinnati Children's can do the production work in-house.

"The GMP facility here is very attractive to us," Cripe says. "If we had to contract with another company to do this work, the increased costs could run into six or seven figures. Just signing the contract could take six months to a year."

By investing in the Translational Core Services, Cincinnati Children's is accelerating the movement of promising treatments from the lab to the bedside, a direction that will deliver powerful resources not just for scientists at Cincinnati Children's, but for researchers worldwide.

And that will lead to better outcomes for children in need.

2010 CINCINNATI CHILDREN'S RESEARCH FOUNDATION

DIVISION ACCOMPLISHMENTS

Adolescent Medicine

We have continued our monthly seminars to improve clinical services by examining clinical behaviors and establishing best outcomes for specific conditions. We focus on conditions that occur frequently or have high morbidity, including asthma, obesity, depression, STI/HIV screening and immunizations. We review current practices and scientific literature to determine national data and evidence-based practices. After establishing clinical markers, we then examine subsequent data and monitor improvement.

The asthma best practices group defined "perfect care" as documenting asthma severity, using controller and rescue medication appropriately for degree of clinical severity, and developing an action plan. Chart surveys revealed that 75 percent of asthma patients in the Teen Health Center received "perfect care." We plan to launch programs to improve clinical outcomes for one additional condition each year.

Paula Braverman, MD, has received extramural funding to develop health, sexual health and HIV prevention curricula for Ohio middle- and high-school students. The Ohio Department of Health posted her report on guidelines for sexual health and adoption education. More recently, Braverman and her team received funding from the National Campaign to Prevent Teen and Unplanned Pregnancy for the "Man2Man" project, currently implemented in area recreation centers and the Hamilton County Juvenile Detention Center. This innovative program includes weekly small-group sessions for high-risk adolescent male students, led by adult male facilitators. The sessions include discussions about adult responsibilities, fatherhood, relationships, decision-making, abstinence, HIV risk behaviors, skills integration and contraceptive protection.

Allergy and Immunology

2010 was a year of progress in the understanding of eosinophilic disorders.

Director Marc Rothenberg, MD, PhD, and colleagues identified the first major gene location (5q22.1) responsible for susceptibility to eosinophilic esophagitis (EE), a severe food allergy that leaves individuals unable to eat a wide variety of foods. Using a genome-wide gene variation analysis, they identified overexpression of the TSLP gene at this chromosomal location. These data implicate the 5q22 locus in the pathogenesis of EE and identify TSLP as the most likely candidate gene.

A $1.6 million federal economic stimulus grant from the National Institute of Diabetes and Digestive and Kidney Diseases helped us launch the Registry for Eosinophilic Gastrointestinal Disorders (REGID). It is the first registry to provide the infrastructure for understanding and treating eosinophilic disorders at a national – and ultimately international - level. Rothenberg developed REGID along with division faculty member Pablo Abonia, MD, and co-investigators James Franciosi, MD, and Keith Marsolo, PhD.

Anil Mishra, PhD, and colleagues identified the significance of induced expression and protein levels of interleukin 15 (IL-15) in human and experimental EE. The researchers found that transcript levels of IL-15 strongly correlated with esophageal eosinophils in patients with active EE. Likewise, the levels significantly decreased in patients with improved, treated EE. Using mouse models, researchers showed the receptor for IL-15, IL-15Rα, is necessary for developing EE. Elevated IL-15 levels in the blood samples of EE patients could potentially serve as a diagnostic biomarker.

Anesthesia

Research growth in the past year has made our division one of the nation's top three pediatric anesthesia departments in grant funding.

Steve Danzer, PhD, received an NIH grant to investigate neuronal circuitry development in epilepsy and autism. David Richards, PhD, is using an NIH grant to investigate mechanisms of synaptic transmission. George Istaphanous, MD, and Andreas Loepke, MD, PhD, are using a Foundation for Anesthesia Education and Research (FAER) grant to investigate mechanisms of anesthetic neurotoxicity. And Senthilkumar Sadhasivam, MD, MPH , has a FAER grant to study the relationship between the genetics of morphine drug metabolism and side effects of morphine after surgery.

The Division of Pain Management, led by David Moore, MD, Jacquelyn Morillo-Delerme, MD, Senthilkumar Sadhasivam, MD, MPH, and Richard Goins, implemented a regional anesthesia service at Cincinnati Children's. During orthopedic and plastic surgery, catheters are inserted around peripheral nerves and local anesthetics are injected to produce selective postoperative analgesia for up to several days. Only a few children's hospitals in the country offer such a service.

The Division of Neurobiology, led by John McAuliffe, MD, MBA, and Michelle Cooper implemented a neuromonitoring service. This is the only such program in a pediatric anesthesiology department in the nation. During spine surgery, neurosurgery or plastic surgery, this service monitors the integrity of the peripheral and central nervous systems. It helps protect patients from injury and enables the surgeons to attempt procedures that would otherwise be judged too risky to perform.

A $1.6 MILLION GRANT FROM THE NIDDK HELPED CINCINNATI CHILDREN'S LAUNCH A NATIONAL REGISTRY FOR EOSINOPHILIC DISORDERS.

Asthma Research

The Division of Asthma Research has one of only 14 NIH-funded Asthma and Allergic Diseases Cooperative Research Center grants. Gurjit Khurana Hershey, MD, PhD, leads a team working to identify epithelial genes important in allergic inflammation.

Epithelial cells have been implicated as critical initiators of allergic inflammation and asthma. However, relevant epithelial candidate genes for asthma have not been identified. We identified six candidate genes and customized an assay that included their non-synonymous and tagging single-nucleotide polymorphisms (SNPs). We then genotyped 1,152 children enrolled in the Greater Cincinnati Pediatric Clinic Repository. Through this work, we identified the combination of SNPs within all six genes that best predicts asthma risk.

Melinda Kovacic, MPH, PhD, is using an NIH grant to identify biomarkers of diesel exhaust particle-induced oxidative stress in asthma. Although oxidative stress is generally accepted as a determinant of asthma, there are no reliable and consistent methods to quantify biologically relevant products of oxidative stress. Our preliminary data suggest that fluorescent plasma oxidation products may provide a relevant way to identify the pathways activated by diesel exhaust particles.

Our investigators also made progress regarding excessive mucus production and mucus plugging, two key pathologic features of asthma. The mechanisms responsible for excess mucus production have remained largely unknown. This year, we found that the serine protease inhibitor, SERPINB4, is strongly induced in respiratory epithelial cells of children with asthma. Microarray analysis revealed that SERPINB3A modulates the expression of multiple genes that regulate mucus production. SERPINB4 may be an important new target for therapeutic intervention.

Behavioral Medicine and Clinical Psychology

Our division took several steps this year to study, develop and disseminate best practices in managing pain as well as in treating attention deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD).

The Center for Attention Deficit Hyperactivity Disorder, a multidisciplinary center hosted by our Division, completed a six-year project funded by the Cincinnati Children's Patient Innovation Fund. The project trained 200 pediatricians to provide evidence-based care for children ages 6 to 12 with ADHD. Data from the project showing improvements in care practices and patient outcomes were published in *Archives of Pediatrics and Adolescent Medicine*.

The center's director Jeff Epstein, PhD, received two NIH awards to further investigate the effectiveness of disseminating this model of care. Epstein developed the ADHD web portal, which allows pediatricians to collect ADHD assessments from parents and teachers online, and provides sophisticated algorithms for scoring assessments and diagnosing the disorder. The portal also allows pediatricians to monitor and titrate medication in real time. This year, the Center began marketing the portal to pediatricians nationwide.

The division also uses technology to improve outcomes in pain management and obsessive compulsive disorder. After moving to a system of electronic medical records earlier this year, we asked patients to enter their outcome data directly into their medical records. This innovation resulted in patient outcomes being collected at 100 percent of visits. Measuring these outcomes allows our psychologists to more effectively deliver evidence-based, individualized care. The system also allows the division to identify and better treat underserved segments of the patient population.

OUR DIVISION OF ASTHMA RESEARCH HAS ONE OF ONLY 14 NIH-FUNDED ASTHMA AND ALLERGIC DISEASES COOPERATIVE RESEARCH CENTER GRANTS.

Biomedical Informatics

Our division provides the core knowledge, skills and equipment necessary to acquire, store and analyze biomedical data using computational systems. We work with medical researchers to incorporate this technology into their work.

The Research Data Center, led by Michael Kouril, PhD, serves as liaison between Biomedical Informatics and technical groups in Information Services at Cincinnati Children's and the University of Cincinnati. Kouril's team has worked to improve the speed of communication between the institutions while maintaining strong data security.

The data warehousing and software development group, headed by Keith Marsolo, PhD, is expanding the framework of our research patient data warehouse to serve as a platform for research registries. When combined with distributed query technologies, this platform can support multi-center registries for managing chronic disease, monitoring product and drug safety, tracking the natural history of disease, and improving quality. It is being piloted in two NIH-funded projects. The first, based at Cincinnati Children's, will be a multi-center registry focused on eosinophilic esophagitis. The second project, with Children's Hospital Boston, will create a registry of more than 60 sites targeted to pediatric arthritis and other rheumatologic diseases.

Eric Hall, PhD, who works jointly with our division and Neonatology, is working with Marsolo to integrate geographic data on preterm births and the distribution of risk factors into the platform, allowing targeted interventions to the most at-risk populations. The team also is establishing a secure, confidential regional perinatal data repository to better recognize and manage neonatal and childhood diseases.

Additionally, they are helping investigators in intestinal rehabilitation to improve care and research by developing a patient registry integrated with the electronic health record.

Biostatistics and Epidemiology

This year, our division launched five designated research units and led an institution-wide data management initiative.

The research units include the genetic epidemiology and statistics unit, headed by Lisa J. Martin, PhD, created to conduct genome-wide association studies. In the past year, Martin collaborated with Marc Rothenberg, MD, and Children's Hospital of Pennsylvania on a paper published in *Nature Genetics* that identified a novel susceptibility locus for eosinophilic esophagitis. Martin is now leading a statistical analysis to identify additional susceptibility loci. She also collaborated with Jessica Woo, MHSA, PhD, to perform an analysis in stroke; and with Cynthia Molloy, MD, MS, on a study of autism.

Three other new research units strengthen partnerships with the newly-created institutes at Cincinnati Children's: The Heart Institute Biostatistics and Epidemiology Unit, directed by Woo; the Perinatal Institute Biostatistics and Epidemiology Unit, directed by Jareen Meinzen-Derr, PhD; and the Cancer and Blood Diseases Institute Biostatistics Unit, directed by Mi-Ok Kim, PhD.

We also launched the Scales Development and Validation Unit, directed by Richard Ittenbach, PhD.

Meanwhile, our division leads the effort to develop Cincinnati Children's new data management initiative. This project is developing advanced data management services for use by medical center investigators. New data management policies and practices are scheduled to begin in the coming year.

We reached an agreement with the University of Cincinnati to include five students a year in the Graduate Biostatistics Internship Program at Cincinnati Children's. Our division also launched two award mechanisms for students and staff: The Frank C. Woodside, Dinsmore & Shohl fellowship for pre-doctoral students and the W. William Luxion travel trainee award.

Bone Marrow Transplantation and Immune Deficiency

The clinical program in Bone Marrow Transplantation and Immune Deficiency performed a record 108 transplants in 2009. This busy program serves as the backbone of our clinical and research efforts as a Jeffrey Modell Foundation and FOCIS center of excellence in primary immune deficiencies. Our investigators also have obtained significant funding for basic science and translational efforts involving bone marrow failure.

A major focus this year has been to collaborate with other divisions at Cincinnati Children's on new research and clinical initiatives.

We are working with the Division of Gastroenterology, Hepatology and Nutrition and the Department of Surgical Services to identify the important clinical phenomenon of graft versus host disease after transplant, and to prepare clinical guidelines for monitoring and treatment.

We collaborated with the Division of Nephrology and Hypertension to describe the incidence of thrombotic microangiopathy after transplantation, and we have published novel clinical and biological diagnostic parameters. A prospective study, now IRB-approved, seeks to further clarify the pathophysiology of this disorder.

We also are testing a bone marrow transplant-specific severity index we developed for post-transplant children admitted to the PICU, in collaboration with the Division of Critical Care Medicine. These data will be reported later in the year.

Clinical Pharmacology

This year, we continued our clinical studies on the most effective use of medications in newborns, children and adolescents. We have ongoing studies in the pharmacogenetics of warfarin, risperidone, and mycophenolic acid (MMF, CellCept®) in kidney transplant patients. We have a pharmacokinetics-pharmacodynamics study involving children with lupus. And we are conducting dose optimization studies for the use of sirolimus in patients with cancer and propofol in morbidly obese patients.

Our investigators study the dose-concentration-response and adverse event relationships of immunosuppressive drugs in children who receive organ transplants. With funding from the NIH and other sources, our research seeks to identify pharmacokinetic, pharmacodynamic and pharmacogenetic factors to explain differences in adverse events and clinical response after transplantation. Our work includes studying the age-dependent disposition of mycophenolic acid in pediatric renal transplant recipients and children with lupus using newly discovered genetic polymorphisms. Our data will help develop dosing algorithms to allow personalized dose tailoring.

We also work with the Genetic Pharmacology Service, the first of its kind in a pediatric institution. This service focuses on reducing adverse medication effects by identifying genetic variations in drug metabolism, providing dose recommendations based on the patient's drug metabolizing genotype/phenotype, and delineating clinically significant drug/drug interactions. This service is a first step towards personalized medicine for neuropsychiatric and anticoagulation drug therapy. Our research focuses on genotyping-phenotyping studies of neuropsychiatric drugs such as risperidone and warfarin. We develop computerized decision support systems that integrate evidence-based medicine, patient genotypes and phenotypes, as well as drug pharmacology and environmental factors.

Clinical Translational Research Center *(formerly the General Clinical Research Center)*

A five-year, $23.5 million grant from the National Institutes of Health has led to several changes in how translational research is organized and supported at Cincinnati Children's.

The University of Cincinnati (UC), Cincinnati Children's, the VA Medical Center and University Hospital received a Clinical and Translational Science Award (CTSA) in April 2009. The grant supports an infrastructure for clinical and translational research and for training investigators in transdisciplinary research. Similar, but less comprehensive, federal grants have supported research at UC and Cincinnati Children's since the 1960s.

The grant also supports the Center for Clinical and Translational Science and Training (CCTST), co-directed by James Heubi, MD and Joel Tsevat, MD, MPH.

Heubi oversees the direction of the program, including the Clinical Translational Research Center (formerly the General Clinical Research Center). Tsevat is responsible for aspects including oversight of Research Education; Biostatistics, Methods and Ethics in Translational and Clinical Studies (BioMETrCS); and Community Engagement and Research.

As part of the effort to obtain the CTSA award, we created Research Central, a single point-of-entry for investigators seeking support for clinical and translational research.

Since its inception, Research Central has handled more than 370 requests for services ranging from study design and data management to accessing technologies such as proteomics, gene therapies and molecular disease modeling.

Our division also provides several educational programs and pilot awards. We have awarded more than $1.6 million for 16 pilot projects designed to bring bench discoveries to clinical application. Seven of these include UC-Cincinnati Children's collaborations.

Critical Care Medicine

Our 35-bed Pediatric Intensive Care Unit (PICU) provides care for more than 2,000 critically ill infants and children per year. This past year, the standardized mortality ratio for the PICU, which compares actual deaths to a predicted number of deaths based on severity-of-illness adjustment, showed that our death rate was lower than predicted, ranging between 0.4 and 1.

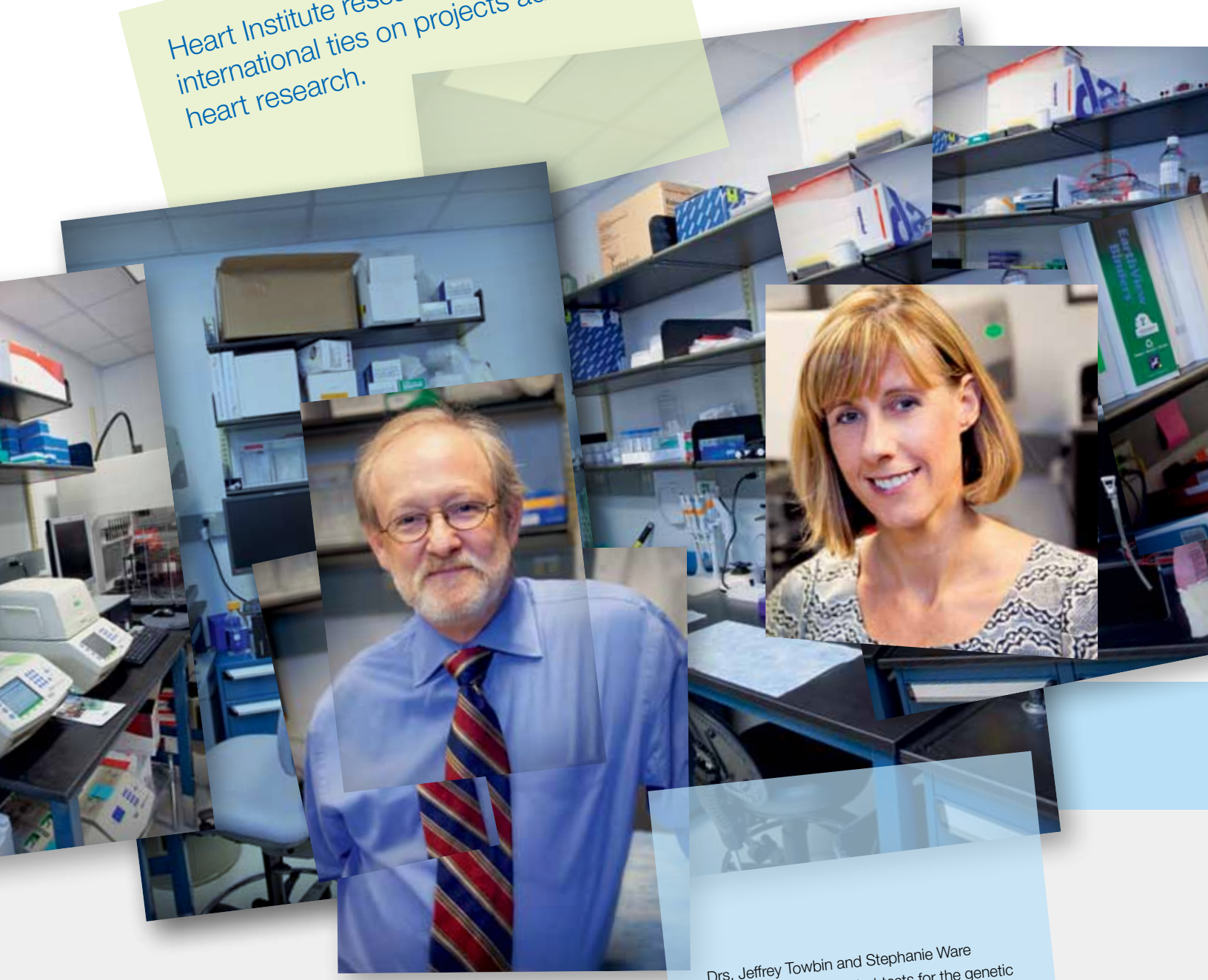
In addition, our rates of catheter-associated bloodstream infections and ventilator-associated pneumonia consistently rank among the lowest in the country.

Our division also made strides in preventing other critical events. The hospital-wide medical response team (MRT) was activated 265 times this year, an all-time high for the medical center. As a result, there has been only 1 MRT-preventable code at Cincinnati Children's since mid-2007. We remain closely involved with the situational awareness initiative, which has significantly reduced the rate of unplanned critical transfers to the PICU.

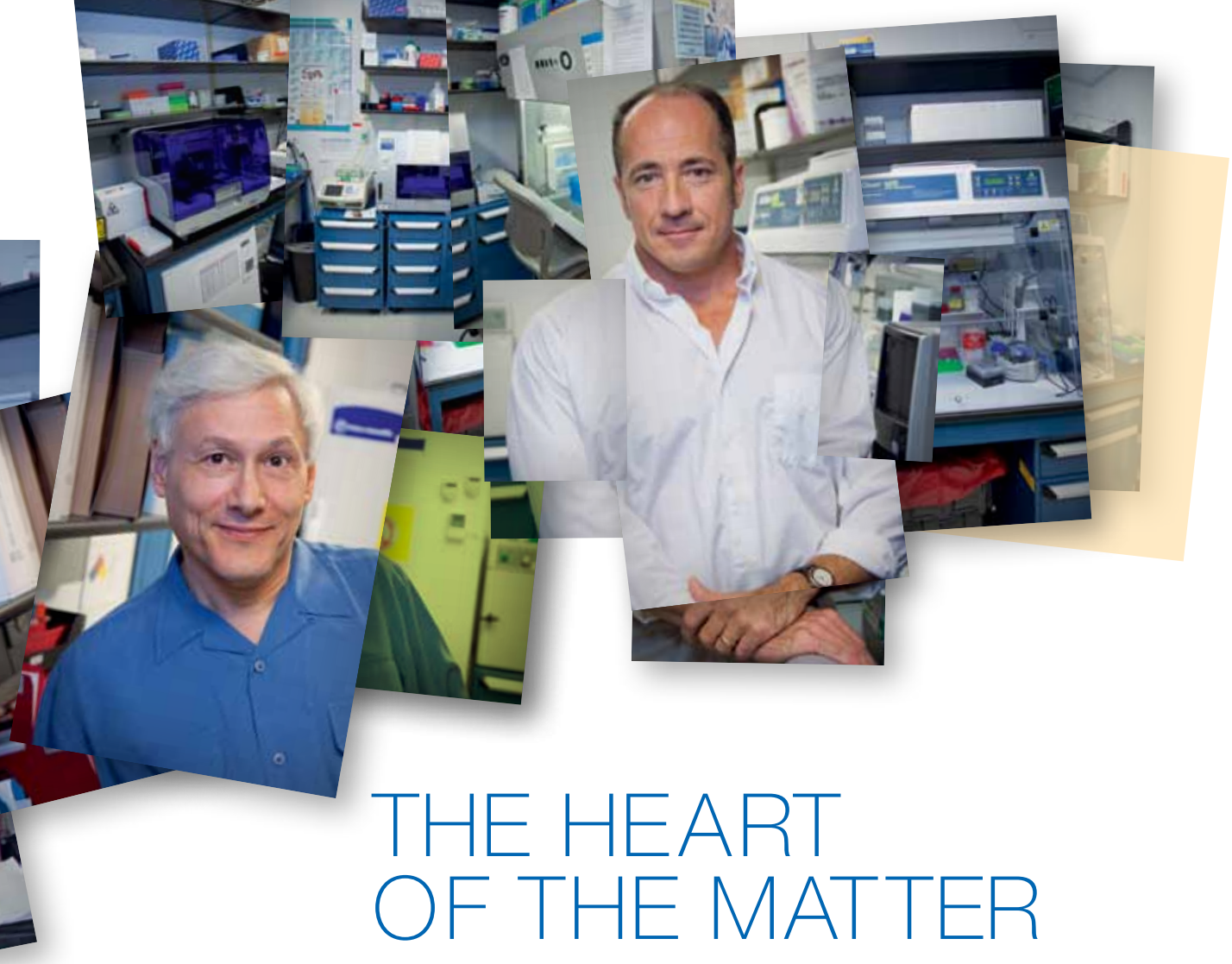
This year, we welcomed Frederick (Rick) Barr, MD, MSCI, to our division. Barr served as director of Pediatric Critical Care Medicine at Vanderbilt University since 2007. At Cincinnati Children's, he will serve as program director for the Clinical Translational Research Center and will be charged with expanding clinical research efforts within the PICU.

WE PERFORMED A RECORD 108 BONE MARROW TRANSPLANTS IN 2009.

Heart Institute researchers have strong international ties on projects advancing heart research.



Drs. Jeffrey Towbin and Stephanie Ware *(above)* created a lab that tests for the genetic causes of heart disease.



THE HEART OF THE MATTER

Heart Institute investigators take science from labs to real life.

Researchers in the Heart Institute at Cincinnati Children's have made a name for themselves as the go-to team for advancing research about heart disease on a scale larger than in Cincinnati alone.

They have made strides in 2010 taking their research global.

Their strong ties overseas with individual research projects have extended their reach. And while their research projects are very different, their mission to connect research and patient care on a large scale is the same.

In the last fiscal year, the Heart Institute drew patients from 43 states, Puerto Rico and at least 13 countries. Investigators' research partnerships have spanned Europe, Australia and Japan.

Jeffrey Robbins, PhD, and Jeffery Molkentin, PhD, both received international science awards from the International Society for Heart Research for their achievements. Robbins won the 2010 Research Achievement Award, and Molkentin was recognized as the 2010 Outstanding Investigator. Jeffrey Towbin, MD, is receiving the 2010 Cardiovascular Disease of the Young Meritorious Achievement Award at this year's American Heart Association Scientific Sessions.

When they talk about the global implications of their research, they speak of practical ways of treating heart disease for real families. They see tangible, targeted treatment as something within their reach. This is how they are getting there.

More Targeted Treatment

It is not enough anymore for scientists to spend their time writing papers about new genes that might trigger heart muscle diseases, says Towbin *(above)*, whose focus is pediatric cardiomyopathy.

He wants to translate scientific discoveries into more targeted treatments. That is why he and colleague Stephanie Ware, MD, PhD, created the Heart Institute Diagnostic Laboratory, a clinical genetic testing lab that provides testing for patients locally and nationally.

That also is why the Heart Institute opened a new weekly cardiomyopathy clinic in 2010, to combine genetic and clinical research to find the genetic causes of pediatric heart muscle disease and screen entire families for potential problems.

It is the first pediatric clinic of its kind to include geneticists and genetic counselors to help find underlying causes of heart disease. And doctors such as Towbin, co-director of the clinic, are looking beyond the walls of the hospital to continue this research.

Towbin is working with scientists in Italy, England and Australia to examine the underlying genetic basis of cardiomyopathies. The team at Cincinnati Children's takes human gene abnormalities and engineers them into mouse models. The mice develop heart muscle problems, then scientists study their hearts to try to understand the mechanisms that cause the problems. They then work internationally to develop therapies that are related directly to the actual abnormalities in the heart.

The goal is to come up with approaches that could improve survival and reduce the number of patients needing heart transplants.

"We have a thirst for understanding these disease processes, and we want to do something about them," Towbin says.

"We want to be able to identify the problem early," he adds. "We want to prevent them from developing disease. From those who develop disease, we want to be able to treat them early and stop the progression. For those that progress, we want to develop a new therapy that helps them avoid going to the next step, which is transplantation. And, oh, by the way, if they need a transplantation, we want to be the ones doing it, because we want to have a great program in that as well. So, it's soup to nuts. It's actually what comes even before soup. It's the utensils."

"We have a thirst for understanding these disease processes, and we want to do something about them."

A $750,000 BURROUGHS WELLCOME FUND GRANT WILL HELP EXPLORE THE RELATIONSHIP OF GENETIC CAUSES OF HETEROTAXY TO CONGENITAL HEART DEFECTS.

What Causes Human Disease?

Having a global impact on pediatric heart disease may come down to answering the questions every patient and family has: Why do some kids get heart disease and some don't? Why are some people born with it and others develop heart problems when they are older?

Stephanie Ware, MD, PhD, a cardiovascular geneticist at Cincinnati Children's, is co-director of the new weekly cardiomyopathy clinic. As both a researcher and a clinician, she sees her role as bridging the gap between work in the lab and work in the clinic.

"Historically, identifying the underlying cause of pediatric cardiomyopathy has been very much a research-based question," she says. "But over the last few years, clinical testing has become available."

Ware's lab focuses on the specific genetic cause of heterotaxy, a rare congenital defect that can cause heart malformations when organs get confused about where they are supposed to end up. A $750,000, six-year grant from the Burroughs Wellcome Fund is helping her lab explore how genetic causes of heterotaxy relate to congenital heart defects.

Ware says she and other investigators want to know the same things as their patients and families.

"This has global implications in the sense that most of what drives the research in my lab is trying to understand and explain what causes human disease," she says. "A lot of families want to know: 'Why did this happen? Is it going to happen again?' That's a globally relevant question. And that's where I hope my impact will be."

Just as proteins clump into plaque that can cause Alzheimer's, proteins in the heart can cluster and interfere with its function. Dr. Jeffrey Robbins is studying to what extent children are susceptible.

Alzheimer's of the Heart

Much of the expanding research at the Heart Institute involves studying what were once thought to be adult problems, such as protein clumping associated with diseases like Alzheimer's and some aspects of dementia.

Jeffrey Robbins, PhD, *(above)* executive co-director of the Heart Institute, is among those trying to understand whether protein clumping is in fact relevant to pediatric disease.

Robbins is working with Atsushi Sanbe, PhD, a former Cincinnati Children's fellow now based at the National Research Institute for Child Health and Development in Tokyo, Japan. They are focused on what is sometimes called "Alzheimer's of the heart." Just as proteins bunch into plaque that can cause Alzheimer's, different proteins in the heart can clump and interfere with normal heart function.

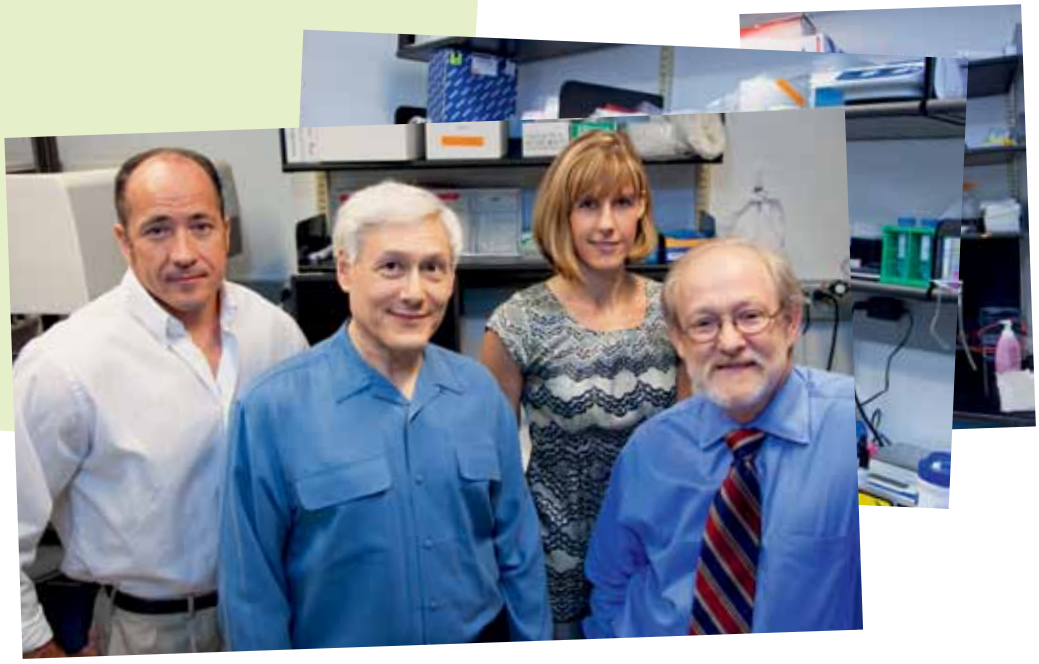
"The idea is that kids are susceptible to these protein clumping diseases, and when this happens, heart function is affected in a very bad way," Robbins says. "It's of significant interest because it looks like this might happen in a lot of childhood diseases."

The researchers hope to understand how the proteins clump and how doctors might disrupt that process.

"We wouldn't actually be curing the primary heart disease," Robbins says. "What we would be curing is a reaction to that primary heart disease that makes it even worse."

Robbins would like to develop imaging capability that could test noninvasively, identify kids who have accumulations of protein clumps and measure which ones might respond to treatment.

"The major advancement in research in the last year is that this protein is widespread in human heart disease, and we know that it can cause heart failure," he says. "So now we need to understand how to diagnose it better, noninvasively, and we need to be able to treat it."



An international team led by Dr. Jeffery Molkentin is studying the role of growth factors in the heart. Their work has already led to a lifesaving treatment.

Identifying the Good and the Bad

The global partnerships between scientists at the Heart Institute and other investigators also hinge on which work is awarded major grants for any given year.

When wealthy French entrepreneur Jean Leducq died in 2002 of heart disease, his heirs decided to use the family fortune to set up a foundation that gives grants to teams of international scientists going after heart disease from novel perspectives.

That is how Jeffery Molkentin, PhD, *(at left)* received a competitive, $6 million, five-year grant that ends this year. He is the United States' coordinator of a study looking at growth factors generated in the heart and their response to injury. The point has been to identify and catalog as many growth factors as possible and genetically manipulate them in mouse models to determine their medical relevance.

"We wanted to identify all of the secreted factors that the heart makes after a heart attack and then figure out which ones are good and which ones are bad," Molkentin says. "The good ones, we could use as drugs. The bad ones, we could try and stop."

Some of the findings have already been medically relevant. Molkentin and other researchers from Germany, Belgium and England found that when the heart secretes a protein called GDF15, it protects the heart. Their study indicates GDF15 keeps the heart from enlarging, and it keeps cells from dying. Now they are measuring GDF15 in the blood to learn how badly the heart is injured. With more research, they hope GDF15 could someday be used as a drug.

Other researchers in the transatlantic network focus on "the bad."

They discovered that an altered form of prolactin, a pregnancy hormone, can cause heart muscle disease in pregnant women and could kill women with postpartum cardiomyopathy. Researchers looked at blocking prolactin release with a drug called bromocriptine.

"It's now a mainstay treatment for women with postpartum cardiomyopathy," Molkentin says. "It's an example of how our network took a secreted factor that causes something bad for the heart, used a drug to stop it, and it cures postpartum cardiomyopathy."

Dentistry

We will upgrade our electronic patient management system, Axium, this year in order to further improve and refine its capabilities.

As part of our ongoing efforts to improve our division, this past year we established a website for employees, residents and faculty. The site is designed to strengthen communication within our division and to help improve the quality and safety of our clinical practices.

The economic downturn affecting our nation had a local impact, resulting in our decision to close two of our three satellite facilities. While difficult, we believe this decision has made use more stable and will better position us for future growth.

We continued our initiative to generate scholarly outcomes. Our faculty and residents published five papers in peer-reviewed journals, and have another three articles in submission. Some faculty also had textbook chapters published or are working on chapters for future publication. Division director Stephen Wilson, DMD, MA, PhD, gave presentations on sedation at conferences in Australia, Boston and Florida. Wilson also directs the Academy's sedation course, including a new component involving sedation emergency simulations using Laerdal simulation mannequins.

This year's second-year residents also contributed to our scholarship. All presented posters at our Academy's annual session. Our residents continue to consistently pass written and oral portions of the American Board of Pediatric Dentistry exams, and consistently perform above average on the advanced pediatric dentistry "exit" examination.

We have investigated several opportunities for collaboration with other divisions, and are awaiting decisions on two HRSA grants submitted this year.

Developmental and Behavioral Pediatrics

In December 2009, we relocated our programs to a new building specifically designed to meet the needs of our patients. Clinical rooms are equipped with dual lighting to allow switching to incandescent lighting when fluorescent lighting is bothersome to patients with autism or other developmental disabilities. Rooms absorb sound to keep down distracting noise and in many exam and treatment spaces, light switches and sinks are hidden so that they do not distract patients. We have 32 examination rooms, another 40 rooms for evaluation and treatment services, three demonstration classrooms, conference and meeting spaces, plus the Rubinstein Library, which offers books for professionals, parents and children and a toy lending library.

Our history of clinical and academic training includes the Leadership Education in Neurodevelopmental and Related Disabilities (LEND) Training Program, one of the largest and longest-standing programs of its kind nationwide. Since 1967, we have graduated more than 1,300 long-term trainees in 14 disciplines. Our DDBP Fellowship Program is at capacity with six fellows as of next year, with additional pediatric trainees enrolled in the Neurodevelopmental Disabilities Residency/Fellowship Program. We also train psychology post-doctoral fellows and residents, offer an undergraduate training practicum in psychology and train master's students in speech pathology.

To coordinate training across the multiple programs within the division, Karen Edwards, MD, MPH was recruited to become our director of training. Edwards previously served as director of education and training at the Westchester Institute for Human Development in Valhalla, N.Y.

OUR DIVISION OF EMERGENCY MEDICINE DEVELOPED A CLINICAL DECISION RULE TO IDENTIFY CASES AT LOW RISK FOR BRAIN INJURY, TO REDUCE UNNECESSARY HEAD CTs AND EXPOSURE TO RADIATION.

Developmental Biology

Cell signaling underlies embryonic development, and when the process goes awry, it can lead to various developmental disorders, including cancer. Our investigators reported several advances in the past year in understanding cell signaling.

The lab of Janet Heasman, PhD, reported in *Current Biology* the major finding that Wnt proteins, known to be important in normal development and in tumor formation, interact with each other to enhance signaling levels, and this interaction is controlled by sulfation of specific tyrosine residues. The lab of Xinhua Lin, PhD, reported in *Developmental Cell* that the range of Wnt signaling is controlled by specific proteoglycans on the cell surface. Christopher Wylie, PhD, and his lab reported in *Development* that expression of survival signals follows the migration of early embryonic migrating stem cells, forming a travelling niche surrounding them as they go. Also, Nadean Brown, PhD, has established a successful institute-wide monthly meeting on Notch signaling, which has led to several major interdivisional collaborative projects.

Our research into organogenesis and stem cells also has been highly successful. A collaboration between the labs of Jim Wells, PhD, and Jeff Whitsett, PhD, published in *Developmental Cell*, identified Sox17 as a major regulator of foregut cell differentiation. Aaron Zorn, PhD, was part of a consortium that published in *Science* the genome of a new model organism; *Xenopus tropicalis*. The lab of Rashmi Hegde, PhD, reported in *Oncogene* that the multifunctional protein Eyes Absent promotes the invasiveness and motility of tumor cells. The Brian Gebelein, PhD, lab reported in *Developmental Biology* regarding a transcriptional network that controls sensory neuron patterning.

The Kenneth Campbell, PhD, lab reported in a series of high profile papers in *Neuron* and *Nature Neuroscience* the roles of several transcription factors and signaling proteins that control mammalian forebrain patterning. The lab of Geraldine Guasch, PhD, reported in *Cell Cycle* the discovery of potential stem cells in the ano-rectal canal, a region with high levels of tumorigenesis in humans. The Brown lab reported in *Journal of Neuroscience* that the transcription factor Rbpj plays a major role in the formation of the mammalian retina.

Drug and Poison Information Center

Our 24-hour hotline for drug and poison information is one of the largest of its kind nationwide and serves a population of 3.7 million in 20 Ohio counties.

Our Center gathers poison control data to provide toxico-surveillance on food poisoning, water quality, substance abuse patterns and terrorism preparedness. We collaborate with regional medical response systems, county disaster committees and the Ohio Department of Health's disaster preparedness and response program. We also participate in a network that sends alerts to 60 regional hospitals on subjects such as H1N1 flu, blue-green algae in local rivers and prescription drug abuse.

This year, after extensive review, we were awarded a five year re-certification by the American Association of Poison Control Centers.

Our Prevention Research Unit, which includes prevention specialists, health educators, pharmacists, law enforcement officers and other health care professionals, implements programs to promote healthy drug-free lifestyles. These programs have benefited more than 500,000 people in Hamilton County.

Our program to prevent violence and delinquency among African-American youth earned an Exemplary Prevention Award from the Ohio Department of Alcohol and Drug Abuse Services. Other services provided by this unit include the REACH and NOMAD projects. We also address health disparity and wellness issues in Hamilton County with the support of the Office of National Drug Control Policy People of Color, Wellness Alliance Coalition Grant and the Grassroots Urban Mobilization Benefitting Ohio Initiative.

Among the staff members receiving awards in the last year: Alysha Behrman, a Florence Nightingale Award; Sarah Lamkin, Cincinnati Children's Woman of the Year; Marsha Polk, Nefertiti Award; Rudy Smith, Cincinnati Children's MLK Humanitarian Nominee; Robin Davis and Patty Klein, American Association of Poison Control Centers certified specialists in poison information.

Emergency Medicine

Even as our staff responded to the H1N1 flu pandemic in fall 2009, our research focus groups surpassed their funding goals while reporting significant accomplishments in clinical and prevention research, quality improvement, education and safety.

Lynn Babcock Cimpello, MD, was awarded a CTSA grant for her work with minor head injuries. Brian Hang, MD, received a grant to develop a clinical tool to predict length of symptoms in concussions. Meanwhile, a clinical decision rule for identifying cases at low risk for brain injury – published in *Lancet*, Oct. 3, 2009 – should help reduce unnecessary head CTs and exposure to radiation. Todd Glass, MD, MS, was the site principal investigator for that project.

Our prevention research team under Jacqueline Grupp-Phelan, MD, MPH, and Michael Gittelman, MD, led the development of key national emergency medical services for children priorities, including mental health screening, smoking prevention in children, and injury control through community interventions.

Led by Evie Alessandrini, MD, and Scott Reeves, MD, our quality improvement group continues to study the impact of ED crowding on quality of clinical care. Terri Byczkowski, PhD, was awarded an AHRQ grant to study the quality of family-centered care provided in the ED.

Interdisciplinary work on the H1N1 influenza pandemic in fall 2009 was an outstanding accomplishment. The medical center significantly expanded ED capacity for influenza patients via overflow clinics at the Burnet and Liberty campuses. This effort was accomplished under the leadership of Joseph Luria, MD, and Julie Shaw, RN, MSN, senior clinical director, with the senior leadership of Michael Farrell, MD, chief of staff; Jackie Hausfeld, RN, MSN; and Char Mason, RN.

Our emergency services safety team, led by Holly Brodzinski, MD, MPH, Rima Rusnak, MD, and Sharon Foreman, RN, also reached a major milestone in July 2010 by reporting 1,000 days between safety events.

The division received the Pediatric Resident Teaching Award in 2010. Faculty also contributed significantly to the 6th edition of the *Textbook of Pediatric Emergency Medicine*.

Endocrinology

As the obesity epidemic continues, the Center for Better Health and Nutrition has received increasing referrals to address obesity in children ages 2 to 5 years.

In response, Nancy Crimmins, MD, began staffing a monthly clinic dedicated to treating obesity in very young children. An exercise physiologist, nutritionist, and social worker also work at the clinic, where we encourage parents to model a healthy lifestyle and set limits.

Crimmins recently presented data at the Endocrine Society national meeting showing that young children referred to Cincinnati Children's during the past two years frequently have body mass indexes within the adult range for obesity. Many of these children already manifest insulin resistance, dyslipidemia and fatty liver disease. Crimmins is working to define the frequency and extent of these co-morbidities of obesity to develop effective interventions.

Clinical fellow Roopa Shankar's abstract, "Infants with Hereditary MEN 2B Should Undergo Prenatal Surgical Referral and Prophylactic Thyroidectomy within the First Month of Life," won the Presidential Poster Competition at ENDO 2010. This competition is reserved for trainees who are both first and presenting author of the abstract.

The poster was a case report on the youngest reported patient in the literature, an infant with inherited MEN 2B and microscopic medullary thyroid carcinoma in the thyroidectomy specimen at 9 weeks of age. The present guidelines give room up to 6 to 12 months of age for prophylactic thyroidectomy. We concluded that this surgery can be performed as soon as one month of age.

Every Child Succeeds

Every Child Succeeds provides a large, evidence-based home visitation program to address the parenting, health education and wellness of first-time young, low-income mothers. We operate through 14 sites (13 Healthy Families America and one Nurse Family Partnership) in seven counties in Ohio and Kentucky. Since our inception in 1999, we have served more than 16,000 families and made more than 330,000 home visits.

In the past year, we launched a unique treatment program for women experiencing maternal depression. Our research reveals that 44 percent of mothers in our home visitation program have measurable signs of clinical depression. Maternal depression makes it difficult for mothers to parent effectively, negatively impacts child development, and provides challenges for home visitors in implementing curricula.

In response, we developed the Maternal Depression Treatment Program, which includes in-home cognitive behavior therapy, an innovative treatment uniquely adapted for home visitation. This treatment program was developed through grants from the Health Foundation of Greater Cincinnati and the National Institute of Mental Health.

This novel maternal depressions project, along with other elements of our program, has attracted interest from other programs nationwide. In fact, Every Child Succeeds was selected by the Pew Center on the States to co-host a national meeting in Washington, D.C., in February 2011, "Home Visitation: Research to Policy to Practice."

The State of Connecticut, The Boston United Way, the State of Arkansas, Arkansas Children's Hospital, and the State of Ohio's Help Me Grow program also have requested more information about our services, including our web-based management and information system, our suite of training modules and our literacy curriculum for young children.

Experimental Hematology and Cancer Biology

Our faculty research led to several important findings in the past year, including a gene therapy trial to combat sickle cell disease, a potential stem cell-based therapy for Hurler syndrome, and new understanding of the mechanisms of bone marrow failure syndrome.

A sickle cell disease study led by Punam Malik, MD, and published in *Blood*, has shown that hyperplastic erythroid cells produce elevated levels of the growth factor PIGF, which in turn promotes inflammation and airway hyper-reactivity. Another study, in mice, reveals that using a lentivirus vector to transfer the gamma globin gene into sickle hematopoietic stem cells results in complete correction of sickle cell disease. These findings have led to a Phase I clinical trial protocol that was recently approved by the Recombinant Advisory Committee at the NIH.

Hurler syndrome is an often-fatal genetic disorder that damages organs and the central nervous system. A study led by Dao Pan, PhD, published in the *Proceedings of the National Academy of Sciences*, reported that developing red blood cells could be used to produce lysosomal enzymes that can prevent or reduce the damage caused by Hurler syndrome. The study reports that cells of children with Hurler syndrome lack a vital enzyme, IDUA. In mice, a single gene insertion using a benign viral vector prompts cells to produce the IDUA enzyme, resulting in normal organ function and significantly improved brain and neurological function.

Fanconi anemia (FA) is characterized by progressive bone marrow failure, developmental defects, chromosomal abnormalities, and cellular hypersensitivity to DNA interstrand crosslink agents. FA genes and associated proteins function to resolve blocked and broken DNA replication forks. In a study published in *Molecular Cell*, a team led by Ruhikanta Meetei, PhD, identified a FANCM-associated histone-fold MHF heterodimer that promotes the remodeling of artificial replication forks and confers cellular resistance to DNA crosslinking. The discovery implicates this novel molecular complex in coordinating DNA damage response in cells.

STUDY FINDINGS PUBLISHED THIS YEAR BY OUR DIVISION OF EXPERIMENTAL HEMATOLOGY AND CANCER BIOLOGY RESULTED IN THE CLINICAL TRIAL OF A TREATMENT THAT APPEARS TO CORRECT SICKLE CELL DISEASE.

Gastroenterology, Hepatology and Nutrition

Researchers in our division have recently published important findings related to diet and fatty liver disease, helped launch a national registry for eosinophilic disorders and taken steps to transform our system of care for intestinal failure patients.

The Cincinnati Steatohepatitis Center, a multidisciplinary clinic for patients with nonalcoholic fatty liver disease, has become a site in the NIH-funded non-alcoholic steatohepatitis (NASH) clinical research network. This network is conducting a multi-center study investigating the natural history and causes of NASH and plans to offer clinical therapeutic trials.

A study led by Rohit Kohli, MD, MS, published online in June 2010 in the journal *Hepatology*, reports that mice became obese when fed high-calorie diets containing either trans-fats alone or a combination of trans-fat and high fructose. Only the group fed the combination diet went on to develop advanced fatty liver disease. This finding highlights concerns about excessive fructose in U.S. diets.

James Franciosi, MD, MS, helped launch the national Registry for Eosinophilic Gastrointestinal Disorders (www.regid.org), which seeks to gather clinical, pathologic, and translational outcome measures for collaborative, multi-site investigations. With the Cincinnati Center for Eosinophilic Disorders, Franciosi also developed two outcome measures for eosinophilic esophagitis: the pediatric EoE health related quality of life measure and the pediatric EoE symptom severity score.

Noah Shroyer, PhD, identified new factors involved in intestinal growth and development, including a network of genes that control cell fate and proliferation of intestinal stem cells. In collaboration with researchers in Developmental Biology, Shroyer is investigating the potential for growing and manipulating intestinal tissue from human pluripotent stem cells. We are also working with colleagues in Surgery and Neonatology, using improvement science to get better outcomes for children with short gut syndrome through standardized care and preemptive approaches to prevent complications of intestinal failure.

General and Community Pediatrics

In two key developments for our division in 2010, we launched a section of Hospital Medicine and improved our care for asthma patients through the asthma improvement collaborative.

The new section of Hospital Medicine, directed by Patrick Conway, MD, MSc, operates as a separate business unit within General Pediatrics. The section's three clinical teams provided care for more than 7,000 patients in FY10 – nearly 25 percent of all unique inpatients at Cincinnati Children's. The clinical teams are: general inpatient service at the Burnet Campus, led by Mike Vossmeyer, MD; the surgical hospital medicine service, led by Ted Sigrest, MD; and the Liberty Campus service, led by Craig Gosdin, MD, MSHA.

We also received approval to launch a fellowship for academic hospitalist leaders and plan to recruit a research director for hospital medicine and research faculty.

The Asthma Improvement Collaborative led by Mona Mansour, MD, MS, aims to reduce asthma-related admissions and emergency visits for Hamilton County children ages 2 to 17 with Medicaid insurance. The collaborative includes several divisions and services within Cincinnati Children's and partnerships with Medicaid managed care organizations, the Cincinnati Health Department, local pharmacies, and the Legal Aid Society of Greater Cincinnati.

The collaborative provides overall care coordination, coordinates transitions to outpatient care after hospital stays, and offers an asthma home health pathway that provides home nursing visits. Patients admitted to the hospital also leave with all medications in hand needed to manage their asthma.

These services have resulted in a 50 percent decrease in the rate of children who return within 30 days for emergency asthma care or a hospital readmission. The length of time between admissions and emergency visits for patients in care coordination also is increasing.

General and Thoracic Surgery

Richard Falcone, MD, received state and local funding for his work in trauma epidemiology, education and prevention. Falcone directs the division's Trauma and Injury Prevention Program.

Michael Helmath, MS, MD, an expert in intestinal rehabilitation, conducts basic research into intestinal failure and intestinal stem cells. With an NIH-funded R01 grant, he is studying the mechanisms of intestinal stem cell expansion following resection. His goal is to understand how intestinal stem cells continually renew the lining of the intestine following intestinal loss.

The Center for Bariatric Research and Innovation, directed by Thomas Inge, MD, PhD, continued its partnership with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to gather data and publish recommendations on the use of weight loss surgery in adolescents. The team is in the fifth of six years of the NIH-funded Teen LABS Study, the largest multicenter study to document outcomes of adolescents undergoing weight loss surgery.

The group has added many other R01-funded ancillary studies. Inge also received ARRA funding for his study, "Assessing the Health Benefits and Risks of Adolescent Bariatric Patients."

Gregory Tiao, MD, completed the last of a five-year NIH Career Development Award. He also received an R03 grant from the NIH to expand his research on virus-induced intracellular signaling pathways and biliary atresia. Tiao serves as the surgical director for liver and intestinal transplantation.

Global Health Center

The Global Health Center contributes to improved child health outcomes beyond our borders through projects that range from vaccine and micronutrient studies in nations with limited resources to building deeper research relationships with scholars worldwide.

Further analysis of data from the unique Mother's Gift study, a project which immunized pregnant women with influenza vaccine, showed substantial protection of both the mother and the infant from influenza. A 2010 report in the *New England Journal of Medicine* described the levels of maternal influenza antibody, and their persistence in the infants for several months. Mark Steinhoff, MD, also reported the effect of maternal influenza vaccine on fetal development, showing a 32 percent reduction in the number of small-for-gestational age infants associated with vaccinated mothers.

More flu vaccine data will be generated by a new study in Nepal that began in 2010. With support from the Bill and Melinda Gates Foundation, we plan to immunize 700 women in the Sarlahi District, while another 700 receive a placebo.

Adekunle Dawodu, MD, continues the first randomized controlled trial (funded by the Thrasher Research Fund) of prenatal vitamin D supplementation in women in the United Arab Emirates. Analysis of the study indicates that 98 percent of the women were vitamin D deficient on enrollment.

In China, Steven Black, MD, is researching the potential impact of childhood flu vaccines. Black has received a CDC grant to assess childhood influenza in China. Results from a retrospective hospital surveillance study – a first of its kind in China – were published in the journal *BMC Health Services Research* in March 2010. A follow-up prospective surveillance study for pediatric influenza in China is planned.

Meanwhile, the Bang Bao Scholar program, sponsored by Cincinnati Children's and the Procter & Gamble Co., is expanding to more nations. After training another four research scholars from China during the second cycle of the program, sponsors announced that the Bang Bao program will be renamed "Healthy Children, Healthy World" and will expand to include scholars from Pakistan, Nigeria, Mexico and Brazil.

BABIES BORN TO MOTHERS VACCINATED WITH FLU VACCINE ARE PROTECTED FOR SEVERAL MONTHS AFTER BIRTH. THEY ARE ALSO MORE LIKELY TO BE BORN AT A HEALTHY SIZE AND WEIGHT.

Health Policy and Clinical Effectiveness *(Effective Sept. 1, The James M. Anderson Center for Health Systems Excellence)*

This year, our division reports progress in three important areas: innovations in chronic disease management, a program to reduce home injuries and a tool to identify children with special health care needs.

Peter Margolis, MD, PhD, and Michael Seid, PhD, are studying a collaborative chronic care network for pediatric inflammatory bowel disease. This network is designed to allow patients and physicians to share information freely, collaborate to solve important problems, and use their collective intelligence and expertise to improve health. This network is being evaluated as a potential demonstration project for similar networks for other chronic diseases.

Residential injury among U.S. children results in more than 1.7 million emergency visits a year and more than $3 billion in medical care costs. The HOME Injury Study, developed by K.J. Phelan, MD, MSc, evaluated a program to reduce childhood injuries by reducing exposure to injury hazards in the home. Home safety interventions included installing cabinet locks, stair gates, smoke detectors and other passive safety aides. The study showed a 68 percent reduction in injuries in households receiving intervention.

Encouraged by these results, the Cincinnati Home Injury Prevention (CHIP) Trial team will begin scaling-up this project with support from the National Institute for Child Health and Human Development. Interventions will be conducted through the Every Child Succeeds home visitation program.

Children with special health care needs account for 12.8 percent of U.S. children, yet their medical expenses account for roughly half of pediatric medical expenses. Improving health outcomes for this population depends, in part, upon accurately identifying children with special health care needs. A study led by Adam Carle, MA, PhD, demonstrated that epidemiologists, clinicians and others can rely on a key identification tool called the Children with Special Health Care Needs (CSHCN) Screener.

Heart Institute

Cardiology, Cardiovascular Biology, Cardiothoracic Surgery, the Center for Better Health and Nutrition

Our Heart Institute is addressing heart disease from a variety of perspectives. We conduct groundbreaking research into the genetic causes and treatment pathways of heart disease, tackle the growing epidemic of childhood obesity, have undertaken an initiative to create safer operating rooms and are translating basic research findings into new treatments for heart disease.

Robert Hinton, MD, from the Division of Cardiology and Katherine Yutzey, PhD, from the Division of Molecular Cardiovascular Biology are collaborating to study the mechanisms of human valve development and disease. Their work combines studies of normal valve development in animal models with analysis of molecular progression of disease in pediatric and adult human tissue specimens. Ultimately, this effort could help identify new therapeutic targets to treat heart valve disease.

In a continued effort to tackle childhood obesity, we have expanded the clinical services of the Center for Better Health and Nutrition to Cincinnati Children's neighborhood locations. We also developed an advanced multi-subspecialty clinic to serve obese children with severe co-morbidities. Beyond our clinic walls, we used support from the Saucony Shoe Company to recruit, outfit and train 40 obese children to complete a 5K race. And using a gift from Ethicon Inc., we sponsored a week-long fitness camp for 50 obese children. The campers' success – losing an average of 4.5 pounds in six days – attracted coverage from NBC's Nightly News.

Our cardiothoracic surgery team is a national leader in managing congenital cardiothoracic problems from fetal development to adulthood. With an overall mortality rate of 1.34 percent, our clinical excellence rivals any national program. Our emphasis on quality improvement also has resulted in our lowest surgical site infection rate reported to date. We are continuing this mission by developing a novel intraoperative improvement initiative dedicated to creating the safest environment for conducting surgical procedures.

Hematology/Oncology

The Oncology program continues its expansion as one of the nation's leading centers for new drug and advanced therapy development for childhood cancer.

Basic research from the laboratories of Nancy Ratner, PhD, and George Thomas, PhD, has demonstrated a key role for altered signaling in mTOR and growth factor pathways in pediatric cancers. Maryam Fouladi, MD, MSc, is leading a national translational study for children with relapsed cancers that combines temsirolimus – an mTOR-targeting drug – with IMC-A12, an antibody that targets insulin-like growth factors. Meanwhile, Brian Weiss, MD, is leading an innovative national clinical trial with Sander Vinks, PhD, and John Perentesis, MD, using pharmacokinetically-guided dosing of the mTOR inhibitor sirolimus to treat tumors associated with neurofibromatosis type 1 (NF1).

Major progress has been achieved in testing genetically engineered viruses designed to infect and kill cancer cells. While use of these agents previously focused largely on adult malignancies, preclinical studies led by Timothy Cripe, MD, PhD, showed that a mutated form of herpes simplex virus kills many types of childhood cancer cells and causes tumor shrinkage in mice. This work has helped establish the rationale for several pediatric clinical trials of oncolytic viruses, including a study of the Crusade Pharmaceuticals HSV1716 vector led by Cripe.

A Hematology research team led by Joseph Palumbo, MD, published an important paper in *Cancer Research* demonstrating the role of fibrinogen interaction with a specific leukocyte receptor in developing colitis-associated colon cancer.

Clinton Joiner, MD, PhD, collaborated with researchers at Yale University to identify phosphorylation sites that play an important role in the regulation of a key red cell salt transporter. This finding, published in the journal *Cell* in August 2009, is a first step in developing therapies to mitigate the abnormal transporter regulation that is characteristic of sickle red blood cells.

Human Genetics

The STAR Lysosomal Disease Center, founded in 1998, provides services, treatments, advocacy and research for more than 350 families affected by these conditions. In particular, we have provided life-changing enzyme therapy for individuals with Gaucher, Fabry, and Pompe diseases and mucopolysaccharidoses I, II and VI. During the past year, the STAR Center played a leading international role in managing care for Gaucher and Fabry disease patients during a manufacturer-related enzyme shortage. Major research progress also has been made toward next-generation therapies for these diseases using substrate synthesis inhibitors, *in situ* molecular engineering, and gene therapy approaches.

Gregory Grabowski, MD, and Hong Du, PhD, have developed a new enzyme treatment for two rare devastating diseases – Wolman disease and cholesteryl ester storage disease – that are expected to move into clinical trials in the next year. Components of this work were funded through the NIH-supported Lysosomal Disease Network. Longer term, this enzyme may have impact beyond these rare diseases. In mice, this enzyme was shown to reverse atheromatous plaques and the inflammatory fatty liver disease that accompanies obesity.

The Velocardiofacial Syndrome Center, led by Howard Saal, MD, FACMG, was established as a multidisciplinary effort to enhance medical care and research for VCF and craniofacial disorders. In October 2009, Cincinnati Children's hosted the Tri-State Craniofacial Conference to share research and clinical information. We also have developed a collection of online information and education videos for families who have children with orofacial clefts.

OUR DIVISION OF HEMATOLOGY/ ONCOLOGY HAS BEGUN CLINICAL TESTING OF GENETICALLY ENGINEERED VIRUSES TO KILL CANCER CELLS.

RESEARCH THAT KNOWS NO BOUNDS

Our researchers show that in a shrinking world, the impact of science is limited only by our imagination.

It started 50 years ago with Albert Sabin and his invention and dissemination of the oral polio vaccine – a scientific "shot heard round the world" that transformed the health of children worldwide. And it continues to grow from there. What follows is just a sampling of the international collaborations between Cincinnati Children's physicians and researchers and their colleagues all over the globe. These collaborations are already resulting in better health outcomes – for children and their families.

"Research is global. There's nothing we do that's not based on what's going on around the world."

Dr. Mark Rothenberg and Israeli colleague Dr. Ariel Munitz just received a grant from the U.S. - Israel Binational Science Foundation to study resistin-like molecule alpha (Relm-a) in the pathogenesis of asthma.

Exploring New Frontiers in Israel

Marc Rothenberg, MD, PhD, *(at right)* director of the Division of Allergy and Immunology at Cincinnati Children's, is a leading authority on eosinophilic disorders, illnesses in which children develop excessive infection-fighting white blood cells in reaction to everyday foods.

But Rothenberg is also one of the driving forces behind a growing collaboration between Cincinnati Children's and pediatric research institutions in Israel. What started as a collegial sharing of knowledge among scientists has grown into an exploration of mutual research and development opportunities.

It is what Rothenberg considers a natural extension of the way researchers today must approach their work.

"Research is global," he says. "There's nothing we do that's not based on what's going on around the world. The experiments we do are based on medical literature, which is a global literature."

Researchers from around the world have explored the genetic roots of allergic and immune response alongside their American counterparts in Rothenberg's lab. They return to their homelands to continue what they've learned and to teach it to others. Israeli researcher Ariel Munitz, PhD, has now returned to Israel after fellowship here, but remains on Cincinnati Children's adjunct faculty. Munitz has weekly teleconferences with Rothenberg's team.

"The idea is to bring more of the greatest minds from Israel to work with us," he says. Annually, he says, some 500 Israeli scientists leave their country to study abroad. Rothenberg wants more of them to study here.

The Israel Science Foundation (ISF) – their counterpart to our NIH – has an annual budget of $60 million, compared to the NIH's $32 billion. Despite the small budget, Israel's discoveries in medical technology and informatics are significant, such as the remarkable miniaturized, disposable cameras that can image internal organs.

"What the Israelis have been able to do with limited research dollars and resources is unbelievable," Rothenberg says. "Israel is at the forefront of bringing innovation to clinical utility."

He believes combining Cincinnati Children's strength in molecular research with Israeli innovation will have a remarkable impact.

"We're a leader in pediatric research, but we want to be the changer, to change the problems," he says. "Are we going to be the ones who transform the genome project from basic research to making a dent in helping children? To bring us closer to doing that, we will need partnerships with innovators who are thinking about this on higher levels."

Dr. Sean Moore *(top)* and Brazilian colleague Dr. Aldo Lima are studying a supplement that heals the intestinal damage caused by chronic diarrhea.

Stopping the Cycle of Diarrheal Disease in Brazil

Poor nutrition is the leading risk factor in more than half of the 10 million deaths that occur worldwide every year in children under 5 years of age. Those who don't die from malnutrition or infectious diseases can suffer stunted growth and reduced cognitive ability. Sean Moore, MD, MS, of the Division of Gastroenterology, Hepatology and Nutrition, is working with colleagues in South America to change this.

During graduate school at the University of Virginia, Moore got involved in a project with The Federal University of Ceará in Fortaleza, Brazil, studying the effects of diarrhea among children in that city's shantytowns.

"It's a vicious cycle," Moore says. "Diarrhea damages children's intestinal tracts, making it harder for them to absorb nutrients. Malnutrition makes them susceptible to further bouts of diarrhea and potentially, to reduced growth and cognition."

In Brazil, Moore met Aldo Lima, MD, a physician-scientist investigating the use of the dipeptide alanyl-glutamine to repair the damage that diarrhea and undernutrition cause to children's intestinal tracts.

Why glutamine? Lima says evidence showed that glutamine promotes intestinal health. "And the intestines use glutamine as nutrition," he says. "So we knew that glutamine could be a good therapeutic nutrient to use for these children." With colleagues at the University of Virginia, Lima developed alanyl-glutamine, a more soluble and stable form of glutamine, as a key component of a novel oral rehydration and nutrition therapy.

With the help of a Cincinnati Children's Child Health Research Career Development Award, Moore is now researching how the nutrient works. He feeds mice a diet similar to that of the children in the slums of Fortaleza – deficient in protein and fat. The mice develop enteropathy much like that of the undernourished children.

"Children's intestinal villi should look like leaves with good surface area to absorb nutrients," says Moore, "but in the undernourished children, the villi looked chopped off, with atrophy or blunting. We see the same effect in the underourished mice."

With alanyl-glutamine supplementation, the villi begin to recover. Moore wants to understand the molecular pathways by which the nutrient stimulates regrowth of the villi and restores gut integrity.

"The data suggest that alanyl-glutamine turns on the epidermal growth factor receptor, which then turns on the repair pathways that tell the cells to grow and preserve barrier function," Moore says.

The NIH has funded Lima's work since 1989, and a new five-year, $30 million Gates Foundation grant will expand his studies on the effects of diarrhea and malnutrition on child growth and development to seven more countries. Moore and Lima hope to find that alanyl-glutamine will break this vicious cycle in children far beyond Fortaleza's shantytowns.

The answers can't come soon enough, says Moore. Besides contributing to half of child deaths worldwide, diarrhea is linked to chronic morbidity in children living in the developing world.

"Mortality from diarrhea has dropped from 5 million kids a year to around 1.5 million," he says. "But the actual attack rates of diarrhea haven't gone down, and if children are having diarrhea every other month, is that affecting how they develop? We have good evidence that it is."

Fogarty fellows Drs. Navjyot Vidwan *(far left)* and Elizabeth Schlaudecker are conducting infectious disease research in India and the Honduras, under the mentorship of Dr. Mark Steinhoff in the Division of Global Health.

Giving Young Scholars Support for International Studies

Support from the Fogarty International Clinical Research Fellowship is giving two young physicians the opportunity to pursue infectious disease research in international settings.

The Fogarty fellowship offers new investigators support for research conducted in resource-limited and transitional countries. For Elizabeth Schlaudecker, MD, and Navjyot Vidwan, MD, it means the opportunity to conduct research in Honduras and India, respectively, with Dr. Mark Steinhoff as their mentor.

Schlaudecker's research in Honduras focuses on influenza.

"People have been shocked to find so much influenza in tropical and subtropical countries," she says. "It was considered a disease of westernized countries that have winter, not something you would see in Africa or Central or South America."

The discovery is particularly important, she says, because flu contributes to what is "the major burden of illness for children around the world – pneumonia and other respiratory infections."

The study will also look at the benefits of using a rapid flu test and a new, safer method of transporting samples for more extensive analysis. But Schlaudecker says the real value will be identifying the respiratory illnesses that afflict the children so they can be treated quickly and appropriately.

Vidwan is exploring whether, and how often, healthy pregnant women in India diagnosed with chlamydia trachomatis infection transmit the bacteria to their babies. India does not routinely test for chlamydia in pregnant women.

Vidwan conducted her research at the Christian Medical College in Vellore. Her team performed rapid testing on 1,200 pregnant women over one year. Although results are still being analyzed, the goal is to evaluate whether screening for chlamydia in this population is beneficial.

"This is the biggest study to date in otherwise normal, healthy women," she says. "Usually these studies are done in high risk populations. This will allow us to learn what the prevalence rate is in a healthy population."

Vidwan hopes the study will help bring positive changes in the care of mothers and babies. "Ideally, our data will identify risk factors associated with chlamydia infections in pregnant women that will guide the development of screening policies," she says. Knowing about the infection could allow doctors to treat moms and prevent transmission to the infants. "Treatment is simple – just one gram of azithromycin."

The large sugars in breast milk bind with pathogens and sweep them from the body.

Drs. Ardythe Morrow and Guillermo Ruiz-Palacios have collaborated for 30 years on the medicinal properties of human milk. A $6 million renewal grant will fund clinical trials of what they've discovered.

Milk as Medicine: Long-Term Collaboration Yields Breakthroughs

Breast milk has long been recognized as "better" than formula for infants in its ability to protect against infection.

For nearly three decades, Ardythe Morrow, PhD, has worked with Guillermo Ruiz-Palacios, MD, of the National Institute of Medical Science and Nutrition in Mexico, Children's researcher Jason Jiang, PhD, and Harvard researcher David Newburg, PhD, to determine just what it is about the milk that provides this protection.

In their work on the Human Milk Program Project, one of the longest-running collaborative studies funded by the National Institute of Child Health and Human Development, Morrow, Ruiz-Palacios, Jiang and Newburg have gone far beyond the "breast milk is good for you" stage.

For starters, their research has revealed that breast milk's infection-fighting ability comes from oligosaccharides, large sugars that contain fucose, a type of sugar that prevents bacteria from adhering to cells.

Fucose is also in the mucosal tissue that lines the intestines and the respiratory tract – two areas where infants are at risk of infection.

"For many pathogens – bacteria and viruses – the initial receptors in the mucosa of the respiratory or GI tract are also fucose-linked," says Ruiz-Palacios, who specializes in infectious disease. "Pathogens use these receptors to initiate infection."

Jiang's lab has reported how fucose-containing oligosaccharides inhibit noroviruses. Newburg's lab at Harvard has determined that the oligosaccharides prevent respiratory and intestinal disease by binding with the pathogens and removing them from the body, rather than allowing them to adhere to the mucosa and start an infection.

The researchers also discovered that not all women produce the same types and amounts of oligosaccharides in their breast milk.

"It is genetically regulated," Ruiz-Palacios says. "There are differences in protection depending on the gene expression of the sugars."

The team just received a five-year, $6 million renewal of the project funding to continue this research. Morrow, who directs the Center for Interdisciplinary Research in Human Milk Lactation, will be lead investigator, and is planning a phase I trial of a synthesized version of oligosaccharides. The substance will be given for medical needs of infants and children (and potentially, adults) when breast milk is not available or to add to its protection.

"We are one of only a few groups in the world working on the idea of using human milk oligosaccharides as a form of medication," says Morrow. "This is one of the most powerful things that Cincinnati Children's could develop."

"The flu vaccine in mothers makes antibodies in the milk that stay elevated for up to a year of breastfeeding."

With an additional $6.7 million from the Gates Foundation, Dr. Mark Steinhoff will expand his study of protecting babies by vaccinating mothers against flu.

Protect the Mother, Protect the Infant

Complications from influenza have been an important cause of serious illness and death among infants in low resource regions. That could change thanks to research by Division of Global Health director Mark Steinhoff, MD *(at right)*.

In 2004, Steinhoff launched the "Mother's Gift" project in Bangladesh. The program vaccinated pregnant women with flu vaccine to assess protection of both the mother and her baby after birth. Initial findings proving the value of vaccinating pregnant women to protect both themselves and their babies in the first 6 months of life were reported in the *New England Journal of Medicine* earlier this year.

Steinhoff's research team is now digging deeper into data from the project, and the results are even more encouraging.

"We analyzed the breast milk from mothers who were vaccinated, and found that the flu vaccine makes antibodies in the milk that stay elevated for up to a year of breastfeeding," Steinhoff says. His team is analyzing if the elevated antibodies will protect the baby from infection by the flu virus for the duration of breastfeeding.

Another finding was that the babies of mothers who got flu vaccine had an increased birth weight and fewer of the infants were small for gestational age. These unique findings suggest that preventing influenza in the pregnant mother benefits the fetus as well.

Steinhoff received an additional grant of $6.7 million from the Bill and Melinda Gates Foundation to continue this research.

For that, he will move the study to Nepal, where researchers will compare results in 1,500 pregnant women who receive the flu vaccine to 1,500 who do not.

"The goal is to see if we can replicate the positive outcomes of the Bangladesh study in another location," Steinhoff says. He anticipates that the project, planned to launch at the end of summer 2010, will take about four years and will span two flu seasons to measure the effect of variations in the flu virus.

The Nepal study is being carried out in collaboration with Johns Hopkins University, the University of Washington and the Institute of Medicine in Katmandu.

The Center for Molecular Medicine established by Dr. Bao in Chongqing was the first pediatric center there to provide tests for genetic disorders, cancer and infectious diseases.

Dr. Liming Bao helps start genetics labs in China; his Chinese colleagues contribute ideas and study data in return.

Establishing Genetic Testing Labs in China

While collaborating on a research project with colleagues back in Shanghai, Liming Bao, MD, PhD, realized the enormous potential and benefits for collaborations between U.S. and Chinese researchers.

Bao, a clinical laboratory geneticist in our Division of Human Genetics, had received his medical degree in China, but came to the U.S. in 1990 to pursue a doctorate in molecular biology. During post-doctoral training at the University of Colorado Health Sciences Center, he combined his love of clinical medicine with his interest in research when he discovered clinical molecular genetics.

He began work on an international study of the relationship between the risks of leukemia and lymphoma and exposure to environmental hazards. More than 20 hospitals collaborated on the study, which was conducted primarily in Shanghai, China.

"It was a dream opportunity to work on an international research project that involved many scientists and physicians from the U.S. and China," he says.

An important part of the project was to establish a clinical and research laboratory to provide clinical testing not widely available in China at the time. The labs would support the diagnosis of leukemias and lymphomas according to international standards. "We needed to make sure that the patients we recruited in China were diagnosed using the same criteria as in the West," he says.

Bao played instrumental roles in setting up and performing studies in the laboratory in Shanghai. He continued his project after moving to Cincinnati Children's in 2001. The lab was a great success; the project recruited more than 2,000 leukemia and lymphoma cases and became one of the largest such studies in the world.

Since then, Bao has been assisting other hospitals in China in establishing clinical genetics laboratories. One of those is at the Children's Hospital of Chongqing Medical University in Chongqing, a municipality in southwestern China with a population of 30 million. The Center for Molecular Medicine in the hospital was the first pediatric center in China that provides comprehensive tests for genetic disorders, cancers and infectious diseases.

Bao spends about 3-4 month each year in China and says the benefits of this globe-spanning collaborations are countless.

"Not only do the genetics labs serve the children, but they have created many opportunities for international cooperation in research and education."

Shedding Light on a Problem in the Middle East

In many countries where the sun shines nearly every day of the year, rickets from lack of sun exposure remains a major health problem among young children.

Adekunle Dawodu, MBBS, of the Global Health Center, thinks the solution could lie partly with their mothers.

"When we see children with bone deformities, rickets, we have always assumed that the children were the problem," says Dawodu. "We now realize that the vitamin D status of the mother is important for the vitamin status of the children. Most children acquire vitamin D at birth from their mother. So vitamin D status in pregnancy is critical. "

One factor that contributes to this deficiency in certain geographic regions, he says, is the cultural norm that requires women to cover themselves so fully when they go outside. "The impact of sun exposure is masked by heavy clothing," he explains.

Dawodu has been conducting a study since April 2008 aimed at improving the vitamin D status of these women – and their children. The study is being conducted with pregnant women in the United Arab Emirates. Participants are placed in one of three groups, each receiving a daily dose of either 400, 2000 or 4000 IU of vitamin D from the 12th week of pregnancy on.

"We want to identify the amount of vitamin D that is appropriate and safe to ensure sufficiency in the mother, and its impact on the infants," Dawodu says.

The study has recruited nearly 190 pregnant women to date. It will end in June 2011, when the last of the women recruited deliver their babies. Thus far, measures of vitamin D levels in study participants substantiate that the women are deficient in the vitamin, Dawodu says.

"Ninety-eight percent of the women participating in the study were deficient in vitamin D at enrollment, " he says, "and we showed that this deficiency occurred all year round - not seasonal as expected."

So far, the results of supplementation are encouraging. Dawodu reports that the mothers' vitamin D levels are improving and there have been no signs of toxicity from the supplementation.

He believes what researchers learn from this and other similar studies could guide dosing recommendations worldwide, and will have implications far beyond healthy bones.

"We now can associate vitamin D deficiency with increased risks of infection, deadly cancers and autoimmune diseases," Dawodu says. "Vitamin D sufficiency is not just important to improving the bone health of mothers and babies. It could also reduce the risk of other serious complications."

Dr. Adekunle Dawodu advocates the sunshine vitamin for mothers to protect babies from rickets.

In countries where clothing restrictions limit sun exposure, vitamin D supplementation could alleviate rickets.

THE PROGRAM WAS DEVELOPED TO SHARE ADVANCES IN PEDIATRIC RESEARCH AND HEALTHCARE BETWEEN CINCINNATI CHILDREN'S AND SCHOLARS IN CHINA.

The Bang Bao Program

The Bang Bao "Healthy Child" Research Scholar Program began in 2004, a collaboration between Cincinnati Children's and Procter and Gamble's Pampers division.

The program was developed to share advances in pediatric research and healthcare between Cincinnati Children's and scholars in China. The first five scholars received a year of research and training at Cincinnati Children's plus $25,000 to continue the research at their home institutions in China.

A second three-year cycle added observerships to the program, in which doctors and researchers visit us for two-month periods to learn about healthcare delivery and the structure of our hospital and research activities.

The program has succeeded on many levels, says Adekunle Dawodu, MBBS, who coordinates the program for Cincinnati Children's.

"Those first five scholars have since achieved significant scholarly activity in their home institutions, " Dawodu says. "But they continue to feel that they are a part of Children's. We have formed strong and lasting relationships as a result."

A third phase of the program, "Healthy Children, Healthy World," will begin in Spring 2011 and will include other countries where the Pampers brand is sold, including Brazil, Mexico, Pakistan and Nigeria.

Although the geographic expansion is exciting, Dawodu says the program's true impact is borderless.

"This training has an impact on health care for children that we will not even know for years to come," he says. "It's good for the visiting researchers, but it is equally a wonderful experience for our institution and an opportunity to build partnerships that will extend far into the future."

Immunobiology

Debroski Herbert, PhD, and Fred Finkelman, MD, are studying a novel method for preventing parasitic helminth (hookworm) infections. They have identified a novel mechanism, published in 2009 in the *Journal of Experimental Medicine*, by which T helper 2 cytokines protect against intestinal worm infections. The cytokines IL-13 and IL-4 induce the differentiation of normal gut epithelium into goblet cells, which then secrete RELM-b. Once produced, RELM-b prevents hookworms from obtaining nutrients from the host gut epithelium. As a result, they starve and are expelled by the host. These insights may lead to new therapies with potential major impact on global health.

Recent findings by David Hildeman, PhD, and his collaborators may lead to a new weapon against sepsis. Hildeman studies the molecular mechanisms regulating the development and maintenance of T cell memory. He and his collaborators have reported in the *Journal of Immunology* that the cytokine IL-7 could prevent mortality in a mouse model of sepsis. The research team is exploring the potential of IL-7 delivery as a treatment for this potentially fatal condition.

Michael Jordan, MD, has been studying how the immune response regulates itself and how things go wrong when this mechanism is broken, as can occur in children with certain immune deficiencies. As part of this endeavor, the Jordan lab has translated some of their laboratory findings into a unique clinical trial for children with hemophagocytic lymphohistiocytosis (HLH). This trial, now open at Cincinnati Children's, seeks to test a novel hybrid approach for treating HLH that combines immunosuppression and chemotherapy. Results are expected within two to three years.

Infectious Diseases

An article published this year in the *New England Journal of Medicine* reviewed the impact of the Rotarix™ vaccine developed by Richard Ward, PhD, and David Bernstein, MD, MA. In Mexico, the first country to license the vaccine, researchers found that in the first two years of using the drug, diarrhea-related mortality fell 41 percent among infants 11 months or younger. The vaccine also was shown to be effective in Africa.

Last year, our NIH-funded Vaccine Treatment Evaluation Unit (VTEU) participated in unprecedented efforts to evaluate vaccines for the novel H1N1 virus that reached pandemic levels in 2009. By December, the unit had performed more 3,000 clinic visits and conducted more than 16,000 antibody tests. Testing showed that although one dose protected adults, two doses were necessary for children.

Neonatal herpes simplex (HSV) infection affects between 1,500 and 4,000 newborns each year in this country. Acyclovir has improved outcomes for many, but mortality and neurologic sequelae remain unacceptably high. Cytomegalovirus (CMV) affects up to 2 percent of all live births and can lead to severe neurologic impairments, hearing loss, even death. Currently, there are no effective interventions against CMV.

Bernstein and Rhonda Cardin, PhD, have evaluated two potential antivirals, N-MCT and CMX001, for activity against HSV and CMV in murine and guinea pig models. Both antivirals led to improved survival and reduced symptoms and thus are promising new drugs for herpes virus infections. Currently, CMX001 is in Phase II clinical trials for other indications.

Nancy Sawtell, PhD, and collaborator Malak Kotb, PhD, Department of Molecular Genetics, Biochemistry and Microbiology at the University of Cincinnati, were awarded a highly competitive NIH challenge grant for their genetic studies of virus-host interactions. Using a technique called quantitative trait loci, these studies will identify common pathways and networks that affect the severity of viral diseases in humans.

Jason Jiang, PhD, garnered additional funding for his studies of noroviruses, which have been linked to food-borne epidemics on cruise ships and in other populations. Jiang is formulating a new vaccine for noroviruses, based on viral entities called P particles derived from a viral capsid protein.

Mayerson Center for Safe and Healthy Children

This year, the Mayerson Center for Safe and Healthy Children recognizes its 10th anniversary. In its first decade, our hospital-based child advocacy center conducted more than 10,000 forensic interviews of children as we helped provide care for victims of physical and sexual abuse. We participate in numerous programs dedicated to eliminating child abuse. We have testified in court about rare cases of medical child abuse and we have testified before Congress regarding issues of child abuse and mental health.

We provide extensive training for professionals involved in caring for abuse victims, including programs for physicians, community mental health providers, pediatric sexual assault nurse examiners, and forensic interviewing courses for protective services workers, law enforcement officers and prosecutors. We also work with parent groups and others through our Stewards of Children sexual abuse prevention program.

Several of our staff members play significant roles in local, state and national programs that seek to eliminate child abuse.

Kathi Makoroff, MD, presented at the 2010 Pediatric Academic Societies annual meeting in Vancouver and was elected to the Executive Committee of the Ray Helfer Society. Barbara Boat, PhD, served as chair of the Ohio Domestic Violence Network Steering Committee on Animal Abuse and Domestic Violence.

Heidi Malott, LISW-S, was elected president of the Ohio Network of Children's Advocacy Centers. She also serves on the Ohio Supreme Court's subcommittee on child abuse and neglect and the Hamilton County Commissioner's task force on community safety from sexual offenders.

Erna Olafson, PhD, PsyD, served as chair of the justice consortium of the National Child Traumatic Stress Network. Erica Pearl, PsyD, was elected president of the Cincinnati Society for Child Clinical Psychologists.

Center director Frank Putnam, MD, testified this year before the U.S. House of Representatives on the impact of trauma on children's mental health. He also presented findings of the Institute of Medicine report on parental depression and parenting to the National Press Club.

Molecular Immunology

Claire Chougnet, PhD, who directs research programs aimed at understanding T cell dysfunction in aging and in AIDS, has developed a new program of research aimed at understanding the development of T cell responses in early life. The ontogeny of immune responses in human neonates is not well understood. Notably, human and sheep studies have suggested that uncontrolled T cell responses are important in the development of bronchopulmonary dysplasia, which develops in about 25 percent of low birthweight preterm infants. In collaboration with Alan Jobe, MD, and Suhas Kallapur, MD, of the Neonatal Institute, Chougnet has set extramurally funded, complementary studies of T cell ontogeny in premature infants, sheep and non-human primates.

The ongoing epidemic of obesity in Westernized countries does not spare children. In a research program that involves fruitful collaboration with Randy Seeley and Matthias Tschoep of the Diabetes and Obesity Center of Excellence, Christopher Karp, MD, and Senad Divanovic, PhD, have discovered a novel link between the immune system and regulation of energy metabolism that affects obesity development under conditions of high fat diet stress. Understanding the details of this unexpected link has promise for developing novel approaches to obesity.

Edith Janssen, PhD, and Jonathan Katz, PhD, have made significant translational strides in characterizing a dendritic cell population discovered by Janssen that orchestrates immune responses to self. Harnessing these dendritic cells significantly increases the efficacy of anti-tumor vaccines in mice. On the other hand, dysregulation of these cells is a major factor in the breaking of peripheral tolerance and induction of type I diabetes in mice. These findings, published in the *Journal of Immunology*, illustrate the therapeutic potential of these cells and exemplify how melding two separate fields can accelerate the understanding of basic immunological principles and open new avenues for therapeutic approaches.

A RECORD 24 KIDNEY TRANSPLANTS THIS YEAR PLACES US AMONG THE NATION'S TOP FIVE BUSIEST PEDIATRIC KIDNEY TRANSPLANT CENTERS.

Nephrology and Hypertension

Through the use of cutting-edge biomarker technology, the division's Biomarker Core is making kidney disease diagnosis faster and more personalized than ever before.

The Biomarker Core grew out of our discovery of urine and blood biomarkers that accurately assess acute and chronic kidney disease. We use these biomarkers to provide a range of services to investigators and clinicians across the globe. To date, we've established more than 20 collaborative research projects and have performed more than 25,000 assays on patient samples.

Acute kidney injury is responsible for more than 4 million deaths worldwide. We are attempting to address this health concern with the launch of our Center for Acute Care Nephrology, a collaborative effort between Nephrology, the Heart Institute and Critical Care.

The mission of this center is to transform clinical care, education and research in nephrology at Cincinnati Children's. It will provide advanced dialysis and acute pheresis care and conduct basic, clinical and translational research projects to help speed diagnosis and improve best practices. The center will also provide specialized fellowship training in critical care nephrology.

Since the founding of our Kidney Transplant Center in 1965, we have performed 500 pediatric kidney transplants. During fiscal year 2010, we performed 24 transplants, a record for our program that places us within the top five busiest pediatric kidney transplant centers in the country.

To maintain the highest level of quality, we have established novel protocols to optimize the care of our patients, establishing our program as one of the premier transplant centers in the Midwest.

Neurology

Tracy Glauser, MD, earned a Cincinnati Children's faculty award for a series of accomplishments in epilepsy research. The *New England Journal of Medicine* published preliminary findings from the landmark Childhood Absence Epilepsy (CAE) study, for which he is the primary investigator. In March, Glauser and his team received an $11.7 million grant to study the long-term outcomes for children in the CAE study. The new study began in July 2010. Glauser co-authored a landmark article on the International League Against Epilepsy (ILAE) reclassification of seizures and epilepsy, the first new reclassification for seizures and epilepsy in more than 20 years.

Led by Donald Gilbert, MD, MS, and Steve Wu, MD, the transcranial magnetic stimulation (TMS) lab is exploring research in neurological function. They study motor cortex physiology in Tourette syndrome and ADHD and are co-investigators in a two-site, five-year NIH study assessing motor cortex and motor function in ADHD. Wu also received a grant this spring from the Tourette Syndrome Association for a one-year study of neuroplasticity and long-term potentiation in Tourette syndrome.

Jerzy Szaflarsky, MD, PhD, and Jennifer Vannest, PhD, are using the TMS lab's new neuronavigation equipment to study aphasia in stroke. The lab is also using TMS in studies to quantify long-term potentiation and depression in humans.

Our Tuberous Sclerosis Complex (TSC) center at Cincinnati Children's launched a 25-center clinical trial to determine if RAD001 is an effective treatment for sub-ependymal giant astrocytomas (SEGAs) in patients with TSC. Center director David Franz, MD, is the study's primary investigator.

A $2 MILLION GRANT WILL FUND OUR DIVISION OF ORTHOPAEDICS' STUDY OF THE HEMIBRIDGE SPINE CLIP, WHICH COULD REVOLUTIONIZE SCOLIOSIS TREATMENT.

Neurosurgery

Kerry Crone, MD, led research to improve outcomes for patients with Chiari malformation, which causes balance and vision problems, muscle weakness and paralysis. Crone's team is using a 20-year database of outcomes-related data to publish a comprehensive analysis of treatment and outcomes.

The division plans to launch a comprehensive, multidisciplinary clinic in the coming year that will provide expertise on Chiari malformation.

Led by Francesco Mangano, DO, and Ki Lee, MD, our surgical epilepsy program provides evaluation and pinpoint-precise surgery for treatment-resistant epilepsy. This past year, the program grew and published highly favorable outcomes.

Todd Maugans, MD, launched research on the acute metabolic and physiologic brain changes that occur when children suffer sports-related cerebral concussions. The research team will use magnetic resonance imaging and quantitative blood flow analysis to study athletes within 48 hours of injury, a period that has not been previously studied.

Using Diffusion Tensor Imaging (DTI), Mangano and colleagues are researching how to predict outcomes for children with hydrocephalus based on pre-and post-treatment diffusion properties. Their work is funded by NINDS.

Ophthalmology

Our Visual Systems Group welcomed a new faculty member to our team this year. Fumika Hamada, PhD, from Brandeis University, studies the molecular mechanisms of heat and pain sensation in drosophila. Her recruitment continues to fulfill our goal of developing a successful visual systems basic science research initiative at Cincinnati Children's. We will continue to study the development and disease processes of the visual system.

Orthopaedics

Eric Wall, MD, received $2 million to fund a multi-center study on a new, minimally invasive scoliosis device invented, developed and manufactured in Cincinnati. The HemiBridge spine clip, roughly the size of a wedding ring, redirects the growth of a young curved spine without the need for rigid fusion. The clip is the first device in the world approved by the FDA to redirect spine growth as part of an investigational study. This small device could revolutionize scoliosis treatment.

The Division of Orthopaedics led the field in podium and poster presentations at this year's annual meeting of the Pediatric Orthopaedic Society of North America. Charles Mehlman, DO, MPH, led the division with podium presentations on supracondylar humerus fractures, brachial plexus injuries and forearm fractures.

The division was ranked among the top five pediatric orthopaedic programs in the country by *US News and World Report*.

Otolaryngology

Our newly formed Communication Sciences Research Center recruited Dimitar Deliyski, PhD, to occupy the first Robin T. Cotton Research Chair in Otolaryngology. Deliyski will build a program that creates and adapts new instrumentation for clinical and translational pediatric voice treatment research. He will also help train students, post-doctoral candidates and junior faculty pursuing careers in pediatric voice research.

Division director Robin Cotton, MD, focused on environmental issues in delivering the Ogura Lecture at the annual Triological Society meeting last summer. This lecture led to the creation of a hospital-wide committee dedicated to making the operating room more environmentally responsible.

Chaired by Cotton, the committee is made up of representatives from throughout the hospital who are working to reduce energy consumption and reduce or eliminate the use of products that contain harmful compounds. They are also working with vendors to encourage the use of environmentally friendly products. The group hopes to eventually expand its focus to include other areas of the medical center.

Pathology and Laboratory Medicine

As our reputation for diagnosing and treating children with hematopoietic malignancies continues to gain national recognition, we are working to build an equally strong research program in cancer biology.

To this end, our research will explore hematopoietic and cancer cell signaling networks at the molecular level. With the Division of Hematology/Oncology, we are building a more comprehensive program of research in leukemia and stem cell biology. This past year, two new researchers joined our faculty. Gang Huang, PhD, studies genetic and epigenetic changes that drive normal cells to become highly malignant. Muhammad Azam, PhD, studies the molecular mechanisms underlying chemotherapy resistance. With a grant from the V Foundation, he will also work on developing therapies to treat BCR/ABL-associated leukemia.

Kathryn Wikenheiser-Brokamp, MD, PhD, and a colleague at Children's National Medical Center have identified DICER1 gene mutations in families with the rare pediatric lung tumor pleuropulmonary blastoma (PPB). They believe the molecular events predisposing to PPB are relevant to other pediatric malignancies. They are currently developing a DICER1-deficient mouse model to identify the role of DICER1 in normal lung development as well as to clarify the molecular events underlying PPB pathogenesis.

In response to the challenges our hospital faced with H1N1 in the past year, we developed and validated a PCR-based assay for the virus prior to clinicians seeing active cases in the community. Ours was the only local laboratory to offer this test in the community; we performed more than 1,500 assays for hospitals throughout the region.

Perinatal Institute
Neonatology, Perinatal and Pulmonary Biology

The Perinatal Institute's Divisions of Neonatology, Perinatal and Pulmonary Biology have developed a center with Pulmonary Medicine and Immunobiology to study bronchopulmonary dysplasia, which commonly affects preterm infants. Through an NIH grant, we participate with five other centers studying the causes, consequences and treatments for bronchopulmonary dysplasia. Our research team includes Alan Jobe, MD; James Greenberg, MD; Suhas Kallapur, MD; Lisa Young, MD; and Claire Chougnet, PhD. They are working to understand the immunological infectious disease antecedents of preterm delivery and accompanying chronic lung disease. Biomarkers and genetic data will be linked to outcomes in infants' pulmonary function after discharge. The goal is to identify the causes and to develop new therapies for the disease.

Another NIH award supports research into the causes of morbidity and mortality in preterm infants. Through a network of 16 participating academic centers, the work focuses on studies related to the common causes of death and illness in preterm infants weighing under 1000 grams. This year the group participated in studies that included optimizing ventilation, safely using oxygen to treat lung disease and minimize retinopathy, managing neonatal jaundice and assessing risks for prematurity. The data have led to collaborative publications that define best practices in neonatology.

We have made significant progress this year in clarifying the genes and processes in the pathogenesis of chronic pulmonary diseases, including cystic fibrosis, COPD, asthma and idiopathic pulmonary fibrosis. Our NIH-funded investigations have defined the roles of a number of stem/progenitor cell genes involved in forming and maintaining normal lung structure. These studies help identify the master regulators of mucus metaplasia that complicates cystic fibrosis, COPD, and other lung diseases. They provide new mechanisms and potential therapeutic targets to influence the way respiratory cells respond to environmental challenges and infection to maintain lung function. The work is directly related to the pathogenesis of common lung diseases affecting children and adults.

Physical Medicine and Rehabilitation

Shari Wade, PhD, was awarded a five-year, $4 million grant from the National Institute on Disability and Rehabilitation Research to study childhood traumatic brain injury (TBI). With collaborators at Case Western Reserve University, Nationwide Children's Hospital and the Ohio State University, Children's Hospital of Denver, the University of Oregon, and Western Oregon University, we will conduct three multi-site randomized clinical trials of interventions designed to improve cognitive and behavioral functioning following pediatric TBI. Given the current dearth of large scale clinical trials, the center has the potential to substantially advance the field of TBI research and evidence-based practice.

Another current highlight in the division is a new Cerebral Palsy (CP) Center. The center will conduct clinical research related to CP within our division as well as in occupational and physical therapy. Clinical director Doug Kinnett, MD, and research director Jilda Vargus-Adams, MD, will work to develop a comprehensive health care delivery system while seeking out and applying new discoveries through research, knowledge, and compassion for improving the quality of life of children with CP.

Plastic Surgery

The Craniofacial Anomalies Team includes plastic surgery, dental, speech pathology, genetics, psychology and nursing. The primary goal is to improve the health outcome for patients with craniofacial abnormalities, such as cleft lip/palate. The division is collaborating with the Division of Developmental Biology to create an exceptional research program focusing on craniofacial anomalies.

Chris Gordon, MD, focuses his research on the molecular biology of bone growth and the genetic basis for facial clefting. He is working to develop a comprehensive research center that will provide insights into factors and mechanisms that underlie craniofacial disorders and that will foster the development of research, technology and therapeutics that can alter the outcome in craniofacial disorders.

Gordon has collaborated with Armando Uribe Rivera, DDS, on basic research that includes "Predictive Genomics: Validation of a Role for miRNA in Hemifacial Microsomia and Robin Sequence." Their work in animal studies include tracheal, ear and facial allotransplantation reconstruction using tissue engineering in a rabbit model.

Their clinical research includes a cost analysis of mandible distraction versus tracheostostomy in congenital micrognathia; neonatal mandibular distraction; a mandibular distraction miRNA study; and a cleft palate study.

Jesse Taylor, MD, and Donna Jones, PhD, demonstrated *de novo* bone growth using allograft, adipose derived from stem cells and growth factors, particularly in the presence of periosteum. The research has illuminated questions regarding the function and structure of periosteum. Through animal studies, the plastic surgery laboratory is working to increase understanding of the biology of periosteum, with the goal of improving the quality of tissue-engineered bone.

A NEW CEREBRAL PALSY (CP) CENTER WILL CONDUCT RESEARCH IN CP AND IN OCCUPATIONAL AND PHYSICAL THERAPY.

ADDING PUNCH TO SCIENCE

Cincinnati Children's is a growing player in multicenter studies

An epilepsy study reveals that one of the oldest, least expensive drugs on the market also works best for short-term treatment of childhood absence seizures.

A statewide collaboration slashes scheduled preterm deliveries by 40 percent in 18 months.

A national registry begins gathering vital data about life-altering eosinophilic disorders

Five major medical centers team up to track the long-term impact of bariatric surgery for obese teens.

These are just a few examples of Cincinnati Children's evolving role as a leader in multicenter collaboration. Be it conducting clinical trials to bring better medications to market, pooling resources to study rare conditions, or sharing best practices that transform care, our medical center does more than cooperate with other institutions on important projects. In many cases, we are leading the effort.

"We have experienced more of a push for multicenter research," says Michael Spigarelli, MD, PhD, medical director of the Clinical Trials Office at Cincinnati Children's. "We're not new to this, but we are seeing a blossoming effect. As we've gained experience, we have realized that we are capable of moving into the leadership role."

As many as 70 new multicenter projects – drug trials, data registries and collaborative studies – could be launched at Cincinnati Children's in 2010.

Cincinnati Children's will use an $11.7 million NINDS grant to continue a 31-center study comparing epilepsy treatments.

Multicenter collaboration speeds the adoption of new, best practices, says Dr. Mitch Cohen.

Our growth story

In 2009, Cincinnati Children's began 63 multicenter drug trials, data registries and other collaborative studies. That reflects a jump from 24 in 2006 and 12 in 2003. By mid-2010, another 35 multicenter projects had been launched, a pace that could exceed 70 new projects by year's end, says Jeremy Corsmo, director of the Office of Research Compliance and Regulatory Affairs.

These projects ultimately will influence treatment for children around the world who suffer from epilepsy, heart disease, cancer, obesity, juvenile arthritis, Crohn's disease, and many other conditions.

Aligned with national goals

In the past decade, the National Institutes of Health and other funding sources have encouraged research centers to work together to accelerate progress in high-priority fields. Pooling data and sharing expertise is useful for many conditions, but is vital for investigators seeking progress against rare or low-volume conditions. Likewise, when more institutions get involved in conducting the research, the quicker they become at adopting new practices based on the results.

"This is very different than one investigator working alone. If you want to look at outcomes, you have to look across institutions," says Mitch Cohen, MD, director of the Division of Gastroenterology, Hepatology and Nutrition.

Experts in this division play key roles in several cooperative efforts, including studies of liver transplant outcomes and a 25-center project called Improve Care Now, which promotes best practices for controlling inflammatory bowel disease. These and other leadership efforts, Cohen says, contributed to Cincinnati Children's ranking No. 1 in the nation in gastroenterology care in 2010 by *U.S. News & World Report*.

Collaborations soar

The number of new multicenter research projects opened each year at Cincinnati Children's Hospital Medical Center.

Source: Office of Research Compliance and Regulatory Affairs.

Dr. Michael Spigarelli directs Cincinnati Children's Clinical Trials Office.

"Of all the medications used in children, only 20 to 30 percent have actually been tested in children."

Sweeping impact on child health

Leading a large multicenter study can bring millions of dollars to a medical center. Collaborating to address high-profile issues can boost an institution's reputation. But most importantly, the results of these efforts can have sweeping impact on child health.

For example, in March 2010, key findings from a five-year epilepsy drug trial were published in the *New England Journal of Medicine*. The study, led by Tracy Glauser, MD, involved 31 medical centers nationwide.

The study reported that ethosuximide (Zarontin) provided superior short-term results for controlling absence seizures when compared with two other leading seizure medications: valproic acid (Depakote) and lamotrigine (Lamictal). Since then, the National Institute for Neurologic Disorders and Stroke (NINDS) has awarded another $11.7 million to Cincinnati Children's and its partners to continue following more than 400 patients for another four years to determine which drug offers the best long-term therapy.

Such direct, comparative drug data remains rare in pediatric medicine.

"Of all the medications used in children, only 20 to 30 percent have actually been tested in children," Spigarelli says. "For the rest, we rely on extrapolating information from adult research. But children are not just small adults. Sometimes drugs tested in adults don't work in children. Other times there can be overdoses or under-doses. It takes these kinds of multicenter drug trials to get the answers about the right dosages for our children."

High-priority topics

The recent surge in childhood obesity has prompted federal health agencies to turn to multiple institutions to dig into causes, prevention and treatments.

As one of the first pediatric centers to provide bariatric surgery for obese adolescents, Cincinnati Children's was a natural to lead a long-term study of surgical outcomes, says Thomas Inge, MD, PhD, surgical director of the Surgical Weight Loss Program for Teens. The first cases here date back as far as 2001.

A sampling of major projects

Obesity

The Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS): Examines the risks and benefits of adolescent bariatric surgery, including effects upon kidney, liver, heart and endocrine function, sleep disorders, nutrition and psychosocial factors.
Funding source: $3.9 million from NIDDK
Participating centers: 5

Epilepsy

Childhood absence epilepsy trial: Continues a 31-center study comparing the effectiveness of three leading medications for controlling "petit mal" seizures. The study will follow 446 patients who participated in a previous epilepsy trial for another four years
Funding source: $11.7 million from NINDS
Participating centers: 31

Rheumatology

Pediatric Rheumatology Collaborative Study Group: Since 1990, Cincinnati Children's has been the headquarters of this group, which conducts multicenter studies of causes and potential treatments for juvenile arthritis, lupus and other conditions. Drugs tested through this group include: etanercept, anakinra, celecoxib, adalimumab, tocilizumab, canakinumab, abatacept, and rilonacept.
Funding source: Varies by project
Participating centers: More than 85 arthritis centers in North America.

Multidisciplinary Clinical Research Center
Encourages cooperative pediatric medical research across disciplines and institutions. Past findings from this program led to the introduction of anti-TNF agents such as etancercept (Enbrel) as important therapies for children with arthritis.
Funding source: National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
Participating centers: Varies according to project.

Pediatric Rheumatology Tissue Repository
Cincinnati Children's stores thousands of samples of patient DNA, serum, plasma and other forms of tissue for use in studying rheumatologic conditions.
Funding source: National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
Participating centers: The repository has been used by hundreds of investigators nationwide.

Gastroenterology

Improve Care Now: This national collaboration shares research data and best practices to help children suffering with ulcerative colitis and Crohn's disease. Among the results: the rate of children in remission from Crohn's disease has grown from 49 percent in 2007 to 66 percent in 2009; and from 53 percent to 65 percent during the same period for ulcerative colitis.
Funding sources: Participating institutions, federal grants and charitable contributions.
Participating centers: 25 centers and more than 2,200 patients

Neonatology

Ohio Perinatal Quality Collaborative
Founded in March 2007, with data coordination managed at Cincinnati Children's, this collaboration of 25 is working on ways to reduce preterm births – the leading cause of infant mortality in the state. In 2010, the collaborative reported that a project to reduce elective preterm deliveries has resulted in 8,000 fewer births at 36-38 weeks, 250 fewer neonatal intensive care admissions, seven fewer deaths and $1 million in reduced medical expenses.
Funding source: Initial funding comes from the Centers for Medicare & Medicaid Services (CMS).
Participating centers: 25 Ohio hospitals, payers and state agencies

Cardiology

National Pediatric Cardiology Quality Improvement Collaborative: This effort seeks to dramatically improve the outcomes of care for children with hypoplastic left heart syndrome, especially during the high-risk "interstage" between the first two surgeries needed to correct this severe heart defect.
Funding source: Joint Council on Congenital Heart Disease National Quality Improvement Collaborative, a part of the American Academy of Pediatrics.
Participating centers: 43

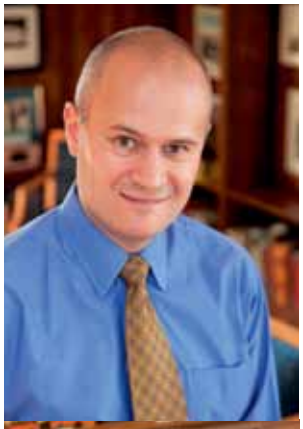
Eosinophilic disorders

Registry for Eosinophilic Gastrointestinal Disorders (REGID): This collaboration of medical centers, professionals and families collects data for a national research registry and provides resources for people living with eosinophilic disorders. The new data warehouse at Cincinnati Children's is supporting the registry.
Funding source: $1.6 million in federal economic stimulus funds
Participating centers: 5

Other

Genomics Control Cohort: This project is collecting DNA, hair, serum RNA and urine samples from more than 1,000 healthy children, aged 3 through 17. These samples will provide investigators with control data for a wide range of studies and allow researchers to track development from childhood through adolescence.
Funding source: Cincinnati Children's
Participating centers: Varies according to project

"One of the reasons Cincinnati Children's is at the forefront of this trend is that many difficult and rare cases come here."



Multicenter projects foster an expectation of excellence, says Dr. Thomas Inge.

Dr. Daniel Lovell co-leads a study group of more than 85 pediatric arthritis centers.

In 2006, the National Institute of Diabetes, Digestive and Kidney Disorders (NIDDK) awarded $6.7 million to the medical center to lead the Teen-LABS project, a five-center observational study of pediatric bariatric surgery. Nearly $800,000 in supplemental awards to the consortium since 2009 will support even more work on this project.

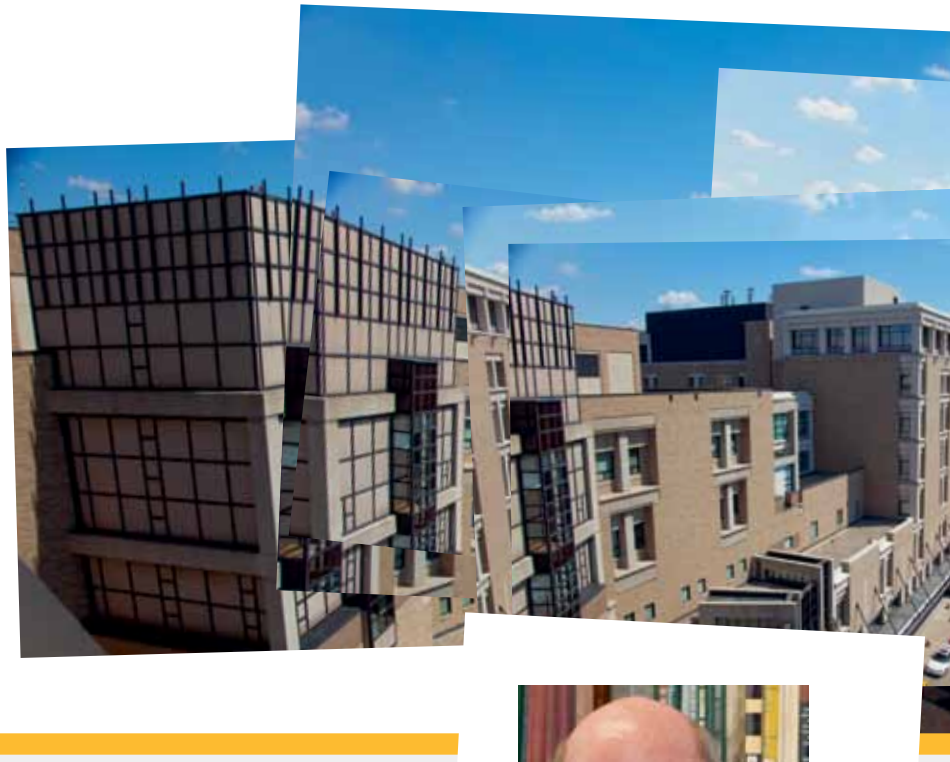
The study plans to follow 200 teens for 10 years after bariatric surgery. So far, more than 160 patients have signed on. Papers based on initial findings are expected to be published after Spring 2011, once the first five years of the project are complete.

"A multicenter approach was necessary because it would take forever for any one institution to gather enough cases to have statistical power," Inge says. "We're one of the biggest centers in the country and we are doing only two to four cases a month; we did even fewer cases in the early years of the study."

In the Division of Rheumatology, researchers here have been involved in multicenter studies for years. Since 1990, Cincinnati Children's has been the headquarters of the Pediatric Rheumatology Collaborative Study Group. Daniel Lovell, MD, MPH, and Edward Giannini, MSc, DrPH, lead this group composed of more than 85 arthritis centers in North America plus affiliated European centers.

"One of the reasons Cincinnati Children's is at the forefront of this trend is that many difficult and rare cases come here," Giannini says. "We also have taken steps to position the medical center to be able to run these multicenter, multinational studies."

At $117 million, Cincinnati Children's is the nation's second largest recipient of NIH funding for pediatric centers.



A plan comes together

The steady rise in the scope and scale of multicenter research at Cincinnati Children's reflects several converging forces.

Foremost is the explosion of research at the medical center. Sponsored research funding has increased tenfold in less than two decades, from $12.1 million in fiscal year 1992 to $137.4 million this year, not including $17.6 million in ARRA funding.

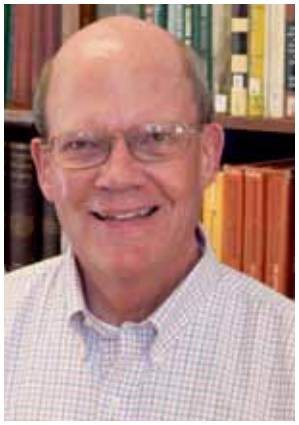
Today, our investigators produce nearly 1,200 peer-reviewed articles and other publications yearly. At any given moment, the medical center leads or participates in more than 1,300 active clinical trials involving children and adults.

Cincinnati Children's has become the nation's second highest recipient of NIH research funding among pediatric centers. This dramatic growth has helped attract more top scientists, who in turn play national and global leadership roles.

This growth didn't happen by accident. Cincinnati Children's has invested deeply in the expertise and the infrastructure needed to conduct sophisticated, large-scale studies.

We pumped more than $50 million into implementing our electronic patient records system and a related data warehouse project that captures medical information for research use *(see article, page 59)*. After nearly three years of setup, tools that will allow many more investigators to access the warehouse began rolling out in summer 2010.

"All of this was planned at the same time," says John Hutton, MD, director of the Division of Biomedical Informatics. "Five years ago, the board of trustees and top executives made a commitment to take better advantage of the digital age. Now that commitment is starting to produce results."



Cincinnati Children's has invested in and planned for an infrastructure to support multicenter trials, says Dr. John Hutton.

Pooled data a boon to research

Our data warehousing capabilities – including technology and expert staff – were vital to launching the national Registry for Eosinophilic GastroIntestinal Disorders (REGID) in 2010. So far, five medical centers plan to feed data into the registry.

Large-scale studies often spin off smaller projects to address specific questions that emerge along the way.

"This project involves state-of-the-art technology and a multi-disciplinary approach that few other institutions could achieve," says Marc Rothenberg, MD, director of the Division of Allergy and Immunology and the Cincinnati Center for Eosinophilic Disorders at Cincinnati Children's.

Another advantage for conducting multicenter research at Cincinnati Children's flows from the recently completed Genomic Control Cohort project, Spigarelli says.

This massive behind-the-scenes effort involved 14 divisions at the medical center and took more than three years to complete. The result: a central pool of data from more than 1,000 healthy children of varying age, race and gender. It contains de-identified genetic information, medical histories – even blood, urine and tissue samples.

This pooled data will make applying for grants and conducting research easier, faster and less costly – not just for investigators within the medical center, but for cooperative projects as well.

"Everybody in medical research knows how hard it can be to recruit children to participate in research, especially the normal controls," Spigarelli says. "This is one of the advantages made possible by the research growth here. We have the expertise and the resources to do something like this."

Patient benefits

In addition to the direct value of multicenter trials, large-scale studies often spin off smaller projects to address specific questions that emerge along the way.

The Teen-LABS project has generated nine ancillary studies and two "sub studies," eight of which are based at Cincinnati Children's. Similar spin-offs are occurring in epilepsy research, perinatal care, gastroenterology and many other fields.

Participating in trials like these gives families direct access to advanced care. Even when families choose not to enroll their child, they still benefit from Cincinnati Children's involvement in multicenter research.

"Being at the cutting edge means we can offer the most advanced care available anywhere, while at the same time measuring the outcomes that will objectively demonstrate value," says Inge.

"Drug development is happening very quickly. We want to be able to say to the drug companies, 'Yes, we can do these studies for you.'"

Dr. Carole Lannon is co-director of the Center for Health Care Quality. Her focus is taking results from large-scale studies into real-world practice that benefits children.

More to come

With more experts and infrastructure in place, Spigarelli, Giannini and others predict that Cincinnati Children's will be playing a larger role in multicenter trials for years to come.

The scientific explosion stemming from the Human Genome Project and related discoveries is still just beginning. And now, federal law requires that new medications marketed for children must be tested in children.

"Drug development is happening very quickly," Giannini says. "As these compounds come up for testing, we want to be able to say to the drug companies, 'Yes, we can do these studies for you.'"

And Cincinnati Children's is taking a lead role in determining how medical institutions can move discoveries made from these studies into real-world practice. In fact, we plan to launch at least 10 multi-site networks for research and quality improvement by 2015, says Carole Lannon, MD, MPH, co-director of the Center for Health Care Quality.

"By collaborating with others to improve care and outcomes for children, we extend our work beyond the four walls of the hospital," she says. "In this way, we hope to have a population impact that's larger than we can reach at our own site."

Researchers believe that will mean better care, sooner, for more children.

"We will be leading more of these kinds of studies," Spigarelli says. "In the past, we often said, 'That's a question we should answer someday.' Our goal is to answer that question now, not 20 years from now. And we have grown to the point where we can say, 'If not us leading these kinds of trials, then who should it be?'"

Planning for the data warehouse directed by Dr. Keith Marsolo *(far right)* goes back more than five years, says Dr. John Hutton.

Data warehouse boosts research

Use to jump from dozens to hundreds of investigators

Medical information from more than 650,000 children can be a powerful thing.

That's how many patient records exist in the new EPIC electronic medical records system at Cincinnati Children's. And now, thanks to a forward-thinking data warehousing project, vast amounts of those records have been scrubbed of personal identifiers and made available to investigators in their quest to improve child health.

The i2b2 data warehouse project sounds like something out of a *Star Wars* movie. In some ways, it may be just as futuristic.

Information from this warehouse has been available only to a handful of early users since the project went live with limited data in early 2008. Even so, the warehouse has helped launch a national registry for eosinophilic disorders, contributes to the Improve Care Now network for inflammatory bowel disease, supports liver transplantation research, and provides data for a major internal study of outpatient outcomes at Cincinnati Children's.

With new user tools that began rolling out in Summer 2010, the number of researchers tapping into the data warehouse is expected to leap from a few dozen to several hundred. And that could have far-reaching impact on research.

"We were the earliest adopters of this approach outside Boston (where the initial software system was developed)," says John Hutton, MD, director of the Division of Biomedical Informatics at Cincinnati Children's. "We were the first major pediatric institution to adopt an integrated strategy for management of both clinical and research data."

Planning for the EPIC electronic medical record and the data warehouse goes back about five years, Hutton says.

"We embarked on two adventures simultaneously," Hutton says. "At the same time we were looking at electronic health records for clinical care, we were concerned about our ability to take advantage of the digital age on the research side."

Keith Marsolo, PhD, director of the data warehouse project, describes EPIC as a way to get medical information into electronic form and the data warehouse as a tool to get that data back out in a form that can be used for research.

EPIC has grown to include information on more than 650,000 patients, with some data going back as far as 2003, including diagnoses, demographics, medications, and lab results.

In months to come, more "legacy" clinical data from various other record-keeping projects are being merged into the system.

"This project unlocks data that has been siloed away in all these different systems," Marsolo says. "It provides one central repository that you can go to."

The data warehouse scrubs these records to eliminate information that could identify the patient involved, which then allows investigators to go to work.

"One of the early uses has been to run cohort identification searches," Marsolo says. "You can ask, 'How many patients are there in the database that meet criteria X, Y and Z?' And it would give you a number."

"That's very powerful," Marsolo says. "People need to know this information for grant applications, for IRB purposes, for pre-submission work. In the past, that could take weeks or months of doing chart reviews by hand."

Since the initial launch, the data warehouse architects have been modifying the system to support research registries.

"Where this becomes really powerful is if you are doing multi-center studies, where you have a lot of historical data," Marsolo says. "The eosinophilic disorders registry is one of the first external registries we are doing. Internally, we are working with liver transplant on a registry that potentially could be a model for all types of transplant."

Psychiatry

Responding to a growing need to prevent and treat pathological aggression in children and adolescents, Drew Barzman, MD, has developed a child and adolescent forensic psychiatry service. The program educates residents on child forensic research and consults on local and regional criminal and civil forensic cases.

Barzman is board certified in both child and adolescent and forensic psychiatry. He and his research team have developed the first reliable clinical tool for predicting inpatient aggression and violence on child psychiatric hospital units. The assessment is currently being used actively in inpatient programs at Cincinnati Children's. Current work is underway to use assessment instruments to determine risk of aggression for children with disruptive behavior disorders and associated psychiatric syndromes in other treatment settings.

Barzman's recent publications address aggression through problem-solving models and the use of pharmacological intervention for specific psychiatric syndromes associated with pathological aggression. Associated studies will examine biological markers associated with pathological aggression.

Jeffrey R. Strawn, MD, a graduate of our child psychiatry residency research program, will continue his work with our division. He published 27 peer-reviewed articles on aspects of post-traumatic stress disorder (PTSD) during his training, including its biology, noradrenergic dysfunction, psychopharmacology, and treatment with pregabalin. Strawn also studied cerebrospinal fluid neuropeptide Y in post-traumatic stress disorder and therapy effects on cerebrospinal fluid neurochemistry.

Children who suffer physical and sexual abuse incur significant disruption in psychological development, social deficits and often, changes in physical health. Our Healing Center clinic treats children from preschool through age 18 who are trauma victims, using cognitive behavioral therapy and evidence-based psychotherapeutic interventions. Through structured assessments at intervals throughout treatment, we have shown that the majority of patients have significantly reduced depression, trauma, anxiety, dissociation and anger.

Pulmonary Medicine

Our Cystic Fibrosis (CF) Center was featured in a *US News and World Report* article outlining what Cincinnati Children's has done to improve care for these patients. The story focused on how including patients and families in managing their care has helped improve outcomes. These and other quality improvement efforts have led Cincinnati Children's to become one of the leading CF Centers in the country, as measured by the CF Foundation through a combination of key metrics. In addition, Cincinnati Children's improved its *US News and World Report* ranking in pediatric pulmonology to number two in the country.

With the goal of becoming the premier center to diagnose and treat asthma, we have combined asthma treatment and research to form a center that includes Pulmonary Medicine, Allergy/Immunology, Adolescent Medicine and General Pediatrics. Our work has included developing an institutional data repository to identify and characterize patients with asthma, facilitate outcomes and other clinical research and promote improvement. We also developed institution-wide outcome measures to track variability, share innovations in care delivery and facilitate research. Our inpatient asthma consult service increased consults by 25 percent this year. We led the evidence-based clinical practice guidelines for managing acute asthma exacerbations and the task force that revised inpatient care to identify and mitigate risk factors for poor asthma control and future exacerbations.

Our Airway Center performed more than 1,200 flexible bronchoscopies this year. It is the largest training center for pediatric flexible bronchoscopy, conducting an annual international post-graduate course attended that over the years has been attended by more than 500 physicians from more than 40 countries. This year, we will expand the course to include a training site in Spain. The Airway Center supports clinical and basic research and attracts referrals from around the world.

Radiology

We had an outstanding year in imaging research. Our faculty authored or co-authored 94 peer reviewed publications, the largest number ever and a 65 percent increase over last year. Our researchers also received significant funding. Primary investigators in imaging received $9.1 million in new direct and indirect grant funding this year, adding to the $11.6 million in imaging grants and $4.9 million in imaging support of other research projects. Additionally, we have been notified of $9.4 million in grant funding to be, or scored so it will likely be, awarded in the coming fiscal year.

Faculty made numerous national research presentations and were recognized with a number of awards for exceptional work. Tal Laor, MD, Eric J. Wall, MD and Andrew M. Zbojniewicz, MD, received the highly coveted Caffey Award for best paper at the Society for Pediatric Radiology Annual Meeting. This is the third year in a row that our faculty have received this honor. Janet L. Strife, MD, received the Gold Medal from the Society for Pediatric Radiology for lifetime contributions to the subspecialty. Neil D. Johnson, MD, served as 2010 president of the Society for Pediatric Radiology.

Reproductive Sciences

The Division of Reproductive Sciences marked its second year at Cincinnati Children's. The division has grown from 19 to 26 members and has significantly expanded both internal and external collaborations.

This year, we recruited two new faculty members from Harvard University: Satoshi Namekawa, PhD, and Yuya Ogawa, PhD. Their research in epigenetic programming and the mechanisms of X chromosome inactivation in germ cells will provide insight into the causes of certain types of birth defects. Namekawa received a Cincinnati Children's Trustee Grant of $60,000 per year for two years for his project, "Regulation of sex chromosome inactivation by DNA repair pathways."

Reproductive Sciences faculty members collaborate with researchers in Developmental Biology, Endocrinology, Experimental Hematology, Visual Systems, Molecular Immunology and the Perinatal Institute on a range of topics. Takiko Daikoku, PhD, has begun collaborating with Cornell University to examine Pten signaling in endometrial cancer.

Director SK Dey, PhD, Namekawa and Daikoku are working with researchers at the University of Utsunomiya on a project exploring BRCA1's relationship to pre-implantation embryo development. Another project with Indiana University-Bloomington explores endocannabinoid signaling in pregnancy.

Dey received NIH ARRA stimulus funding for the study, "Aspects of Blastocyst Implantation," bringing total direct costs to $592,000.

Sanjoy Das, PhD, received an NIH ARRA grant of $740,000 over two years for his work, "Molecular Signaling in Decidualization."

Huirong Xie, a postdoctoral fellow, and Xiaofei Sun, a graduate student, trained staff of the Transgenic Core to transfer sperm cryopreservation techniques. Sperm cryopreservation is an efficient, cost-effective alternative to embryo cryopreservation for most strains of transgenic mice. In the first eight months of the service, 61 projects were completed for Cincinnati Children's and University of Cincinnati affiliates, providing revenue for the Transgenic Core and saving divisions costs in storing their transgenic lines.

OUR CYSTIC FIBROSIS (CF) CENTER, FEATURED THIS YEAR IN A *U.S. NEWS AND WORLD REPORT* ARTICLE, HAS BECOME ONE OF THE COUNTRY'S TOP CF CENTERS.

Rheumatology

Genetic risk factors identified for juvenile idiopathic arthritis (JIA) may have important implications for the disease. Our innovative translational research continues to focus on the molecular basis of JIA, using large-scale genomic and gene expression JIA datasets to define the disease at a molecular level.

Recent published data support reevaluating the clinical criteria for defining JIA subtypes. The data include high-resolution HLA allele types, single nucleotide polymorphisms (SNP) and gene expressions. We have identified risk factors in common with other autoimmune diseases and have found evidence in cohorts of JIA patients and controls that associate JIA with 3q13, a region containing the T-cell receptor co-stimulatory molecule CD80. We also identified the gene expression signature of Macrophage Activation Syndrome (MAS); candidate biomarkers for the early diagnosis of MAS; and a novel genetic marker strongly associated with MAS. MAS is a manifestation of JIA associated with high morbidity and is the leading cause of JIA-related mortality.

We continue to improve care and outcomes for children with JIA using quality improvement (QI) techniques. Daniel Lovell, MD, led a national JIA quality measures workgroup to develop measures to assess the outcomes of children with JIA. Esi Morgan DeWitt, MD, will use these measures to coordinate QI efforts among a national consortium of pediatric rheumatology centers in the coming year.

Hermine Brunner, MD, and her team identified features that impair the quality of life of children and adolescents with lupus – fatigue, joint and chest pain, and neurocognitive symptoms. In multicenter and multinational collaborations, this research team developed outcome measures for pediatric lupus clinical trials. They established clinically relevant differences in lupus disease activity; developed flare criteria; and created a standardized battery to test neurocognitive functioning of children with lupus. With the Division of Nephrology at Cincinnati Children's, they developed what is to our knowledge the first biomarker for lupus nephritis to predict renal flares. In collaborative research with our Pediatric Pharmacology Unit, they determined customized dosing of mycophenolate mofetil for optimal disease control in childhood-onset systemic lupus erythematosis.

Skin Sciences Program

Neonatal skin hydration decreases rapidly after birth, then increases over the first month. Transition from high to low humidity may initiate filaggrin proteolysis to water-binding free amino acids (FAAs). We examined FAAs in vernix and infant stratum corneum. FAAs are low at birth, higher one month later, but lower than adult levels. FAAs are higher at 24 hours in vernix-treated than vernix-removed skin, suggesting that vernix provides FAAs to plasticize the skin before adaptive changes can occur. Coupled with the healing, anti-infective and anti-oxidant properties, the water-binding function of vernix is essential for premature infants who often lack vernix.

Chronic irritant contact hand dermatitis (ICD) is common in healthcare workers. A polymorphism at position -308 on the TNFa gene has been associated with skin irritation. We examined the TNFa -308 genotype and atopy among healthcare workers with ICD and their responses to repetitive hand hygiene and lotion treatment. Both TNFa -308 and atopy influence irritation, recovery and effectiveness of common skin care products in chronically damaged and normal skin. The AA/GA genotype experienced more irritation than genotype GG. Targeted genotyping for TNFa -308 and atopy could reduce occupational skin disorders through treatment and prevention.

Long-term transgene expression via follicular gene therapy may be useful in treating diseases such as X-linked hypohydrotic ectodermal dysplasia, where mutations in EDA1 and receptor EDAR cause abnormal hair shape and lack of eccrine glands. We used a high titer of VSV-G-pseudotyped lentiviral vector encoding insulin-like growth factor binding protein 5 (IGFBP-5) to transfect curly and straight human hair follicles before grafting onto SCID mice. Overexpression of IGFBP-5 in hair xenografts resulted in decreased extracellular matrix proteins and disassembly of adhesional junctions. The resulting hair twisted shafts have an unusual deposition of hair cuticle. Lentiviral transduction is useful for analyzing genes regulating human hair morphogenesis.

Sports Medicine

We continued our growth this year, adding four new staff: Nicholas Edwards, MD, MPH, researcher and clinician; Catherine Quatman, PhD, post-doctoral fellow and physical therapist; Staci Thomas, MS, clinical research coordinator; and Daniel Carson, MS, CSCS, research assistant.

Kevin Ford, PhD, received a three-year NIH grant to determine growth-related sex differences that increase knee load and risk of ACL injury in adolescents. Ford also was named a fellow in the American College of Sports Medicine (ACSM) and elected co-chair of the ACSM's Biomechanics Interest Group.

Greg Myer received his PhD from Rocky Mountain University this year. His research focus is developing an algorithm to predict knee abduction in females, a major risk factor for ACL injury.

We received our fourth consecutive award from National Football League Charities for "Longitudinal Study of ACL Reconstruction Outcomes: Knee Mechanics and Quadriceps Strength." Our goal is to understand mechanisms associated with abnormal knee mechanics and decreased functional performance in athletes with ACL reconstruction.

Tim Hewett, PhD, Ford and Myer gave invited symposia at annual meetings of the American College of Sports Medicine and World Congress on Exercise in Medicine. Myer and co-authors Ford, Divine, Wall, Kahanov and Hewett received the Clint Thompson Award for Clinical Advancement for their paper, "Longitudinal Assessment of Noncontact Anterior Cruciate Ligament Injury Risk Factors during Maturation in a Female Athlete: A Case Report."

Mark Paterno, PT, MS, MBA, received the American Orthopaedic Society for Sports Medicine 2010 NCAA Research Award for his paper, "Biomechanical Measures during Landing and Postural Stability Predict Second Anterior Cruciate Ligament Injury After ACL Reconstruction and Return to Sport." The award is given to the best paper pertaining to the health, safety and well-being of collegiate student-athletes.

Urology

The division moved from fifth to fourth in Pediatric Urology in this year's *US News and World Report* survey, in large part due to our continued research and clinical advances.

Pramod Reddy, MD, who was appointed director of the division this year, is principal investigator for the division's NIH basic science research investigating innervation of the developing bladder in *Xenopus*. He completed Phase I of a clinical trial with Novartis on neurogenic detrusor overactivity and is recruiting for Phase II. In a study with Pfizer, he is testing fesoterodine in children's overactive bladders.

Director of urology clinical research W. Robert DeFoor, Jr., MD, is lead investigator on the subcontract for the NIH clinical trial "Randomized Intervention for Children with Vesico Ureteral Reflux (RIVUR)." DeFoor completed two clinical trials this year on the efficacy of gentamicin bladder irrigations.

Led by Paul Noh, MD, we performed 54 minimally invasive pediatric urology robotic cases this year, with decreased pain, blood loss and length of stay. The procedures included pyeloplasty, nephroureterectomy, ureteral implant, cecostomy and nephrectomy.

We continue our affiliation with Arkansas Children's Hospital. Our physicians travel there monthly to perform complex genitourinary procedures for children and urologic procedures for children with spina bifida. They also train surgical and nursing staff to manage pre- and post-op care.

Shumyle Alam, MD, spoke at the International Children's Heath Initiative Partnership in Ecuador in June. His presentation focused on work with our Urogenital Center.

Eugene Minevich, MD, lectured and performed surgery at Shaare Zedek Medical Center in Jerusalem, Israel. Minevich served on the executive committee of the American Association of Pediatrics Section of Pediatric Urology, as program chair of the Society of Pediatric Urology annual meeting and co-chair of the International Pediatric Urology Symposium in Israel in May.

Our Center for Disorders of Sex Development launched its first clinic in January 2010. The Center collaborates with the divisions of Pediatric Urology, Endocrinology, Psychology, Gynecology and Human Genetics.

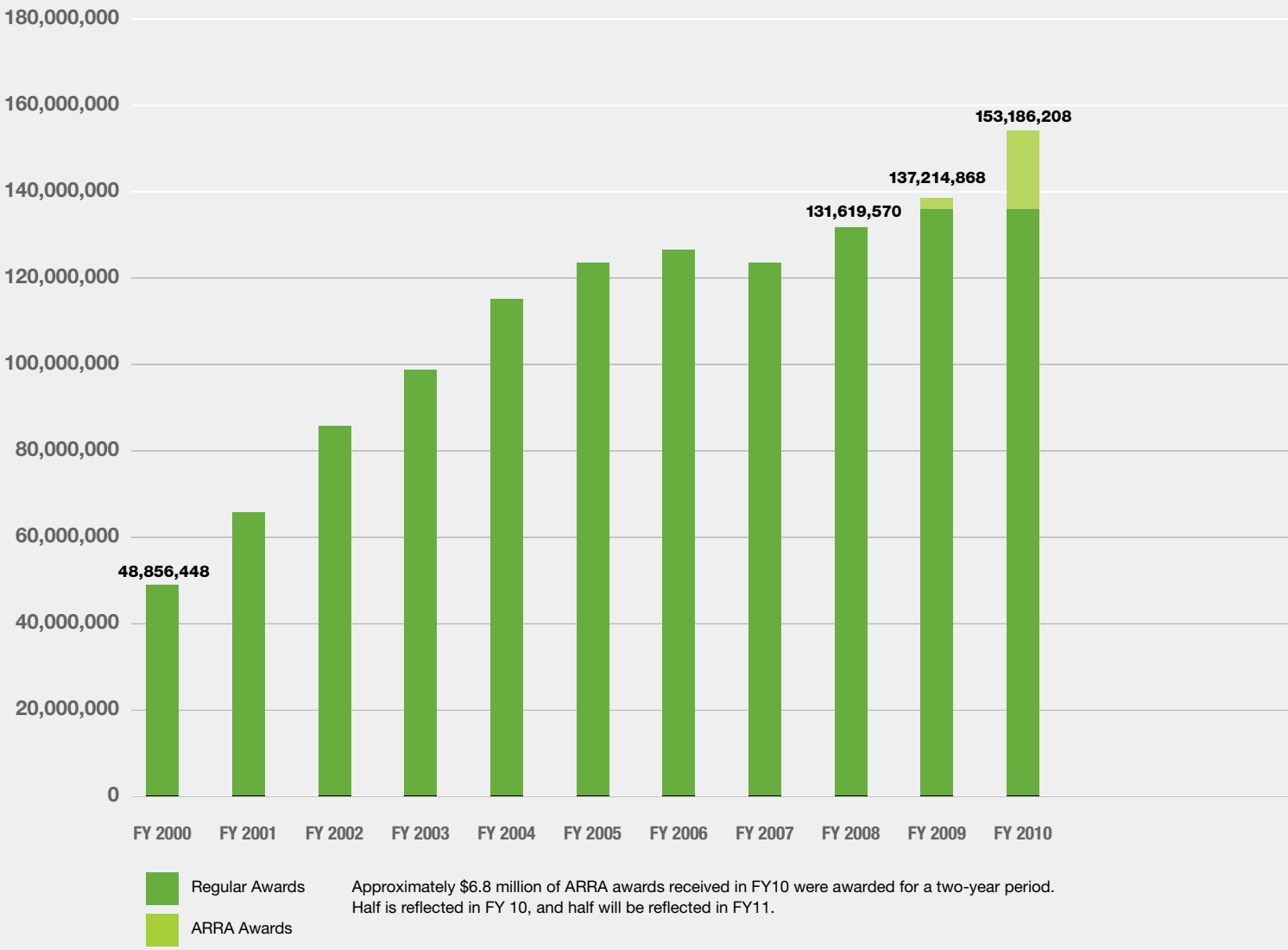
OUR DIVISION OF RHEUMATOLOGY HAS IDENTIFIED GENETIC RISK FACTORS WITH IMPORTANT IMPLICATIONS FOR DIAGNOSING AND TREATING JUVENILE IDIOPATHIC ARTHRITIS (JIA). THEY ARE ALSO STUDYING OUTCOMES TO IMPROVE THE CARE OF CHILDREN WITH JIA.

AWARDS & FUNDING

Cincinnati Children's Research Foundation 2010

Overall Sponsored Program Awards

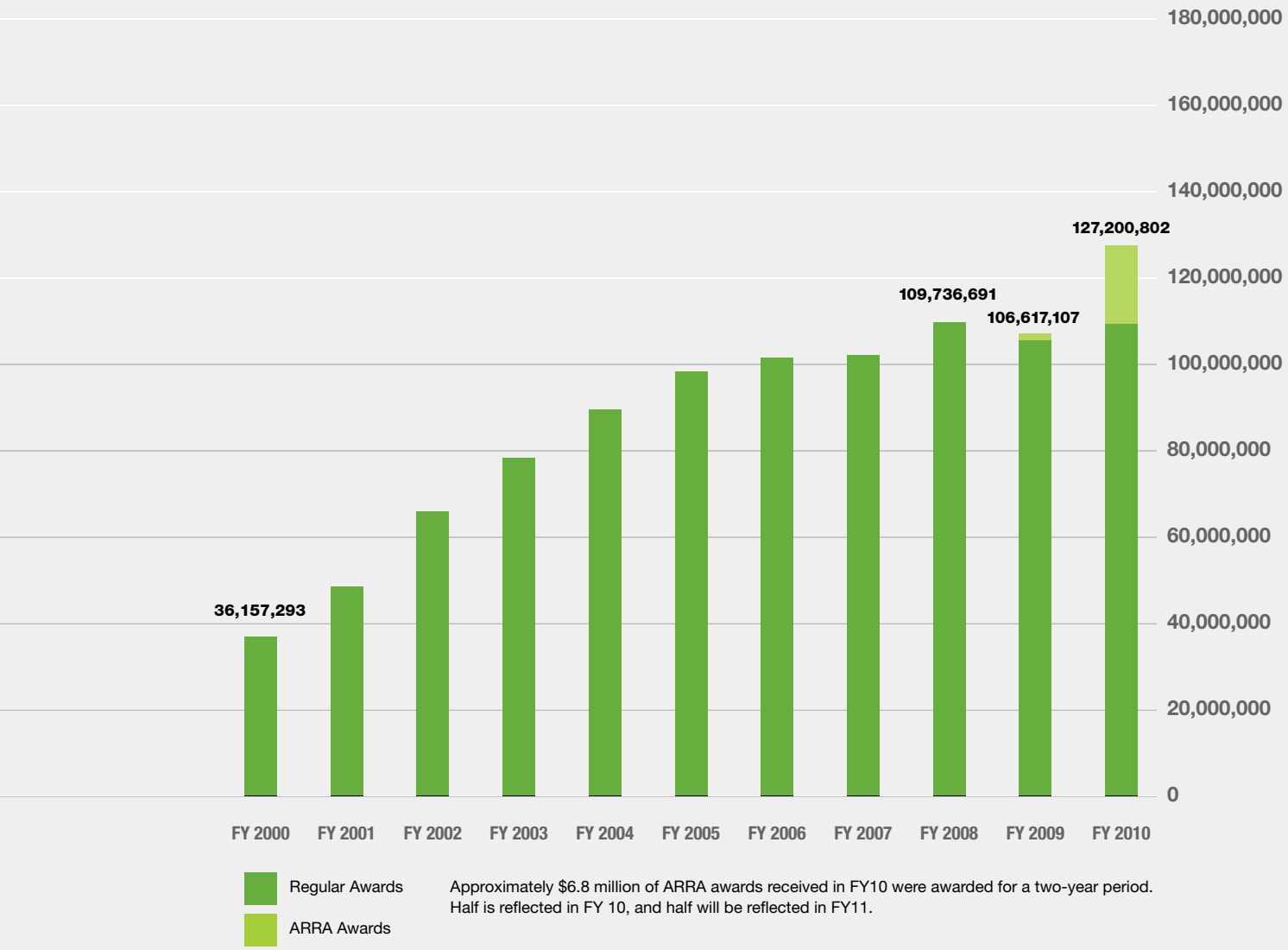
Total Costs (Prime and Sub-awards)



Approximately $6.8 million of ARRA awards received in FY10 were awarded for a two-year period. Half is reflected in FY 10, and half will be reflected in FY11.

Federal Awards

Total Costs (Prime and Sub-awards)



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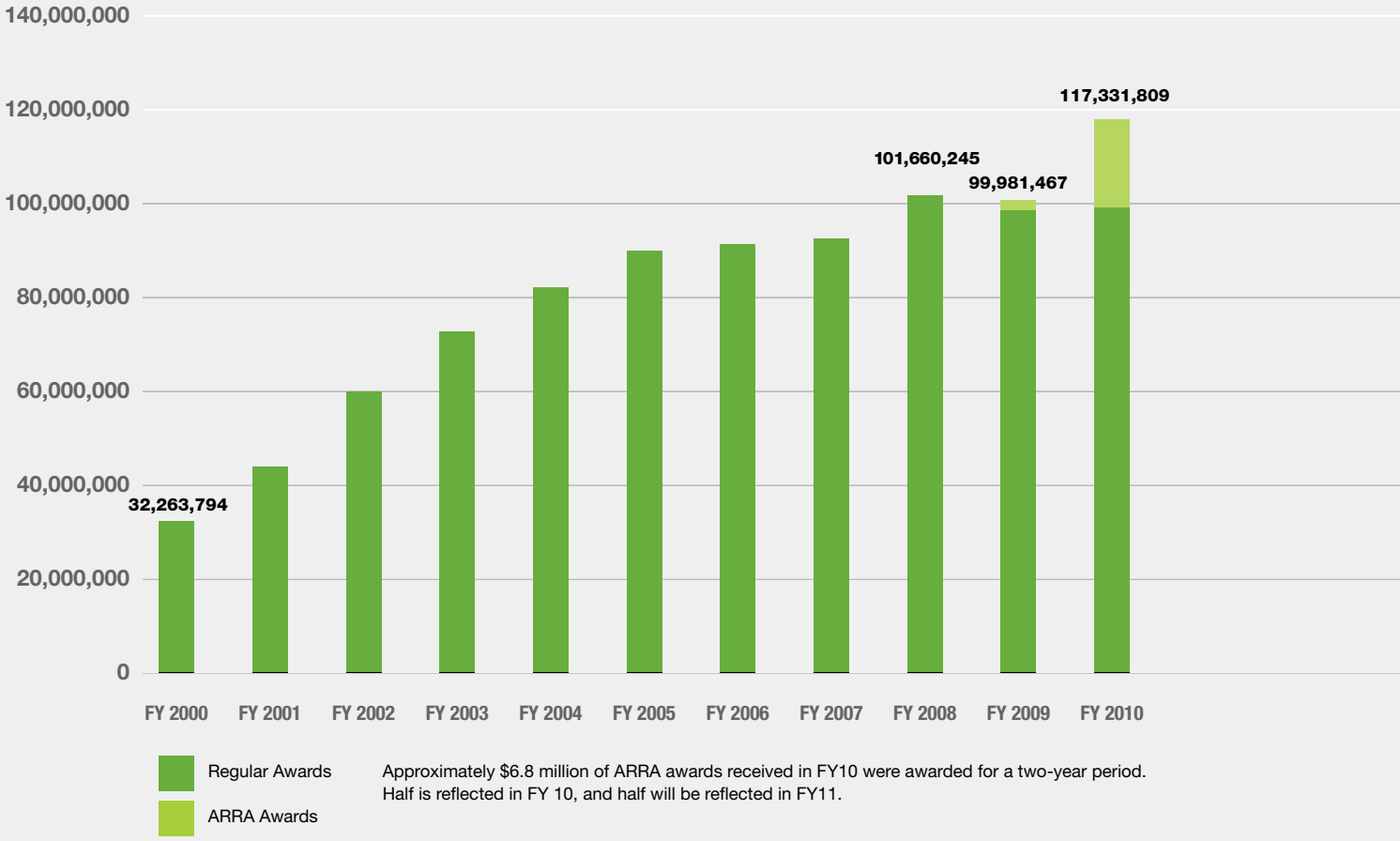
AWARDS & FUNDING

National Institutes of Health Awards

Total Costs (Prime and Sub-awards)



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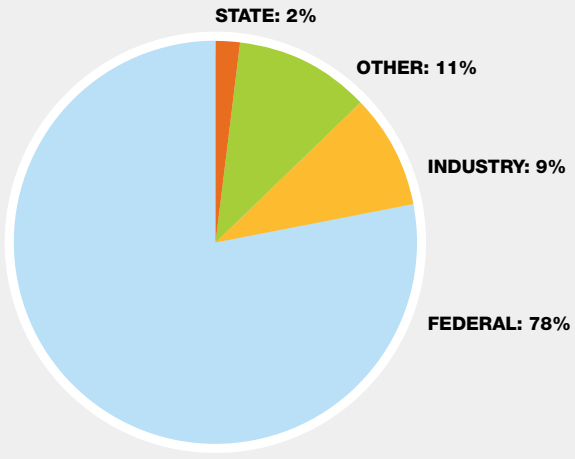
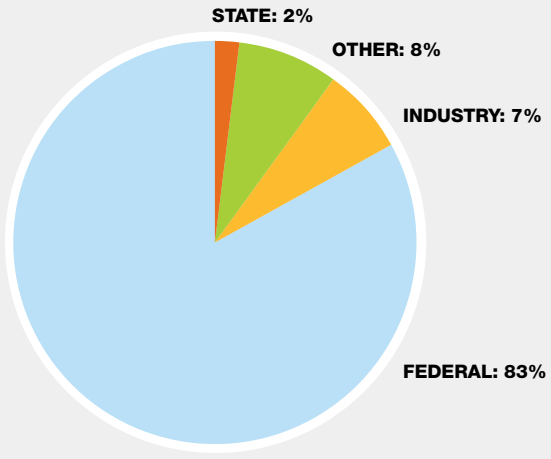
Distribution of Funding



FY **2009**



FY **2010**

Sources of Federal Funding

National Institutes of Health (NIH)	**117,331,809**
Health Resources and Services Administration (HRSA)	**1,976,289**
Department of Defense (DoD)	**1,692,032**
Centers for Disease Control (CDC)	**1,455,747**
Department of Education (DoED)	**1,071,323**
Agency for Healthcare Research and Quality (AHRQ)	**999,843**
Food & Drug Administration (FDA)	**772,888**
Substance Abuse & Mental Health Service Administration (SAMHSA)	**677,168**
Administration on Developmental Disabilities (ADD)	**487,104**
United States Air Force (USAF)	**400,001**
National Science Foundation (NSF)	**294,859**
Social Security Administration (SSA)	**25,000**
Department of Health and Human Services (DHHS)	**16,739**
Total	**127,200,802**

Foundation and Other Agency Awards

Gates Foundation	**1,442,687**
Cystic Fibrosis Foundation	**1,026,313**
American Heart Association	**798,200**
The Children's Tumor Foundation	**505,700**
March of Dimes	**462,643**
American Cancer Society	**388,700**
Robert Wood Johnson Foundation	**371,064**
Foundation LeDucq	**326,242**
First 5 LA Commission	**307,000**
National Football League Charities	**249,837**
Flight Attendant Medical Research Institute	**239,547**
Cancer Free Kids	**221,000**
Miscellaneous Other (90)	**6,476,562**
Total	**12,815,495**

FACULTY & CLINICAL STATISTICS

Department of Pediatrics and Cincinnati Children's Research Foundation Faculty

Total Faculty Members

Full-time/primary appointments in Pediatrics	**519**
Part-time/primary appointments in Pediatrics	**44**
During fiscal year 2010	**78** new faculty members were appointed **24** departed (including retirement)

Pediatric Faculty by Rank and Track

	Clinical	Adjunct (part-time)	Research	Field Service	Tenure Track	Tenured
Instructor	**12**	**3**	**17**	**4**	**0**	**0**
Assistant Professor	**112**	**18**	**65**	**6**	**34**	**0**
Associate Professor	**69**	**12**	**22**	**6**	**10**	**27**
Professor	**37**	**11**	**2**	**3**	**0**	**93**
Total	**230**	**44**	**106**	**19**	**44**	**120**

Gender Distribution (Includes Full-Time and Part-Time Faculty)

	Full-time	Part-time	Total
Males	**302**	**21**	**323**
Females	**217**	**23**	**240**

Minority distribution (Includes Full-Time and Part-Time Faculty)

	Black	Hispanic	Asian	Total
Full-time Males	**5**	**5**	**43**	**53**
Full-time Females	**9**	**2**	**24**	**35**
Part-time Males	**0**	**0**	**1**	**1**
Part-time Females	**0**	**0**	**2**	**2**

Clinical Activity

Admissions (Excludes Short Stay Admits)

Type	Number
Medical	**12,523**
Surgical (I/P Surgeries)	**5,667**
23-Hour Admissions	**14,791**

Outpatient Visits

Type	Number
Surgical Procedures	**25,492**
Emergency Room Visits	**125,130**
Primary Care (PPC) Burnet, Hopple & Batesville	**66,004**
Sub-specialty Care Burnet	**420,636**
Outpatient Liberty	**124,888**
Outpatient Mason	**87,431**
Outpatient Anderson	**52,899**
Outpatient Eastgate	**21,548**
Outpatient Harrison	**15,789**
Outpatient Fairfield	**51,282**
Outpatient Kentucky	**48,795**
Outpatient Kenwood	**646**
Outpatient Drake	**16,114**

Training

Students

Junior Medical Students in the Pediatric Clerkship	**152**
Senior Medical Students entered Pediatric Training	**24**
Senior Medical Students entered Medicine/Pediatric Training	**3**
Triple Board	**0**
Pediatrics/PM&R	**0**
Pediatrics/Neurology	**1**
Pediatrics/Genetics	**0**

Residents

Pediatrics	**110**
Medicine/Pediatrics	**29**
Pediatric Physical Medicine and Rehabilitation (PM&R)	**6**
Dental	**10**
Psychology	**5**
Psychology/Child Psychiatry/Pediatrics	**13**
Human Genetics/Pediatrics	**5**
Neuro/Pediatrics	**16**
Dermatology	**1**
Anesthesia	**6**
Surgery (includes General Surgery, Cardiothoracic, Neurosurgery, Otolaryngology, Ophthalmology, Plastic, Orthopedic & Urology	**95 rotating**
Radiology	**35 rotating**

Pediatric House Staff Recruitment 2009

Pediatric Candidates Interviewed	**292**
Medicine/Pediatric Candidates Interviewed	**67**
PM&R Candidates Interviewed	**6**
Psychiatry/Child Psychiatry/Pediatrics Interviewed	**13**
HG Pediatrics Interviewed	**3**
Neuro/Pediatrics Interviewed	**14**

FACULTY & CLINICAL STATISTICS

Training, continued

Fellows

Adolescent Medicine	**5**
+ Pediatric/Adolescent Gynecology	**2**
Allergy/Immunology	**5**
Anesthesia	**8**
Cardiology	**9**
Child Abuse	**1**
Critical Care	**11**
Dental	**0**
Developmental Disabilities	**3**
Emergency Medicine	**9**
Endocrinology	**8**
Gastroenterology	**11**
+ Pediatric Transplant Hepatology	**1**
General Pediatrics	**2**
Hematology/Oncology	**14**
+BMT	**1**
Infectious Disease	**4**
Medical Biochemical Genetics	**0**
Medical Genetics	**1**
Neonatology	**14**
Nephrology	**6**
Neurology	**1**
+ Movement Disorders	**0**
+ Pediatric Epilepsy	**1**
+ Pediatric Neuromuscular	**0**
+ Headache	**1**
Neurophysiology	**0**
Neurosurgery	**1**
Ophthalmology	**0**
Orthopedics	**2**
+ Orthopedic Spine Surgery	**1**
Otolaryngology	**6**
Pathology	**4**
Plastic Surgery	**1**
Pharmacology	**0**
Psychiatry	**6**
Psychology	**15**
Pulmonary	**7**
Quality Scholars in Transforming Health Care	**14**
Radiology	**11**
+ Body MRI	**0**
+ Neuroradiology	**1**
Rehabilitation Medicine	**2**
Rheumatology	**6**
Sleep Disorder Medicine	**1**
Sports Medicine	**2**
Surgery	**2**
+ Colorectal Surgery	**1**
+ Fetal Surgery	**1**
+ Pediatric International Surgical Fellow	**1**
+ Trauma Surgery	**1**
+ Vascular Anomalies	**1**
Urology	**3**

Total, Clinical Fellows 195

Total, Research Postdoctoral Fellows 135

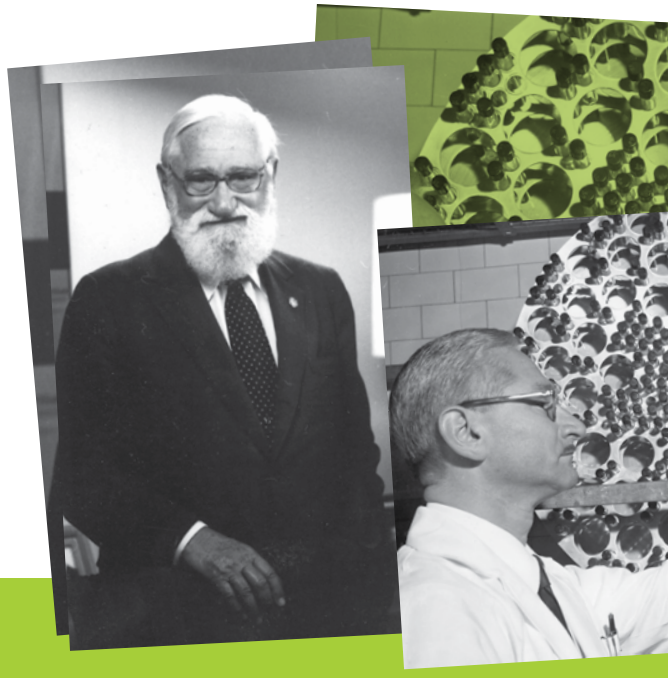
Publications	
Peer-reviewed articles	**984**
Non-peer-reviewed articles	**127**
Books (edited or authored)	**6**
Chapters of books	**36**
Online site contributions	**5**
Total, Fiscal Year 2010	**1,158**

Summer Research Programs	
High School Interns	**17**
Undergraduate Students	**95**
Medical Students	**17**

Procter Scholars

Name	Discipline	Project
Third Year		
Noah Hillman, MD	Neonatology	Lung development and lung injury with the goal of understanding components of neonatal resuscitation
Second Year		
Kimberly Czech, MD, PhD	Nephrology	Altered gene expression in pediatric patients with focal segmental glomerulosclerosis (FSGS)
Alan Kenny, MD, PhD	Neonatology	Characterize mechanisms regulating foregut organ induction and identify genes induced in the endotherm in response to mesodermal signaling
First Year		
Eric Mullins, MD	Hematology/Oncology	Mechanisms linking hemostatic factors to neuroinflammatory disease
Ajay Perumbeti, MD, FAAP	Hematology/Oncology	Genetic approaches to correct human sickle cell anemia
Charles Samson, MD	Gastroenterology/Hepatology & Nutrition	Homeostatic responses to gut injury in inflammatory bowel disease
Jason Fischer, MD	Pediatric General & Thoracic Surgery	EGFR inhibition and its antiangiogenic role in pediatric solid tumors
Sundeep Keswani, MD	Pediatric General & Thoracic Surgery	Molecular mechanisms of regenerative wound repair

Our Global Reach Started Early



A tribute to Albert Sabin, MD

On April 24, 1960, more than 20,000 children in the Cincinnati area lined up to become the first U.S. children to receive their doses of the Sabin oral polio vaccine.

It was the first of many "Sabin Sundays" and a major step forward in the near-total global eradication of a once deeply feared childhood disease.

The live oral vaccine developed at Cincinnati Children's by Albert Sabin, MD, vastly amplified the early gains against polio made by the injected Salk vaccine, which was based on a killed virus. As vaccination programs mushroomed worldwide, hundreds of thousands of lives were spared from the paralytic disease.

While a few new cases of polio still occur in remote parts of the world, the United States has not seen even one case of "wild" polio infection since 1979 – an historic achievement.

Fifty years later, Sabin's legacy lives on at Cincinnati Children's and the University of Cincinnati College of Medicine, where researchers also have developed a rotavirus vaccine, now used worldwide, and are studying vaccines for norovirus and other conditions.

At a ceremony marking the 50th anniversary, David Bernstein, MD, MA, director of the Gamble Program for Clinical Studies and Albert Sabin Professor of Pediatrics at Cincinnati Children's, offered these words: "My first mentor told me that if you're a physician, you may influence hundreds, maybe thousands of lives. If you are a researcher, you may influence millions of lives…Vaccines have extended life more than any other medicine."

More about Sabin's contributions

- Tens of millions of people in Mexico, Holland, England, Sweden, Czechoslovakia and even the Soviet Union received the vaccine in the late 1950s before it was approved for use in the United States.
- Sabin also developed vaccines for Japanese B encephalitis (widely distributed to U.S. military in the Pacific theatre during WWII) and Dengue Fever.
- Sabin authored more than 350 scientific papers on topics including pneumococcal infections, encephalitis, and possible links between viruses and cancer.
- He was the first to isolate the parasite that causes toxoplasmosis.
- In coming years, more details about Sabin's legacy will become available to historians thanks to a grant to the University of Cincinnati from the National Endowment for the Humanities. More than 35,000 letters and thousands of photographs related to Sabin's crusade to eradicate polio will be digitized. The collection is expected to be complete in June 2013.

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513-636-4420

Editorial:
Tim Bonfield
Tanya Bricking Leach
Mary Silva

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Cincinnati Children's Hospital Medical Center
MLC 9012
3333 Burnet Avenue
Cincinnati, OH 45229-3039