Cincinnati Children's

CINCINNATI CHILDREN'S RESEARCH FOUNDATION ANNUAL REPORT 2011

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This report highlights our research activities of the past year. A more detailed look at our research, publications and faculty will be available online later this year at www.cincinnatichildrens.org/research11

DISCOVERING THE SOURCE

Long ago, early explorers searched for the sources of the world's great rivers, often through great adversity.

"Discovering the source" became a life's work for some of these explorer-discovers. In this year's Annual Report, we focus on our research that strives to "discover the sources" of disorders and diseases. We showcase our exploration of the underlying mechanisms and fundamental processes occurring during the earliest stages of development that later adversely impact children's and adults' health. We highlight this work of discovery because understanding such mechanisms is essential to developing the early interventions or therapies that will prevent or obviate adverse outcomes and alter the developmental origins of pediatric and adult disease.

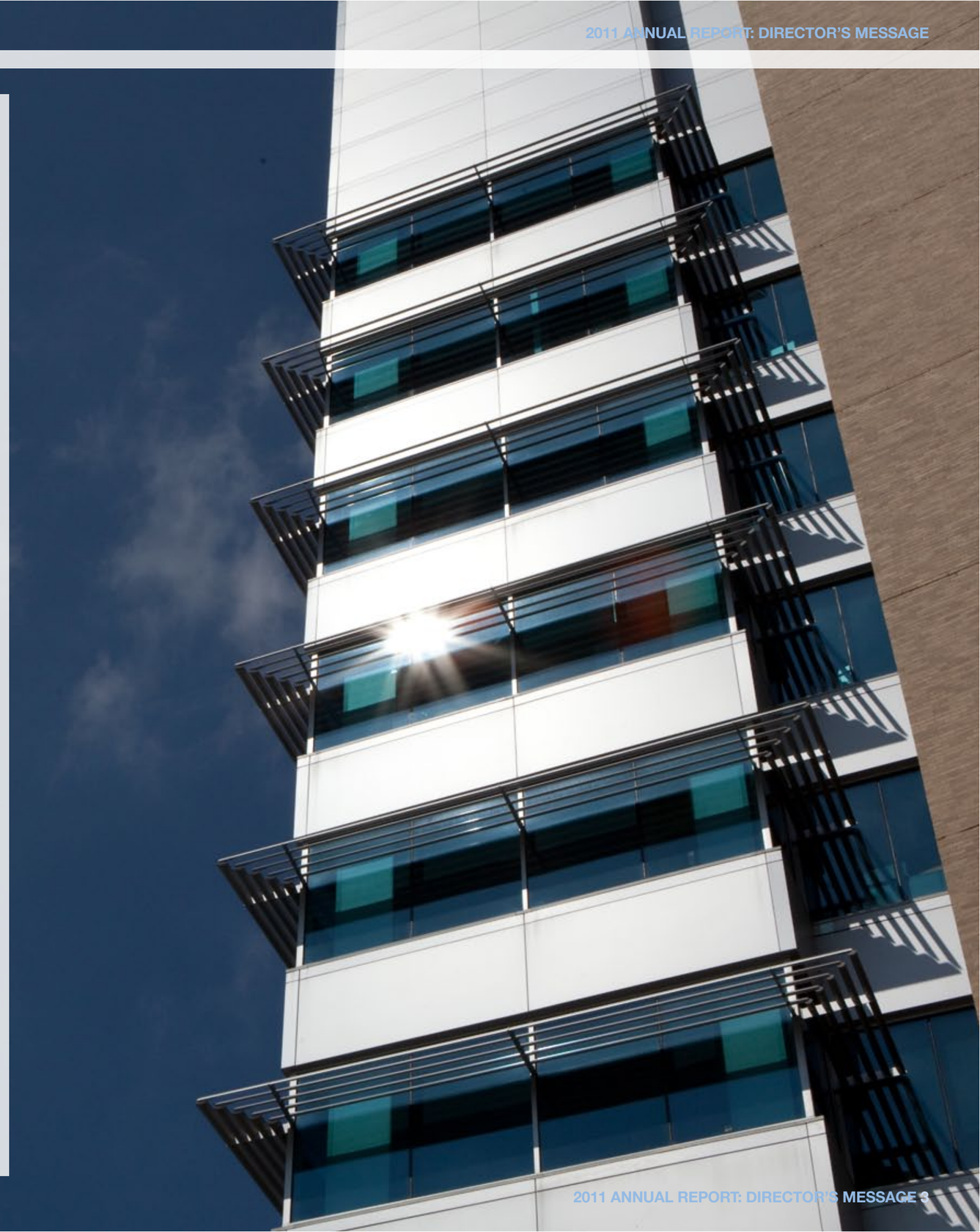
Arnold W. Strauss, MD,
is Director of the Cincinnati Children's Research Foundation and Rachford Professor and Chair of the Department of Pediatrics, University of Cincinnati College of Medicine

Today, we work to repair congenital defects and cure children whose health problems began before birth or early in life. We ask, "What basic mechanisms cause these problems?" with the goal of "discovering the source." How can we treat these developmental origins of disease? Even better, how can we prevent or mitigate these adverse fetal and infantile events? These are the questions that fuel the daily work of our research teams. In this Report, you will learn about researchers who explore the timing and quality of the embryo's uterine implantation and its potential impact on infertility and prematurity. You will read about how advances in assisted reproduction, although bringing the joys of parenthood to many, also raise important questions about the long-term health of the children born as a result. We highlight an effort to determine the molecular origins of craniofacial deformities. This is just one of many collaborations between our developmental biologists who study organogenesis and stem cell biology and clinicians who treat and surgically repair congenital anomalies. In other examples, you will discover how our developmental neuroscientists are exploring early brain formation. They seek to understand how the amygdala, a part of the forebrain that controls the fear response, originates and how abnormalities in this and in brain white matter formation lead to neurological and behavioral deficits and disabilities. And finally, you will meet a cardiologist whose research led her to develop a breakthrough imaging technique for children at risk of heart and vascular disease with the goal of developing timely interventions to prevent long-term damage. These stories feature our collaborative research environment, the interactions of clinicians and scientists, that are a keystone of our approach to "discovering the source."

You will also learn, through Divisional summaries and the statistical data at the end of this Annual Report, of the innovative clinical care and the extraordinary educational accomplishments achieved in 2011.

To continue "discovering the source," our Cincinnati Children's Research Foundation (CCRF) Strategic Plan emphasizes future development along themes of Innovative Therapeutics and Diagnostics, including Medicinal Chemistry; Regenerative Medicine, Stem Cell Biology and Organogenesis; Inflammation and Immunity; Environment-Phenome-Genome Interactions in Health and Disease; Protein Sciences and Structural Biology; Health Services, Outcomes and Quality and Systems Improvement; Genomics and Epigenomics; and Bioinformatics and Systems Biology. These themes will be supported by an expanded infrastructure of cores, epidemiology and biostatistics, and data management to expand multi-site and multi-disciplinary patient-related studies.

I am continually impressed and inspired by the depth, breadth and quality of our clinical care, education and research accomplishments. This summary of our 2011 achievements, with more detail on the CCRF website, demonstrates why Cincinnati Children's is the leader in academic pediatric medicine. We invite you to explore CCRF, share our sense of excitement in the discoveries of our extraordinarily talented investigators, clinicians and educators, and to learn how we, like those early explorers, are "discovering the source" to improve child health. ■



FROM THE BOARD

This has been a year of enormous challenges for our nation and our world. Economic difficulties, particularly those facing our country, have been a wake-up call to all of us.

And in healthcare, we hear this call loudly and clearly.

At a time when resources are more precious and precarious than ever, healthcare organizations and the sciences that support them must seek solutions to health problems that are fundamental, meaningful and sustainable.

That is what the research featured in this year's report is about.

Our scientists are looking for solutions to health problems that go beyond just repairing damage once it happens. They are looking to the source of what causes that damage to prevent it from happening in the first place.

The articles featured in these pages are about research into the earliest stages of where health problems begin. You will learn about how our scientists have discovered that the reproductive process itself not only sets the course for a child's health, but for the health of his or her children. You will read about researchers who study the timing of brain development *in utero* to understand how premature birth affects critical functions. You will meet a doctor whose research in vascular imaging led to a breakthrough early detection method for children predisposed to heart problems.

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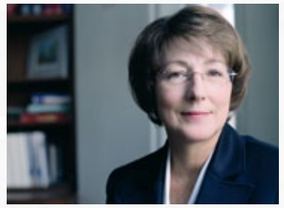


Nancy Eddy, PhD
Research Chair
Board of Trustees

This is science at its best. It provides insights into aspects of development previously shrouded in mystery. With every step, our scientists gain more knowledge of how, why and when things go wrong. They become better equipped to answer the questions that face doctors at the bedside. And they get closer to offering solutions and hope to sick children and their families.

This year, Cincinnati Children's received nearly $113 million in NIH funding for our research. Our total federal funding was $132 million — 86 percent of our research funding. At a time when science is scrutinized more than ever and when more scientists are competing for fewer dollars, this is a testimony to the strength of our research program and the caliber of our researchers.

We are extraordinarily proud of the reputation that our scientists have earned. We are committed to ensuring that the exceptional work being done here at Cincinnati Children's continues. It is work that is bringing new discoveries about human development and how that development veers off course. It is vitally important work that will ultimately lead to answers that change that course for good. ■

ALIVE, BUT WELL?

SCIENCE CREATED IVF BABIES AND NOW WONDERS ABOUT THEIR LONG-TERM HEALTH

Every year in this country, 60,000 babies are born who would not be here had nature been left to its own devices.

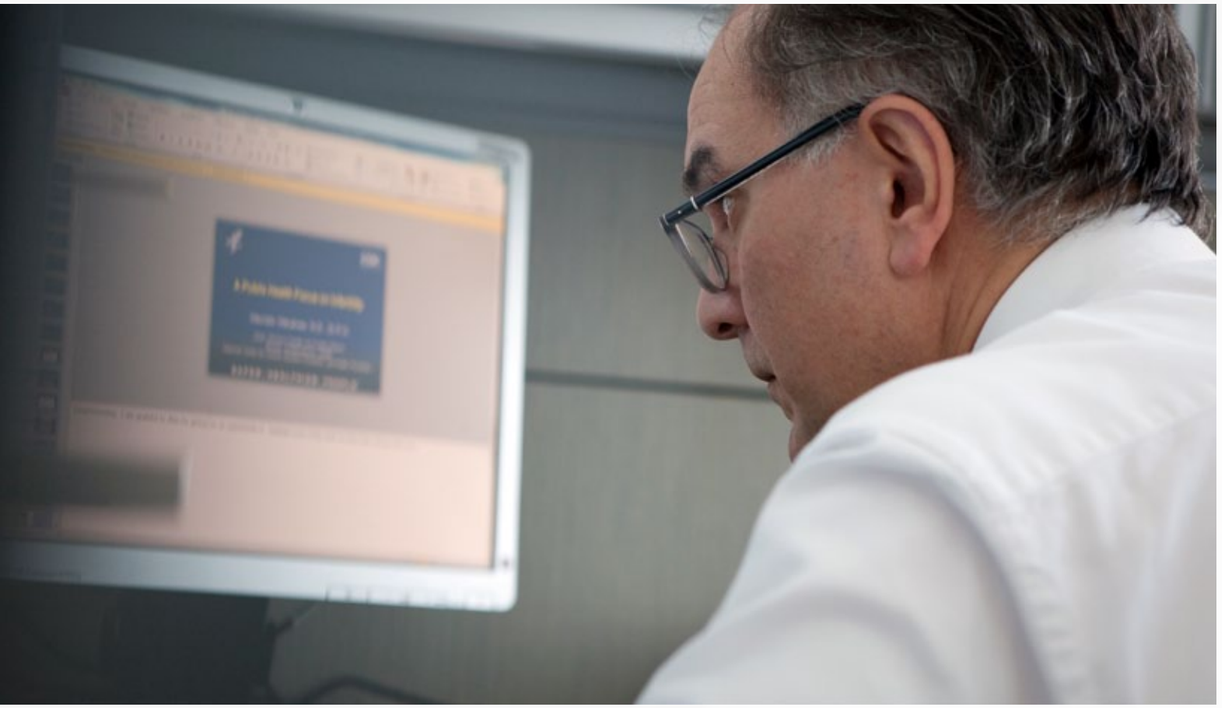
They are babies conceived as a result of *in vitro* fertilization (IVF). The procedure was introduced just a little more than three decades ago, with the first successful "test tube" baby born in 1978. Worldwide, there are now some 3 million people alive as a result of science's intervention in the fertilization process.

But are they well?

"For many the answer is 'yes,'" says Maurizio Macaluso, MD, DPH, epidemiologist and Director of the Division of Biostatistics and Epidemiology at Cincinnati Children's. "But infertility treatments like IVF are also associated with increased risk of adverse health outcomes, both for the mother and for the infants."

Federal law mandates that all clinics that perform IVF send data to the Centers for Disease Control and Prevention (CDC), which in turn publishes an annual report with summary statistics for each program. "The national data collected so far for IVF focus on whether it resulted in a live birth," Macaluso (right) says. "That's the measure most people want to see."

"Most people" in this case are the hopeful, determined couples who are unable to conceive naturally. They put body and soul through a roller coaster ride of hormone treatments, clinic appointments and agonizing wait-and-sees in their drive to become parents.



For tens of thousands of families each year, the rigors of IVF pay off with the birth of a baby — often, more than one baby — which seems a happy ending. But it is not the end of the story, says Macaluso.

A growing body of research, including the surveillance data collected by the CDC, indicates that IVF-conceived individuals are at increased risk of health problems, and he wants to understand why.

Infertility is common, affecting 10 to 15 percent of couples during their reproductive years, and many of these couples use fertility drugs and intrauterine insemination to conceive. But IVF and other forms of assisted reproductive technology (ART), which are based on extracting the eggs from a woman's body before fertilization, have higher success rates.

Some 150,000 IVF procedures are performed every year in the U.S. to bring about those 60,000 babies, Macaluso says. In 2006, about 3,300 ART procedures were performed for Ohio residents, with 1,500 live-born children.

Macaluso is familiar with the numbers because before coming to Cincinnati Children's in spring 2011, he directed the Women's Health and Fertility Branch of the CDC, and one of his responsibilities was to oversee the data collection from the nearly 500 centers around the country that perform IVF and contribute to the CDC reports.

Time for a better look

Although the national focus is mostly on the effectiveness of IVF technology and whether the procedure results in live births, it has limited use for looking at safety. Macaluso thinks it is time to dig deeper into IVF's outcomes.

"IT IS IMPORTANT THAT WE UNDERSTAND HOW INTERVENTIONS IN THE REPRODUCTIVE CYCLE LINK TO HEALTH PROBLEMS LATER IN LIFE."

He wants to understand how assisted reproduction affects the long-term health of people born as a result.

It is already known that IVF results in a higher number of multiple pregnancies. Whereas the chance of a natural multiple pregnancy is around 1 to 3 percent, in IVF pregnancies the rate runs between 20 and 40 percent.

Macaluso says a multiple pregnancy can cause complications for the mother and puts the babies at risk of preterm delivery, low birthweight and more. "There is increasing evidence that multiple births are associated with longer-term adverse outcomes for the infant – developmental disabilities and birth defects."

Armed with this evidence, the American Society for Reproductive Medicine, the Society for Assisted Reproductive Technology and the CDC are promoting the use of single embryo transfers in IVF.

But this has not yet translated into practice in the nation's fertility clinics. Only 7 percent of women under 35 choose to use single embryos when they have IVF.

The risks of upping the odds

For most couples, the reason is financial. Infertility treatments are covered by insurance in only 15 states currently, Macaluso explains. And it is costly – anywhere from $12,000 to $20,000 per procedure. Most young couples can afford only one try – which means they want as many embryos transferred as possible.

"The more embryos transferred, the more likely it will lead to a live birth," Macaluso says, "but the advantages are offset by the increased risk of multiple pregnancy."

And by the health risks that extend beyond infancy. Research now indicates that people who were low birthweight babies are more likely to be obese, to have diabetes and to suffer hypertension by the time they reach age 50. Because the oldest of those born from IVF are still in their early thirties, there is no way yet to predict whether this same health pattern will emerge for these individuals.

Changes in DNA

Scientists have also discovered differences in the DNA expression of people born via IVF, which may put them at higher risk for conditions like cancer or diabetes later in life. In a study published last year in *Human Molecular Genetics*, researchers found epigenetic differences in the DNA of children conceived by IVF compared with those conceived naturally.

INFERTILITY AFFECTS 10 TO 15 PERCENT OF COUPLES

NEARLY 150,000 IVF PROCEDURES ARE PERFORMED EVERY YEAR IN THE U.S.

60,000 BABIES ARE BORN FROM THOSE PROCEDURES

Further complicating the picture is the fact that IVF and assisted reproductive technologies are the only forms of infertility treatment for which clinics are required to report outcomes, Macaluso says.

"Drugs that produce ovarian hyperstimulation may have the same adverse impact on health that IVF has, but we can only guess at the number of multiple pregnancies and potentially adverse health outcomes for the infants that come out of those procedures," he says. He suspects that the numbers are significant because the procedures are less expensive than IVF, but because they are not monitored, there are no good data for estimating how many.

The cause

The looming question is whether the differences seen in IVF babies — from low birthweight and preterm delivery to cancer risk — are the result of the IVF treatment itself or other issues, such as the parent's infertility.

"It is difficult to disentangle the effects of the technology from the effects of the underlying conditions that cause the infertility in the first place," Macaluso says. "Attributing specific adverse outcomes to the technology or the infertility itself is difficult. On the other hand, it is clear that transferring more than one embryo into the uterus is the main cause of the large excess of multiple pregnancies, and that in turn must be the cause of a large proportion of the adverse health outcomes associated with IVF."

Encouraging a better way

Macaluso believes that one way to improve outcomes, regardless of the cause, is to get more insurance companies to cover the IVF procedure. He advocates that health insurers cover repeated single embryo transfers, which would eliminate the risk of multiple pregnancies and lower the number of preterm births and their associated problems, while keeping the overall success rates high.

"Today many insurance policies and some state regulations allow up to a certain number of IVF cycles; couples who choose single embryo transfer do the right thing but are punished by this system. Instead, they should be given the incentive of free additional cycles to reward their safe choice."

While at the CDC, Macaluso worked with a national health insurer to develop a benefit that covers two sequential single embryo transfer cycles. If the first one fails, a couple gets a second try, still covered by insurance. "The success rates are a little lower with single transfers," he says, "but that would be offset by the benefit of replacing the multiple births with singletons."

Looking over the long term

Another way to improve outcomes is to get a long view of how people born from IVF are faring, something Macaluso hopes to do at Cincinnati Children's. He sees an opportunity to develop a longitudinal study with what he terms a "well-knit network of neonatologists" in this region.

"The possibility exists that we could get very rich information about the outcomes of assisted reproduction techniques," he says. "This could provide us with the next level of information if we could put together the right study."

The study might replicate and expand on an initiative he started with several states while at the CDC. "We would link the mode of conception and assisted reproduction procedure used with the information available from vital records kept by the state departments of health."

The goal would be to link information from the IVF clinics and the vital record to hospital discharge summaries as well as disease and cancer registries, providing a long view of the individual's health.

Without question, assisted reproduction has brought happiness to hundreds of thousands of couples and has given life to millions. But it also has raised important health questions for those millions of people — questions that Macaluso believes merit further exploration.

"It is important that we understand how interventions in the reproductive cycle link to health problems later in life," Macaluso says. "Investing in better reproductive health is a very effective way of preventing disease in the next generations." ■

DIVISION ACCOMPLISHMENTS

Adolescent Medicine

A significant paper, featured in *Pediatrics*, demonstrated that girls are maturing at younger ages than previously reported. The findings were an outgrowth of our "Continued Studies of the Environment on Puberty" project, a longitudinal, NIH-funded, multisite study headed by Frank Biro, MD, principal investigator. Members of our Division of Biostatistics and Epidemiology and the University of Cincinnati Department of Environmental Health also participate in this project, which studies the influences of environmental exposures on timing of puberty and risk of breast cancer. A related NIH project, "Impact of Peripubertal Exposure to Xenohormones on Fat Distribution and Cytokines," explores environmental exposures on the relationships between bone mineral content, insulin resistance and cytokines during pubertal maturation.

Our Asthma Innovation Laboratory bridges research and healthcare improvement. Clinical activities, led by Maria Britto, MD, MPH, are housed within the Teen Health Center. The lab develops care delivery innovations, translates existing research resources into practice-friendly tools, and uses quality improvement methods to enhance care. In the past year, our interventions helped 60 percent of our patients with poorly controlled persistent asthma achieve good control, compared to 25 percent the prior year. We will serve as a pilot site for a comprehensive, Epic-based population management system and improving coordination between primary and specialty asthma care.

Last year we launched the Office for Faculty Development (OFD), housed within the Division of Adolescent Medicine. The office is directed by Jessica Kahn, MD, MPH, Assistant Chair of Academic Affairs and Faculty Development. Goals include promoting recruitment and retention; improving promotion rates and leadership opportunities for women and minority faculty; and enhancing work-life satisfaction.

Allergy and Immunology

Marc Rothenberg, MD, PhD, Director of the Division, received an NIH MERIT Award from the National Institute of Allergy and Infectious Diseases (NIAID) to extend funding of his long-standing investigation into "Regulation of Gastrointestinal Eosinophils." Rothenberg's work seeks to increase understanding of gastrointestinal eosinophils, their involvement in immune responses, and viable methods to block their role in causing disease.

Established in 1986, the Method to Extend Research in Time (MERIT) Award provides long-term support to exceptional investigators to promote their continued work and lessen research-associated administrative burdens. Each year, NIAID grants approximately 12 MERIT Awards.

The National Registry for Eosinophilic Gastrointestinal Disorders (REGID) was launched in the past year by J. Pablo Abonia, MD, Assistant Professor of Pediatrics in the Division of Allergy and Immunology, along with colleagues of the Cincinnati Center for Eosinophilic Disorders (CCED) and the Division of Biomedical Informatics.

REGID (www.regid.org) is a collaboration of medical centers, professionals, families and individuals whose mission is to improve knowledge, research, and outcomes for people living with gastrointestinal disorders. REGID is not only a national registry of people affected by eosinophilic gastrointestinal disorders, but also a forum to enhance the connection of people to resources and research. REGID is funded by the National Institute of Diabetes and Digestive Kidney Diseases (NIDDK).

Meanwhile, Karl von Tiehl, MD, Assistant Professor of Pediatrics in the Division of Allergy and Immunology, was highlighted in the MTV series "True Life: I'm Allergic to Everything," which premiered an episode featuring a Cincinnati Children's patient who has an eosinophilic disorder and is working through food trials to increase the number of foods that are safe for him to eat.

James M. Anderson Center for Health Systems Excellence

The Chronic Care Innovation Lab focused on improving asthma control for a cohort of 60 teens whose asthma had been poorly controlled the past year. We combined our full set of evidence-based tools for medical and environmental therapy with enhanced self-management support and outreach by phone, text and collaboration with schools. We addressed barriers such as medication access for patients without insurance, transportation for medical appointments, and connections to mental health services. Overall, 60 percent of the cohort had a clinically meaningful improvement in asthma control compared to 25 percent the previous year. Our lab also is collaborating with the University of Buffalo's Center for Socially Relevant Computing to develop a wearable air quality sensor to warn teens with asthma about areas with elevated dust, mold and other pollutants.

Collaborative Chronic Care Networks, or C3Ns, combine data registries, delivery systems and technology to improve individual and system health. The C3N continued to work with ImproveCareNow to build the nation's most comprehensive database of children with Crohn's and ulcerative colitis. We created an information "commons" to overcome barriers to sharing information and helped a network of 30 pediatric gastroenterology care centers increase their remission rates for patients with Crohn's disease and ulcerative colitis from 55 percent to 76 percent without new medications.

Anderson Center faculty also worked with clinical divisions to build outcome measures into Epic, our electronic health record. We identified 67 conditions and defined more than 400 measures. Data and run charts are being generated for 35 conditions and 200 measures. Half of these are process-of-care measures, with the remaining representing patient outcomes. This work represents a major step in our strategic initiative to develop tools for measuring and improving outcomes for 100 diseases and complex disorders.

Anesthesiology

Our Chronic Medical Pain Center, launched this year, expands a multi-disciplinary clinic that had involved more than five divisions. The new center, led by Kenneth Goldschneider, MD, FAAP, and Alexandra Szabova, MD, also creates a basic science and clinical research program. The center is better positioned to develop new therapies and offer improved inpatient service to children from throughout the Midwest with complex pain conditions.

Twenty-four faculty members presented 74 national and international lectures on pediatric anesthesia, pain management and developmental neurobiology, an all-time high. John McAuliffe III, MD, MBA, initiated a first-of-its-kind monthly teleconference on intraoperative neurophysiological monitoring with the University of Florida.

Our pediatric anesthesia fellowship program, led by Paul Samuels, MD, received a five-year re-accreditation, the maximum time possible. Meanwhile, Goldschneider and Eric Wittkugel, MD, co-edited a book on pediatric anesthesia with a colleague from Melbourne, Australia.

Several of our faculty also took on prominent leadership roles in their fields. C. Dean Kurth, MD, was elected to the Board of the Society of Pediatric Anesthesia and to chair the Pediatric Anesthesia Leadership Council. Paul Samuels, James Spaeth, MD, and Anna Varughese, MD, MPH, became members of the Pediatric Anesthesia Program Directors, Wake-up Safe Collaborative and Quality Council, respectively, for the Society of Pediatric Anesthesia. John McAuliffe was elected to the board of the American Board of Neurophysiological Monitoring. Meanwhile, Steve Danzer, PhD, and Andreas Loepke, MD, PhD, served on research study sections for the National Institute for Health and Society of Pediatric Anesthesia.

Asthma Research

Our Asthma and Allergic Diseases Cooperative Research Center (AADCRC) is one of only 12 such centers in the United States. Gurjit Khurana Hershey, MD, PhD, is the principal investigator of the center, which received a renewal of its NIH-funded U19 grant this year. The center's overarching hypothesis is that epithelial cell genes play a central role in the pathogenesis of allergic disorders. Thus far, more than 40 peer-reviewed papers and five review articles or chapters have resulted from this grant.

Cincinnati Children's was selected this year to join the Inner City Asthma Research Consortium (ICAC), funded by the National Institute of Allergy and Infectious Diseases (NIAID). The consortium, which includes 11 research centers, is the nation's largest effort to study the factors that promote asthma in an inner city environment. Hershey is the principal investigator for the Cincinnati Children's subcontract. The consortium's objectives include conducting clinical studies to improve asthma control, to prevent asthma among inner-city children and to improve asthma phenotyping using validated biomarkers.

In a new project, Tesfaye Mersha Baye, PhD, is directing an NIH-funded study to identify asthma genes that may not be found equally across population groups. His project will involve screening the genome of people with African American mixed ancestry to map potential asthma liability genes.

Behavioral Medicine and Clinical Psychology

Over the past 18 months, 68 percent of all grant applications submitted by our faculty to the NIH or foundations have been funded or have received a fundable score. This is particularly impressive given the competitive climate for funding at NIH. We attribute these successes to recruiting and retaining some of the most talented behavioral scientists in the country, infrastructure investments in the Grants Office and the Divisional Data Core that have helped produce the most competitive applications, and an ongoing commitment to mentoring and peer review that injects each grant application with the collective expertise of all research faculty.

Susmita Kashikar-Zuck, PhD, recently completed a five-year, multisite clinical trial to study cognitive behavioral therapy (CBT) for treating juvenile fibromyalgia. The study, funded by the National Institute for Arthritis and Musculoskeletal and Skin Diseases (NIAMS), found CBT to be a safe, effective and durable intervention for reducing disability and depressive symptoms. This is the first rigorously controlled trial of CBT for pediatric patients with fibromyalgia. Results will soon be published in the journal *Arthritis and Rheumatism*.

The transition from K-series career development awards to investigator-initiated R01 grants is an essential step for faculty to sustain their research programs. Kevin Hommel, PhD, used a K23 award to develop a group-based treatment and an individually tailored telehealth treatment for pediatric inflammatory bowel disease (IBD). He obtained an R01 grant from NICHD to examine the effect of these treatments on medication adherence, disease severity, quality of life and healthcare utilization. Korey Hood, PhD, utilized a K23 award to document how depression in adolescents with type 1 diabetes can have a negative impact on disease management. He also received an R01 grant from NIDDK to conduct an intervention to reduce depression in this high-risk pediatric population and to improve their diabetes management.

Biomedical Informatics

A three-year, $12 million Agency for Healthcare Research and Quality grant enabled John Hutton, MD, and Keith Marsolo, PhD, to create a registry that links with electronic health records (EHRs) for quality improvement research. Developers in our Division are using SHRINE and i2b2 informatics platforms to create a registry for providers in the ImproveCareNow Network, a group focused on pediatric inflammatory bowel disease (IBD). The registry will be used to compare effectiveness of treatment strategies for pediatric IBD patients.

Our data warehousing group extended i2b2 into a platform that supports registries and general clinical research. One special effort is the "chart review" mode, offering a longitudinal view of a patient's de-identified record. Adding de-identified notes and other features will allow i2b2 to function as a de-identified medical record. Other efforts involve integrating Cincinnati Children's biorepository with i2b2 so researchers can explore the link between genotype and phenotype.

Our software development group created a variety of systems: one examines susceptibility to norovirus; one is a regional home injury intervention study; one is a multicenter phase II clinical trial for stroke patients; and another, a tool to monitor use of outpatient space. They also support the informatics needs of several regional quality improvement networks.

Rollout of the new research network environment (RNE) was the focus of Research IT, led by Michal Kouril, PhD. The RNE will improve connectivity with outside institutions and flexibility for the demands of research. Jason Lu, PhD, is developing network approaches to study molecular mechanisms underlying human diseases. In one project, Lu has identified 30 subspecies of blood lipoproteins that may cause human atherosclerosis. He uses this to map transcriptional networks controlling surfactant homeostasis in the lung.

Andrew Spooner, MD, CMIO, is leading EHR projects to implement population management programs and to comply with medication reconciliation regulations. He has presented on the pediatric uses of EHRs, including sessions at the annual American Academy of Pediatrics meeting.

Jun Ma, PhD, and his group published extensively this year. Ma and team provided the first demonstration of the role protein stability plays in forming a normal concentration gradient of the morphogen protein Bicoid in Drosophila embryos.

Biostatistics and Epidemiology

The Division continued its strong research program through collaborations with 54 other divisions and publication of 74 peer-reviewed articles. Key articles covered the safety of MRI scans, neurobehavioral assessment of newborns, developmental disabilities of cochlear implant recipients, genetics of obesity and statistical issues in longitudinal data analysis. We also participated in 43 collaborative grants and received three new extramural awards and seven institutional awards.

Our team continued to lead the institution-wide effort to build a strong Data Management Center, including developing its vision, mission and organizational structure and launching the search for a faculty director. The center has hosted a series of educational events to promote excellence in data management and is finalizing its marketing plan and web page.

We also are engaged in research education and training activities that serve pediatric residents, fellows, junior faculty of Cincinnati Children's, and graduate/post-graduate students in other units in the University of Cincinnati.

In January 2011, we began to reorganize and expand our faculty, strengthening our ability to collaborate with other divisions and to develop independent research. Two faculty positions have been filled and a national search continues.

Bone Marrow Transplantation and Immune Deficiency

Our Bone Marrow Transplant Program is a leader in diagnosing and treating hemophagocytic lymphohistiocytosis (HLH), with children travelling to Cincinnati from across the U.S. and other nations for therapy. This year Rebecca Marsh, MD, and Lisa Filipovich, MD, published data in the journal *Blood* about the outcomes of two transplant strategies and identified reduced intensity transplantation as the optimal approach.

The Fanconi Anemia Comprehensive Care Clinic continues to expand. We offer life-long care to more than 150 children and adults with this rare disorder. Most children with Fanconi anemia eventually develop marrow failure and require transplantation. We have completed an important study of endocrinological abnormalities in this population, led by Susan Rose, MD, Division of Endocrinology. We also have explored the mechanism of endocrinopathy in a mouse model study lead by Qishen Pang, PhD, Division of Experimental Hematology. This study showed that oxidant stress causes tissue damage in Fanconi anemia. Parinda Mehta, MD, has used these data to develop a novel clinical trial using an anti-oxidant food supplement.

Transplant associated thrombotic microangiopathy (TMA) is a severe complication of transplantation, commonly leading to organ failure and death. Sonata Jodele, MD, in collaboration with the Division of Nephrology, has launched a study of proteomic biomarkers of TMA that may predict occurrence of the disorder 10 to 14 days before clinical presentation.

Bone marrow transplant is associated with significant morbidity and mortality, and a significant proportion of children will require intensive care. We have collaborated with Ranjit Chima, MD, and Derek Wheeler, MD, FAAP, to analyze intensive care outcomes in this high-risk population. The data show that 82 percent of children admitted after stem cell transplant survive and leave the ICU. These outstanding results were presented at the annual meeting of the American Society of Bone Marrow Transplant and the Society for Critical Care Medicine.

DECODING THE MYSTERIES OF DEVELOPMENT

OUR SCIENTISTS BREAK GROUND IN REPRODUCTIVE BIOLOGY

Biology books say life begins simply: sperm meets egg.
Yet very little else is simple about the early development of human life.

So many things can go wrong at so many stages, it is a wonder any of us make it to birth.

As scientists at Cincinnati Children's delve deeper into the mysteries of early development, their discoveries could have far-reaching implications for fertility science and understanding the origins of diseases and conditions in children and mothers.

S.K. Dey, PhD, Director, Division of Reproductive Sciences, focuses on a crucial initial stage of pregnancy – the implantation of a blastocyst into the uterus. His work reveals how complex this basic step can be.

"The quality of pregnancy is a critical factor, since subtle changes *in utero* can have profound consequences later in life," Dey (at left) says.

Dey joined Cincinnati Children's in 2008 to launch the Division of Reproductive Sciences. The Division's research is part of a major initiative at Cincinnati Children's to understand and prevent birth defects as well as to combat mortality and life-long health problems related to premature birth.

The Division now has five faculty whose research includes pre-implantation embryo development; the onset of uterine receptivity; implantation; decidualization; placentation; causes of preterm labor as well as epigenetic programming of parental germ cells and mechanism of X-chromosome inactivation by large non-coding RNAs. Faculty members study the implications of signaling pathways in ovarian and uterine cancers as well as the interactions between environmental estrogens and the body.

High stakes research

Premature birth is a major cause of infant mortality worldwide and is an especially serious issue in the United States.

According to a landmark report issued in 2009 from the National Center for Health Statistics, more than 560,000 premature births occur each year in the U.S. In fact, the U.S. ranks 30th in infant mortality, behind most European countries, Canada, Australia, New Zealand, Hong Kong, Singapore, Japan and Israel. Yet much of the research effort to understand the mechanisms of prematurity is still in its infancy.

"We understand very little about the processes of healthy reproduction, but it begins with maternal health. The mechanisms underlying implantation and intrauterine life have long been hidden from us," says Jeffrey Whitsett, MD, Co-director of the Perinatal Institute. "It is increasingly clear that, although we inherit our genes from our parents, intrauterine growth and development are influenced by many factors that influence the function of our genes that have consequences throughout life. The health of the mother, her nutrition, and environmental exposures may have important impacts on the developing infant. Maternal health is a critical factor for the developing fetus."

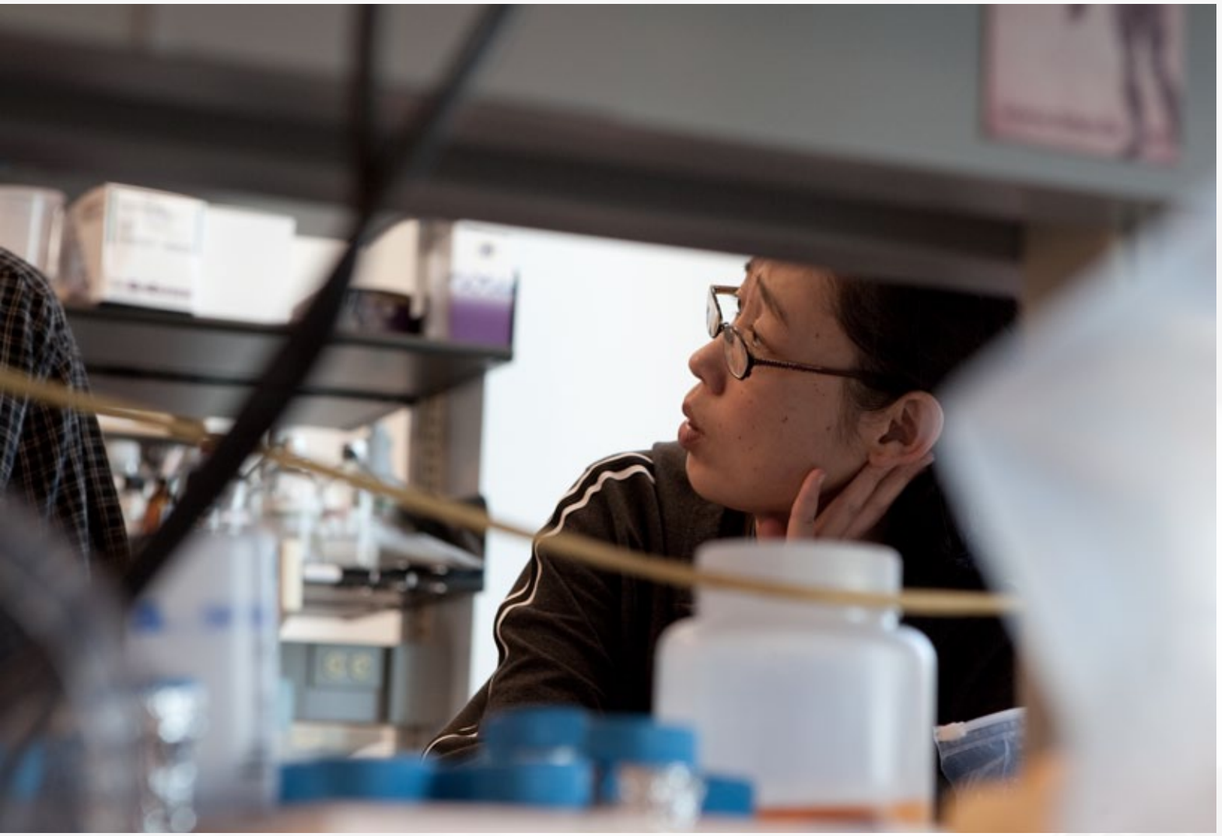
Understanding the mechanisms at work during early development can have long-term, life-long implications, Whitsett says. "Babies that grow poorly *in utero* can do poorly later in life. They are more likely to develop diabetes, heart disease, and hypertension later in life, and they are more likely to die earlier."

Understanding implementation

Dey has devoted much of his career to understanding those early developmental mechanisms. His research is focused on pinpointing the molecular landscape that helps prepare the blastocyst for implantation and prepares the uterus to receive it. At Cincinnati Children's, Dey's lab has developed mouse models to identify implantation pathways, confirm their function and determine that similar pathways exist in human development.

Successful pregnancy, he has found, depends on many factors moving together in a microscopic dance.

"The embryo must reach the blastocyst stage with primarily two cell types – the inner cell mass and an outer lining called the trophectoderm, later forming the trophoblast, for anchoring into the maternal womb. The blastocyst also must acquire implantation competency," Dey says. "Meanwhile, the uterine lining must differentiate into a receptive stage. These windows must coincide," he continues. "Only then can the intense interactions take place to carry out the connections between the blastocyst, trophectoderm and the luminal epithelium of the uterus."



And all of this happens very quickly.

"This is a very dynamic phase. Things move rapidly," Dey says. "Even when everything goes perfectly, the window for successful implantation is open only for a short time. If these windows are even slightly out-of-phase, implantation may fail or become abnormal, compromising pregnancy outcome."

Dey and colleagues have identified several signaling pathways involved in the implantation process. Some seem to function independently; others in cooperation.

"Our mission is to find the major pathways, the places where multiple pathways converge," Dey says. "These will be the most likely therapeutic targets for assuring successful implantation."

His key projects include:

- Understanding the role that Cox-2 derived prostaglandins play in female reproduction. Among the findings: a particular molecular signaling network has been found to play a critical role in embryo implantation; described as the cPLA2α-Cox2-PPARδ-Vegf pathway.

- Examining the roles growth factor pathways play in the implantation process. Successful implantation depends, in part, on proper function of a specific signaling network in the uterus – Lif-Hb-Egf-Hoxa10/Msx-Ihh/Bmp/Wnt. Further research has shown that Msx genes, an ancient gene family known for their role in craniofacial and neural crest development, have fundamental functions in uterine biology and implantation in mice.

"EVEN WHEN EVERYTHING GOES PERFECTLY, THE WINDOW FOR SUCCESSFUL IMPLANTATION IS OPEN ONLY FOR A SHORT TIME. IF THESE WINDOWS ARE EVEN SLIGHTLY OUT-OF-PHASE, IMPLANTATION MAY FAIL OR BECOME ABNORMAL, COMPROMISING PREGNANCY OUTCOME."

- Studying the role played by the immunophilin FKbp52, which is critical progesterone receptor activity in the uterus. Deficiency of this factor can result in implantation failure. Studies in mice have shown that the problem can be reversed with high doses of progesterone supplementation.

- Studying the role of cannabinoid/endocannabinoid signaling in pregnancy events. This research has shown that aberrant endocannabinoid signaling is associated with abnormal embryo development and ectopic pregnancy.

In the past year, Dey has added to these understandings with new findings related to the mammalian target of rapamycin 1 (mTORC1) signaling and preterm birth. Details of these findings were recently published in the journal *PNAS*.

"We have been able to completely rescue preterm birth resulting from heightened mTORC1 signaling in mice," Dey says.

Influencing pathways

While understanding the mechanisms of implantation can help ensure a successful start to a pregnancy, much research and debate continues about factors that can disrupt the process.

Estrogen and progesterone are the primary forces guiding early development, along with other molecules, Dey says. The optimal balance of these hormones can be disrupted in various ways, ranging from gene defects to external insults such as poor health, bad diet, substance abuse or exposure to toxins.

"Can we influence these pathways? Yes, in some cases," Dey says.

For example, Cox-2 inhibitors, which help block inflammation in other conditions, can reverse preterm birth in mice. Likewise, rapamycin can correct problems of heightened mTORC1 signaling. The challenge is to move these discoveries from animal models into humans for further evaluation.

"Someday, it may become possible to give a woman a gene screening test before pregnancy and discover her risk factors for unsuccessful implantation," Dey says. "Based on the results, targeted treatments could be administered to better prepare her."

How far away might that day be? Dey says translational research will take years to complete.

More to come

In addition to implantation, scientists at the Perinatal Institute study many other aspects of early development.

A new study led by Whitsett and Valérie Besnard, PhD, breaks ground by demonstrating how the mother's genotype plays a major role in determining the timing of birth. The researchers also found that mothers influence fetal lung growth and maturation — factors crucial to perinatal survival — in more ways than previously understood.

Meanwhile, an ongoing series of experiments led by Alan Jobe, MD, PhD, Director, Division of Perinatal Biology, and Suhas Kallapur, MD, explores how maternal-fetal infections and inflammation can disrupt pregnancy and trigger premature birth.

Previous studies have shown that as many as 60 percent of premature births show evidence of intrauterine infection. New studies are seeking ways to prevent, detect and treat such infections. Better understanding the infection process also is helping define optimal times for delivering infants in high-risk pregnancies.

"Terrible problems can occur if an infant is delivered too prematurely. However, allowing a baby to remain too long in a bad uterine environment also results in terrible problems," Whitsett says.

Meanwhile, several members of the Perinatal Institute are exploring the maternal-fetal microbiome – the inner universe of bacteria that live in all humans. Early research indicates that maternal diet as well as antibiotic medications can alter this microbiome and potentially influence the course of pregnancy.

Explosive advances in DNA sequencing technology have made it possible to study not just the human genome but also the genetic mix of bacterial strains that lives inside us. In years to come, profiling how the bacterial mix varies among mothers and their developing babies could have far-reaching impact on finding ways to prevent premature birth, Whitsett says.

"This is a very exciting time," Whitsett says. "These technologies are enabling us to gain insights into uterine biology, implantation and programming of the fetus that were impossible just a few years ago." ■

Center for Clinical and Translational Science and Training

In 2010, the Center for Clinical and Translational Science and Training (CCTST) graduated its first class from the CCTST Community Leaders' Institute. The six-week program trains participants in critical aspects of community and translational research to help increase academic-community collaboration and promote the use of data to improve services and programs. As a result of the institute, 100 grant proposals were submitted, and 73 percent of participants received grants worth a combined $1.8 million.

The MS in Clinical and Translational Research program now has 57 students. Meanwhile, our Certificate in Clinical and Translational Research program, launched in 2009, has enrolled 44 students and has produced 12 graduates. Online versions of the certificate program and our curriculum in Clinical Research Informatics are in development. The CCTST also has supported new and competitive renewal applications for T32s and K12 grants and is developing a K-Club to support career development for young investigators.

The CCTST also has supported efforts to increase integration among several offices and committees that perform scientific review throughout the academic health center. Ultimately, the entire campus will require scientific review prior to IRB submission. The CCTST will support investigators whose protocols undergo pre-review. Work is continuing to develop a community-wide harmonization of the review processes at IRBs for the 17 hospitals in Greater Cincinnati, with much of the preliminary ground work completed during 2010. During the last year, the CCTST has sponsored cross-campus town hall meetings for education and debate on industry-academic relationships and intellectual property and are planning meetings on biobanking and responsible authorship.

Clinical Pharmacology

Our Division will use its first NIH pediatric clinical and developmental pharmacology training grant to train a new generation of clinical investigators to develop ways to improve the use of medicines in children. Many medicines used in children have not been scientifically evaluated for use in children, and far fewer medicines have been developed specifically to treat childhood diseases.

Our investigators study the dose-concentration-response and adverse events relationships of immunosuppressive drugs in pediatric patients receiving organ transplants. Our ongoing research includes studying the use of mycophenolic acid (MMF, CellCept) in pediatric renal transplant recipients and children with lupus. Our data will help develop web-based dashboards and dosing algorithms to allow personalized dose tailoring.

In the past year, we completed an important study that will help provide personalized propofol anesthesia doses during bariatric surgery for morbidly obese adolescents. We also have worked with colleagues in anesthesia to reduce adverse events and drug interactions related to morphine and other pain medications by using patients' drug metabolizing genotypes and phenotypes to adjust dose levels.

Our new pharmacometrics program trains students, fellows and junior faculty in PK/PD modeling and simulation, data analysis and individualized dosing algorithm development.

We also continue to work with the Genetic Pharmacology Service, the first of its kind in a pediatric institution. This service is a first step towards personalized medicine for neuropsychiatric and anticoagulation drug therapy. Our research focuses on developing computerized decision support systems for neuropsychiatric drugs such as risperidone and warfarin.

Critical Care Medicine

Jennifer Kaplan, MD, MS, received an investigational new drug approval from the Food and Drug Administration to conduct a phase 1 trial of PPAR-γ agonism in pediatric septic shock. This study reflects a natural progression of basic science research efforts in the Division. The concept of PPAR-γ agonism as a therapeutic strategy in sepsis was demonstrated in pre-clinical studies led by Basilia Zingarelli, PhD. Kaplan's phase 1 study is the first direct translation of our basic science research to the bedside of critically ill children.

Zingarelli, a nationally recognized researcher who has been with our Division since it formed in 1994, has been appointed Director of Basic Research to provide expanded oversight for our growing research portfolio. She also has been named president-elect of the Shock Society, an international organization dedicated to improving the care of victims of trauma, shock, and sepsis.

Brian Varisco, MD, who was recruited to Cincinnati Children's to serve as a physician-scientist in pediatric Critical Care Medicine, has secured K-level funding to continue his studies of the mechanisms of chronic lung disease.

He achieved this milestone under the mentorship of Jeffrey Whitsett, MD, Director of the Division of Pulmonary Biology and chief of the Section of Neonatology, Perinatal and Pulmonary Biology.

Dentistry

This has been a productive year for our clinical program, which includes our main site on the Burnet Campus, an office in Fairfield and cases requiring general anesthesia conducted at the Burnet and Liberty campuses.

In the past year, we served patients from 31 states and several nations. More than 50 percent of the children we see are medically compromised, which requires coordinating care with a wide range of other Cincinnati Children's services including Hematology/Oncology, Transplant, Genetics, Otolaryngology, Dermatology, Plastic Surgery, Oral Surgery, Gastroenterology, Pulmonary, Developmental and Behavioral Pediatrics, Teen Health and Aerodigestive.

Our program has generated research articles and our faculty have made numerous presentations to professional societies. Division Director Stephen Wilson, DMD, PhD, was a guest speaker at a symposium on sedation. Murray Dock, DDS, was invited to speak at the Israeli Society of Pediatric Dentistry on treating craniofacial anomalies. Faculty members also serve in the national board examination process, the Commission on Dental Accreditation and several task forces of the American Academy of Pediatric Dentistry (AAPD).

Each year we accept five new residents from across the nation. Our second-year residents presented posters of their research projects at the AAPD annual meeting in New York City. Topics included children's temperamental and behavioral traits and their predictive values during sedations, referral patterns of pediatric dentists, effects of snacking on carious lesions, effects of midazolam on memory of operative events and continued root development in traumatized teeth treated with antibiotics.

Developmental and Behavioral Pediatrics

In September 2010, the Maternal and Child Health Bureau awarded funding to establish DBPNet, the first national research network of developmental-behavioral pediatric programs. Our Division is one of 12 leading programs nationwide to join the network. David Schonfeld, MD, Division Director, serves on the network's executive committee and co-chairs the research protocol development and review subcommittee. Together, the network includes 93 DBP faculty, 46 fellows and more than 100 affiliated psychology faculty.

In June 2010, Cincinnati hosted the 37th National Conference of the Spina Bifida Association (SBA). The SBA awarded Sonya Oppenheimer, MD, former Division Director, with a lifetime achievement award in recognition of more than 30 years of contributions to the field.

In December 2010, the Division hosted a visit by Tim Shriver, PhD, Chairman and CEO of Special Olympics. Shriver provided the pediatric grand rounds "Special Olympics: Advancing the Health of People with Intellectual Disabilities," discussed how to build community support to promote the health of Special Olympics athletes, and met with researchers within the Division to explore potential areas of collaboration. Subsequently, Katy Krohn, PhD, a LEND trainee and psychology post-doctoral student in the Division, was selected as a student delegate to the 2011 Special Olympics World Summer Games in Athens to continue her research in collaboration with regional Special Olympics.

In July 2010, the Rubinstein-Taybi Syndrome (RTS) Program and the RTS-OKI (Ohio, Kentucky, Indiana) Support Group hosted an international RTS conference that involved more than 120 families, 20 speakers and more than 50 volunteers.

Developmental Biology

Collaboration is the highlight of our Division this year. Joint appointments between Developmental Biology and the clinical divisions have created a matrix structure that has helped break down barriers between divisions and created a platform for projects that link both basic science and clinical divisions.

This matrix has produced groundbreaking original research. A recent paper in *Nature* documented the first example of organogenesis of intestinal tissue from human pluripotent stem cell cultures. The principal investigators, including Chris Mayhew, PhD, and Aaron Zorn, PhD (Developmental Biology), Vladimir Kalinichenko, MD, PhD (Neonatology/Pulmonary Biology), Susa Wells, PhD (Hematology/Oncology), and Noah Shroyer, PhD (Gastroenterology), was headed by Jim Wells, PhD (Developmental Biology). Second, a team of PIs including Alex Kuan, MD, PhD (Developmental Biology), Yi Zheng, PhD (Experimental Hematology), and Richard Lang, PhD (Ophthalmology), headed by Yutaka Yoshida, PhD (Developmental Biology), published a paper in *Proceedings of the National Academy of Sciences* showing that disruption of the intracellular signal RhoA altered the balance between differentiation and proliferation in the progenitor cells of neurons in the central nervous system.

Review articles spanning basic and clinical arenas are being published by investigators who cross divisional boundaries. In *Current Opinion in Hematology*, Shroyer, Tiffany Cook, PhD (Ophthalmology), Brian Gebelein, PhD (Developmental Biology), and H. Leighton Grimes, PhD (Immunobiology), discuss the roles of transcription factor Gfi1, whose actions are conserved in evolution from fruit fly development to human hematopoiesis. Disregulation of Gfi1 in humans leads to abnormal hematopoiesis and malignancy. This work arose from a research collaboration between Gebelein and Grimes that first identified this evolutionarily conserved developmental mechanism.

Collaborations are also identifying mechanisms underlying specific pediatric disorders. In a paper in *The Journal of Bone and Joint Surgery*, Chris Wylie, PhD (Developmental Biology), and Roger Cornwall, MD (Orthopedic Surgery), identify a failure of normal satellite cell function and thus muscle growth as the primary defect in the contractures caused by neonatal trauma to the brachial plexus.

Drug and Poison Information Center

Our Drug and Poison Information Center (DPIC) 24/7 hotline served a population of 3.7 million in 20 Ohio counties this year. With 27 specialists certified in poison information and 51 staff certified in national incident management systems, DPIC is one of the largest centers in the country.

Continued collaboration with medical response systems, disaster committees and the Ohio Department of Health's Disaster Preparedness and Response program included working with a Health Alert Network to send fax alerts to 60 regional hospitals on subjects such as swine H1N1 flu, tsunami-related radiation from Japan, blue green algae in local rivers, as well as drug abuse reports related to "bath salts," synthetic marijuana and prescription drugs. The Center added special pharmacovigilance and medical communication units interfacing safety surveillance with the drug industry. The Center continues to gather and evaluate data on food poisoning, water quality, substance abuse patterns and terrorism preparedness.

Our Prevention Research Unit implemented programming to promote healthy and drug-free lifestyles. Our services include the REACH and NOMAD projects to prevent delinquency and violence. The Office of National Drug Control Policies has supported a People of Color Wellness Alliance (POCWA) Coalition Grant and a Grassroots Urban Mobilization Benefiting Ohio initiative to respond to health disparities and wellness issues prevalent among local minorities. Our efforts earned an Exemplary Prevention Award from the Ohio Department of Alcohol and Drug Abuse Services.

Staff awards in the last year also included a Pease Award nomination for Jon Colvin and a YMCA Black Achiever Volunteer of the Year Award for Alysia Longmire. Huston Smith received a POCWA Gems Award. Program recognition included a State of Ohio Outstanding Community Service Commendation, and a Health Communication Scholarship. Robin Brannen, RN, and Stephanie Ketcham, RN, were certified as specialists in poison information.

Emergency Medicine

We exceeded our research goals this year by submitting 34 grants, including seven as a co-investigator and four via new faculty and industry. We became a principal investigator within the Pediatric Emergency Care Applied Research Network (PECARN) with St. Louis Children's Hospital and Children's Hospital of Wisconsin.

Lynn Babcock, MD, and Scott Reeves, MD, published a study on cervical spine injury in *Annals of Emergency Medicine*. Benjamin Kerrey, MD, Matthew Mittiga, MD, and Andrea Rinderknecht, MD, presented innovative work on resuscitation procedures; Babcock presented pioneering work on mild traumatic brain injury. Gary Geis, MD, Derek Wheeler, MD, and Mary Patterson, MD, MEd, received a grant for sepsis identification through simulation.

Jacqueline Grupp-Phelan, MD, MPH, and team continue to publish work in mental health screening, smoking prevention, injury control and cultural issues across ethnic groups. In quality research, Evaline Alessandrini, MD, MSCE, and Srikant Iyer, MD, MPH, presented work at the PAS meeting and published in *Pediatrics, Academic Emergency Medicine,* and *Clinical Pediatric Emergency Medicine*. Holly Brodzinski, MD, and Jennifer Reed, MD, received Place Awards for institutional outcomes research.

Javier Gonzalez del Rey, MD, MEd, received funding to expand our primary care residency and hand-offs by pediatric residents. Education faculty contributed to several papers and to Fleisher and Ludwig's *5-Minute Pediatric Emergency Medicine Consult*.

Joseph Luria, MD, led the clinical team through leadership development and launched a multidisciplinary team for patient experience. Our Emergency Department safety team reduced medication errors and had no serious safety events for 1,342 days through June 30, 2011, while caring for more than 146,000 patients at two emergency departments and three urgent care centers. Improvement work included reducing time to antibiotics in febrile, neutropenic patients (Alessandrini), sedation in children with abscesses (Brodzinski) and reduced length of stay in the fast track (Iyer).

Endocrinology

Philippe Backeljauw, MD, and his team conduct extensive research involving patients with Turner syndrome (TS). MRI studies reveal that 18 percent of patients had partial anomalous pulmonary venous return (PAPVR). Another study found that hypertension in girls with TS continues to be under-recognized. The team reported evidence of increased arterial stiffness among girls with TS, which increases risk for cardiovascular disease later in life. New studies will focus on evaluating large vessel disease, airway dysfunction and abnormalities of glucose metabolism.

Many pregnancy complications, such as preeclampsia and intrauterine growth retardation (IUGR), are characterized by abnormal placental development. Research by Stuart Handwerger, MD, and his colleagues examines the roles played by protein hormones, transcription factors and other signaling molecules in placental development, which may lead to new therapies. This work has shown that placental development is critically dependent upon the transcription factors TFAP2A and NR2F2, both of which modulate cell structure, cell growth and hormone expression. Handwerger, in collaboration with Jerzy Stanek, MD, PhD, and Rachel Sheridan, MD, of the Division of Pathology, have observed markedly decreased levels of TFAP2A in preeclampsia and IUGR placentas. Similar NR2F2 studies have not been completed.

Jonathan Katz, PhD, conducts research on type 1 diabetes focused on three areas: the roles plasmacytoid dendritic cells and natural killer T cells play in mice that are protected from disease; the role merocytic dendritic cells play in breaking peripheral T cell tolerance to islet cell antigen; and the potential use of small molecule inhibitors to destroy diabetogenic CD4+ and CD8+ T cells. This work includes studying a novel therapeutic strategy in collaboration with David Hildeman, PhD, in the Division of Immunobiology.

Every Child Succeeds

Every Child Succeeds (ECS) is the largest of three agencies in Greater Cincinnati that provide home visits for at-risk families with new children to support wellness, parenting skills and successful early childhood development. ECS programs run through a child's third birthday.

We track outcomes by collecting data at every home visit, using an innovative data management system – eECS – built for the program by colleagues at the University of Cincinnati. Our measures include the Parenting Stress Inventory, Home Safety Inventory, the Ages and Stages questionnaire and the Bracken and Dial-3 tests.

Every Child Succeeds has played a leading role in using home visits to address maternal depression, which can interfere with other preventive services and undermine child outcomes. Through a grant from the National Institute on Mental Health, Robert Ammerman, PhD, and colleagues conducted a clinical trial of cognitive behavior therapy adapted for the home-visit setting. The study reported that 70.7 percent of depressed mothers enrolled in ECS recovered after receiving therapy provided by master's level therapists; compared to a 30.2 percent recovery rate for those who did not receive in-home therapy. Gains were sustained at three months following treatment. This therapy is now offered to all depressed mothers in ECS. The approach also has been shared with home visiting programs in Massachusetts and Connecticut.

ECS continues to collaborate with local health networks, social service organizations and the business community to address the challenges of early childhood development. In February 2011, Every Child Succeeds joined the Pew Center on the States to host a national summit focused on quality in home visitation. Pew has invited ECS to continue as co-presenter for 2012.

Experimental Hematology

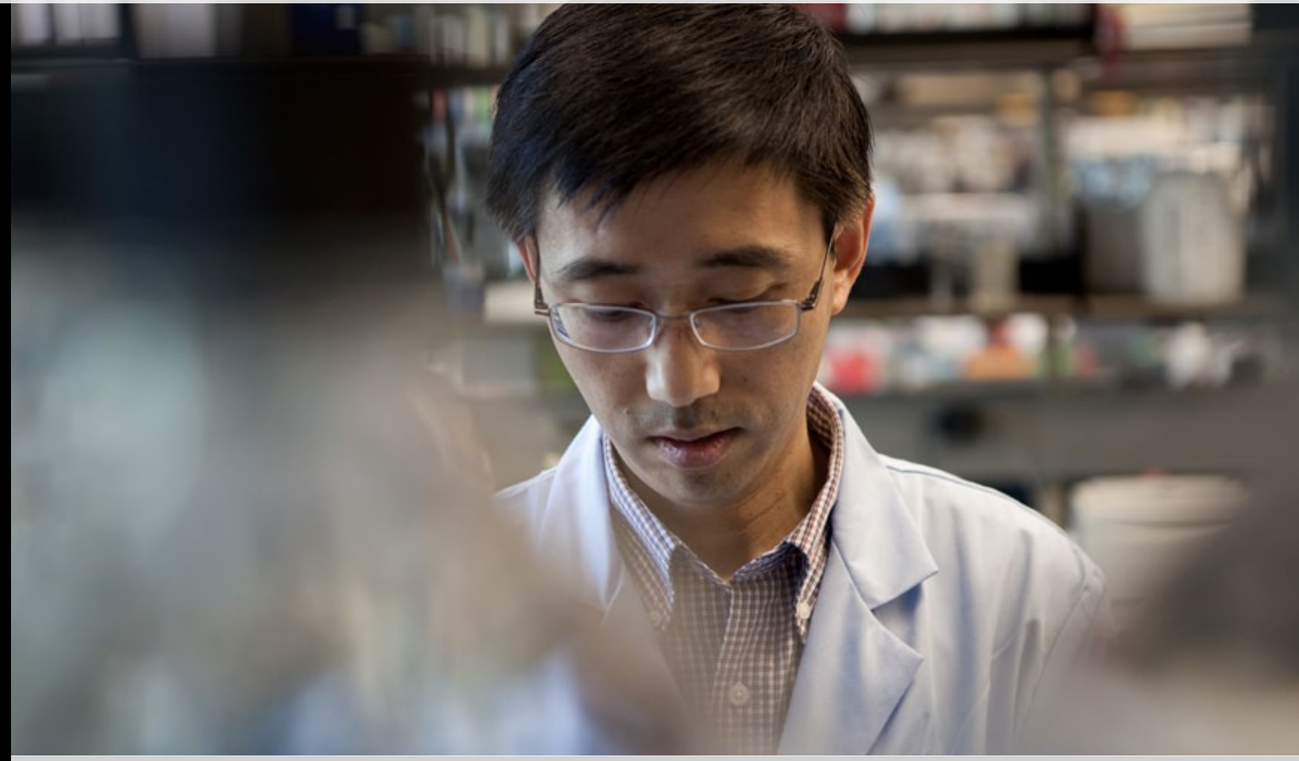
Patients with Fanconi anemia (FA) have a high risk of developing acute myeloid leukemia (AML). In a study published in *Blood*, Qishen Pang, PhD, and colleagues reported that a small portion of leukemia-initiating cells are responsible for leukemia progression in these patients. They found that the IL-3 receptor-α (IL-3Rα) is overexpressed on a subpopulation of pro-genitor cells from FA patients with AML. Treating leukemia-initiating cells with a neutralizing antibody inhibited proliferation and signaling. This further establishes IL-3Rα as an important cell-surface marker and a potential therapeutic target for FA patients who develop leukemia.

Normal T-cell biology involves coordinated signaling between T-cell receptors and a protein called interleukin-7 receptor (IL-7Ra), which is vital to the formation of white blood cells. Studies led by Fukun Guo, PhD, and Yi Zheng, PhD, published in *Proceedings of the National Academy of Sciences*, unveiled a process of coordinated cellular communications by a critical signaling molecule, Cdc42, that is vital to development and maintenance of T cells. If the process breaks down, T cells do not fully mature. Instead they proliferate rapidly in an immature state, then die off early, which could disrupt the immune system's normal defensive functions. The work reveals novel molecular pathways affected through Cdc42's central regulatory role in T-cell biology and implicates Cdc42 for future diagnostic or therapeutic approaches for diseases affecting the immune system.

A team of investigators led by Hartmut Geiger, PhD, identified a molecular communications pathway that could lead to treatments that boost success rates for bone marrow transplants. The findings, published in *Nature Medicine*, describe the role of a signaling protein, granulocyte colony stimulating factor, in releasing stem cells from bone marrow into the blood circulatory system. The study further reports that this process can be sharply enhanced by the anticancer drug erlotinib.

MAKING FACES

A NEW TEAM BRINGS RESEARCHERS AND SURGEONS TOGETHER TO EXPLORE THE ORIGINS OF FACIAL DEFORMITIES



Dr. Rulang Jiang studies miscommunication among neural crest cells.

Our faces are windows to who we are – we use them to engage with others, we anguish over them as teenagers. A face can cause us to fall in love, make us smile or strike fear in our hearts.

And when a face does not develop as it should, it can shatter a life.

Doctors in the Division of Plastic Surgery at Cincinnati Children's perform as many as 800 surgeries a year to repair craniofacial deformities. Most of those surgeries are to repair deformities that happen during fetal development.

Now, the medical center has recruited a research team to study what goes wrong during development to cause facial deformities. The researchers hold dual appointments in our Divisions of Developmental Biology and Plastic and Reconstructive Surgery.

Lead researcher on this new team is Rulang Jiang, PhD. Jiang comes to Cincinnati Children's from the University of Rochester School of Medicine and Dentistry, where he has focused his career on understanding what happens in early development to cause cleft lip and cleft palate.

He has discovered a career's worth of complexity in just this one area.

"When you look at an intact baby face versus a baby with a cleft lip, how do you imagine what might have occurred during embryogenesis?" he asks.

Five not-so-easy pieces

The midfacial region that surrounds the oral cavity actually develops from five separate parts, Jiang says. "Not only are the facial prominences growing and merging at the same time, they are doing so as the cranium and the brain are expanding. So children with cleft lip, even though the phenotype may be similar from one child to another, the underlying causes could be dramatically different because so many regions of this craniofacial complex could be affected."

Dr. Samantha Brugmann thinks missing cilia could lead to facial deformities.

Jiang is particularly interested in the neural crest cell, a multipotent cellular nomad that arises from the early spine and travels throughout the body, setting up camp everywhere from the head to the heart to the gut. Neural crest cells play a major role in forming all the facial structures, including bones, cartilage, teeth, nerves and connective tissue.

As the neural crest cells begin to give shape to those five facial parts, what Jiang describes as "highly regulated, finely tuned cross-talk" across a complex network of molecular pathways directs the cells to migrate and proliferate on cue to form the framework of the face.

When that cross talk is disrupted or misunderstood, cells can overgrow, get off track and fail to form the structures properly.

Chris Runyan, MD, PhD, in his third of a six-year residency in craniofacial plastic surgery, sees daily — and is learning to repair — the damage that results from these missed signals. Although surgeons can restore facial structure and function with good cosmetic results, he says, it is not an easy road for kids.

"In these young patients, the face is growing so it's difficult to get a fix with just one shot," Runyan says. "The average kid with cleft lip and palate has six surgeries in a lifetime. Many have many more than that."

Models for study

Jiang uses mouse models to study the complexity of the signaling network and how things go wrong. In the embryonic stages — when most of the facial framework develops — the cellular and molecular processes involved are remarkably similar in humans and mice.

"More than 98 percent of the genes in humans have counterparts in mice," says Jiang. "So what we learn using mouse models can often be directly applied to understanding the genetic basis in humans."

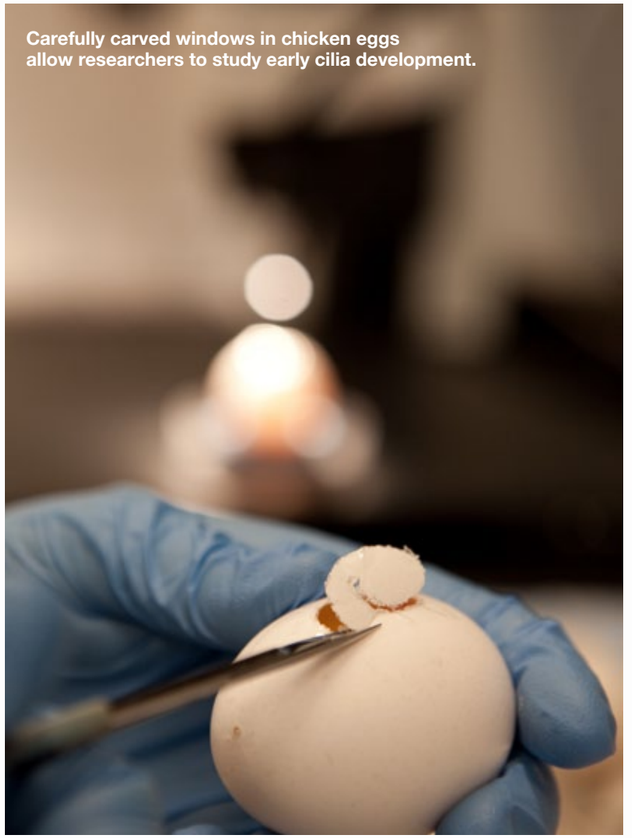
Over more than a decade of studying these models, he has learned a great deal – including that there is still much to learn.

"We already know a lot about the genetic pathways at this point. What we need to understand more about is, what might be disrupted at each step in the molecular and cellular processes? What are the relationships between the molecules and pathways? And at the cellular level, how do they come together to control proliferation or migration of the cells?"

Cellular behavior is one area of focus for Samantha Brugmann, PhD. Brugmann is part of the newly formed craniofacial research team. She, too, has a dual appointment in plastic surgery and developmental biology.

Brugmann studies how the skeletal structure in the midline of the face forms – the portion that gives rise to the forehead, bridge of the nose and the philtrum, that small indentation just above the upper lip.

With the help of a three-year, $747,000 grant from the National Institute of Dental and Craniofacial Research, she is using an avian model to explore how defects in the cilia of neural crest cells might lead to facial deformities.



Carefully carved windows in chicken eggs allow researchers to study early cilia development.

Cellular GPS

Brugmann believes that cilia on neural crest cells act as antennae, picking up molecular signals that direct their travels and tell them what to do. If those antennae are missing or defective, they can lose their way or continue to divide when they should be differentiating into skeletal elements.

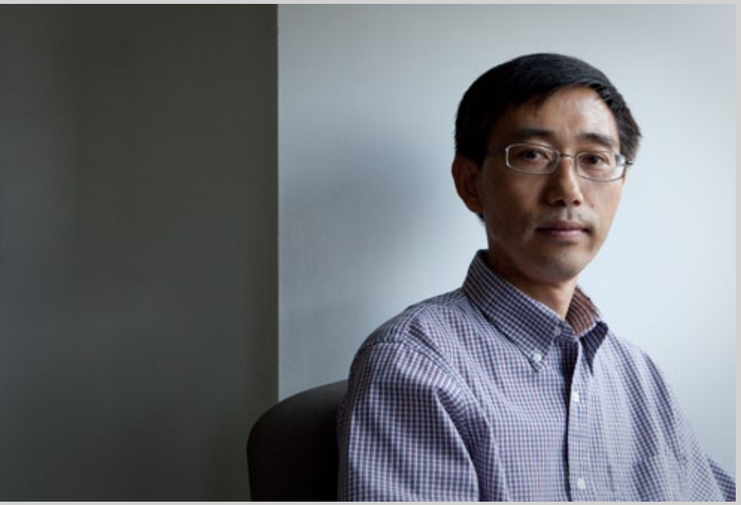
"We're using these models to look at how neural crest cells behave when they don't have cilia. Can they start in a very dorsal location and migrate all the way into the mandible, maxilla and frontonasal area – or is their migration affected by not having cilia?"

She suspects that their migration might be affected by missing cilia; the embryos of chicks without cilia show signs of facial deformities. Brugmann attributes this in part to their inability to pick up signals from the hedgehog molecular pathway, which is crucial to proper development.

"When the cilia were defective, the neural crest cells couldn't receive signals properly to tell them what to do and how to develop into the facial skeleton," she says. "They were able to form skeletal elements, but they either were not in the right place, or they were duplicated. So the face started to get very, very wide."

Her research will explore the role of the cilia in picking up these crucial signals by testing cells with cilia — and without.

"We'll do migration assays to see if we put neural crest cells with cilia here, and we put the hedgehog signal over there, will the cells migrate towards the signal? And if they don't have cilia, will they start searching around and not have directed migration anymore?"



Dr. Jiang says basic research is improved by close collaborations with clinicians.

Cilia's growing role

Appreciating cilia's role in early development is a departure from earlier thinking that they were merely vestigial organelles, Brugmann says. New genetic studies have proven their importance, and ciliopathies – diseases caused by defective cilia – are a new and growing area of research.

"There's been a lot of interest in studying cilia, especially when people started to realize a lot of receptors are preferentially located there and that major developmental signaling pathways are affected when there's a defect in cilia."

While there is much basic science still to be understood about facial deformities, Jiang and Brugmann are eager to work in collaboration with clinicians.

"There are always important issues in basic biology that we need to understand. But working with the craniofacial surgeons, we can learn about clinical applications that basic scientists don't often think about," Jiang says.

Likewise, the surgeons hope to gain more insight into the problems they encounter.

"As surgeons, we can treat the problems, but we don't have an explanation of how they develop," says Runyan. "Better understanding could help us provide better treatment. It's exciting to have basic scientists to work with on this." ■

"WHEN YOU LOOK AT AN INTACT BABY FACE VERSUS A BABY WITH A CLEFT LIP, HOW DO YOU IMAGINE WHAT MIGHT HAVE OCCURRED DURING EMBRYOGENESIS?"

Lab technician Emily Cross (top) works with plastic surgery resident Dr. Chris Runyan (center) and Brugmann to find better ways to repair facial malformations.

Gastroenterology, Hepatology and Nutrition

Staffed by nine pediatric hepatologists, our Chronic Liver Disease Program serves a national and international referral population. We provide comprehensive evaluation and innovative treatment for all medical and surgical aspects of liver disease, including evaluation and follow-up for children who need liver transplants.

Our faculty members are leading several NIH-funded multicenter studies to advance understanding, diagnosis and treatment of pediatric liver disease. Our work includes developing a high-throughput gene chip to diagnose mutations in children with genetic liver diseases; an ongoing trial to determine the efficacy of corticosteroids in children with biliary atresia; studying the role of immune dysregulation in acute liver failure; seeking biomarkers and therapies for fatty liver disease; and developing therapies for bile acid disorders.

Our Intestinal Rehabilitation Program is becoming a leader in improving care for children with intestinal failure. The survival rate without significant liver disease among our patients is one of the highest nationwide.

Our research initiatives include evaluating biomarkers to identify acute bloodstream infections, predicting the need for liver/bowel transplant among patients on total parenteral nutrition (TPN), and developing methods to grow and expand intestinal tissue from patients with intestinal failure. We continue to participate in the 15-center Pediatric Intestinal Failure Consortium.

Meanwhile, the number of patients receiving multidisciplinary care for IBD continues to grow, with children from more than 25 states seen over the past year. Our state-of-the-art services include diagnostic imaging that does not require radiation exposure, and psychology interventions for nonadherence.

We continue to contribute to international genome-wide association studies to identify susceptibility genes specifically for pediatric-onset disease. Our investigators also have received NIH funding to develop the PROTECT study, the first multicenter trial in North America for newly diagnosed children with ulcerative colitis. Within this trial, we will develop a model to predict individual therapeutic responses and clinic outcomes based on biomarkers developed here. Collaborators include the Divisions of Pulmonary Biology and Biomedical Informatics.

Under the leadership of Kevin Hommel, PhD, in the Adherence Center, we also will be one of three centers to participate in the first randomized, controlled trial of telehealth interventions to improve medication adherence in children with IBD. Knowledge gained from these studies will be rapidly translated to practice through our collaborations with Peter Margolis, MD, PhD, and the ImproveCareNow quality improvement network.

General and Community Pediatrics

Our faculty members have been working to better understand the social determinants of asthma and ways to intervene to mitigate socioeconomic risks. Jeff Simmons, MD, and Robert Kahn, MD, MPH, have linked measures of financial strain to a four-fold gradient of asthma readmission risk, making financial strain a more important predictor of readmission than race or insurance status. Their fellow, Andrew Beck, MD, has found strong correlations between a family's financial strain and neighborhood measures of socioeconomic risk based on census data. He has found a 20-fold gradient of asthma admission risk between different neighborhoods in Cincinnati.

These clinician-researchers have contributed to the institution-wide asthma quality improvement work led by Mona Mansour, MD, MS, and Carolyn Kercsmar, MD, MS. Many interventions have been implemented that have decreased 30-day readmission rates by 45 percent among children covered by Medicaid, and decreased 90-day readmission rates by 25 percent.

Our online Master's Degree in Education for Healthcare Professionals Program was launched in 2002 in collaboration with the University of Cincinnati College of Education. A certificate in medical education program was added in 2004. Developed and run by Kadriye Lewis, EdD, and Raymond Baker, MD, MEd, these programs were the first totally on-line programs of their kind in the United States.

To date, more than 240 students have enrolled, with 51 master's degrees and 31 certificates issued to professionals from 34 states, Puerto Rico and four countries. The program has been highly successful in enhancing the development of academic medical education leaders. Graduates hold leadership positions including a dean, GME program directorships and a departmental vice chair. A survey of 12 master's program graduates reports that former students have collectively published 52 peer-reviewed papers, obtained $4.25 million in funding for 21 grants and have received 37 teaching awards.

General and Thoracic Surgery

Michael Helmrath, MD, an expert in intestinal rehabilitation, focuses his basic science research on intestinal failure and intestinal stem cells. He is studying the mechanisms of intestinal stem cell expansion following resection with funding from the NIH. His research will help better understand how intestinal stem cells can help to compensate following intestinal loss.

Thomas Inge, MD, PhD, directs the Center for Bariatric Research and Innovation, which partners with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to gather data and publish evidence-based recommendations for use of weight loss surgery in adolescents. The Teen LABS study, funded by the NIDDK, is the nation's largest multicenter study of adolescent weight loss surgery.

Gregory Tiao, MD, continues to develop his research in biliary atresia. Tiao received NIH funding during the past year.

Sundeep Keswani, MD, an expert in fetal surgery, focuses on the molecular mechanisms involved in fetal regenerative wound healing. Keswani is leading an initiative to create a clinical center of excellence in pediatric wound care. His basic science research may eventually lead to a wide range of therapeutics for diseases characterized by excessive fibroplasia.

Global Health Center

The Mother's Gift influenza immunization trial is a Bill & Melinda Gates Foundation-funded prospective trial of influenza immunization during pregnancy. The study, which is carried out with collaborators in Nepal, follows an earlier Gates Foundation-funded project in Bangladesh. We will recruit 1,600 pregnant women, randomize them to receive influenza vaccine or a placebo, then assess maternal, newborn and infant outcomes up to 6 months of age. Recruitment began in May 2011. By the end of June, 300 mothers had been recruited and immunized. The project also is developing PCR capability within Nepal to diagnose and characterize influenza viruses.

A study by Adekunle Dawodu, MBBS, is evaluating prenatal vitamin D supplementation in women in the United Arab Emirates. The study, funded by the Thrasher Research Fund, has completed enrollment and follow-up of patients. Initial findings indicate that 98 percent of women are vitamin D-deficient upon enrollment. This high prevalence of vitamin D deficiency during pregnancy could have significant adverse effect on the mother and the growing fetus. This study will provide the first data to determine the efficacy of high-dose vitamin D to prevent deficiency in mothers and their newborns in a high-risk population.

In FY2011, the International Visitors' Office within the Global Health Center facilitated more than 150 guests from 39 countries who visited more than 30 divisions at Cincinnati Children's to learn from our world-renowned faculty.

Heart Institute

The Heart Institute launched the advanced heart failure and mechanical circulatory support service this year to provide ventricular assist devices to patients from neonates to adults who have end-stage heart failure. We implanted 10 Berlin EXCOR devices within the last year.

An extensive renovation of our outpatient clinic area created a more welcoming environment for patients and families. We more than doubled the clinic area to more than 40,000 square feet, adding 16 patient care rooms, separate MRI and echo reading rooms, and creating separate spaces for pediatric and adult patients with congenital heart disease. New technology allows cardiologists to remotely supervise all echocardiograms.

Our quality improvement and clinical excellence program implemented a dashboard of crucial measures including safety and quality, family satisfaction, clinical functions and resource use.

In cardiac research, faculty findings published October 2010 in the *Journal of the American College of Cardiology* showed that mutations in the nebulette protein isoform are associated with lethal cardiac structural abnormalities, including dilated cardiomyopathy and endocardial fibroelastosis. Study authors included Enkhsaikhan Purevjav, MD, PhD, Michael Taylor, MD, PhD, and Jeffrey Towbin, MD.

Our work in molecular cardiovascular biology also progressed significantly this year. Jeffrey Molkentin, PhD, studies intracellular signaling pathways and transcriptional regulatory circuits that control mammalian cell growth and differentiation. Jeffrey Robbins, PhD, established the means to direct the heart to synthesize normal and mutant proteins and to turn these on and off at will. This allows scientists to establish cause-and-effect relationships between mutant proteins and the development of cardiac disease. Stephanie Ware, MD, PhD, continued work with X-linked heterotaxy (HTX-1, MIM 306955), a rare developmental disorder characterized by disturbances in embryonic laterality and other midline developmental defects. Ware uses this genetic defect to study the underpinnings of early axis formation and its importance for cardiogenesis.

Hematology

The Division of Hematology was established in October 2010 as part of the newly formed Cancer and Blood Diseases Institute. Clinton Joiner, MD, PhD, was named Division Director. The Division has nine faculty members and encompasses two comprehensive treatment centers for sickle cell disease and bleeding disorders. We also care for numerous patients with rare blood disorders and collaborate closely with the Division of Experimental Hematology and Cancer Biology on a range of basic, translational and clinical research studies.

The Divisions of Hematology and Experimental Hematology received a five-year, $3.5 million award from the National Institutes of Health as a Center of Excellence in Molecular Hematology. One of six such programs in the country funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the center provides core services to laboratories studying hematopoiesis and blood disorders, as well as enrichment programs and pilot funding to facilitate hematology research.

The professional activities of our faculty also reflect their national and international reputations. Joiner presented a plenary address to the First Global Conference on Sickle Cell Disease in Accra, Ghana, in July 2010. Joseph Palumbo, MD, spoke at the 10th International Congress on Inflammation, in Paris, in June 2011 and at the national meeting of the Federation of American Societies of Experimental Biology. Charles Quinn, MD, presented at World Sickle Cell Disease Awareness Day, sponsored by the Centers for Disease Control in Atlanta in June 2011. And Theodosia Kalfa, MD, PhD, was invited to speak in September 2011 at an international symposium in Paris organized by the French Institut National de la Transfusion Sanguine.

Human Genetics

Gregory Grabowski, MD, You-Hai Xu, PhD, and Ying Sun, PhD, participated in collaborative studies with colleagues in Boston and Ottawa to demonstrate a mechanistic link between Gaucher disease and Parkinson's disease. Based on these results, additional ongoing studies may lead to novel treatments of Parkinson's and other common neurodegenerative diseases.

Kejian Zhang, MD, MBA, worked with researchers at the National Institutes of Health and Stanford University to delineate the phenotype and molecular genetic characteristics involved in developing familial hemophagocytic lymphohistiocytosis and associated lymphoproliferative syndromes. These studies expanded the basic knowledge about the pathogenic mechanisms of these diseases and point toward targets to improve treatment outcomes.

William Nichols, PhD, reports significant advancements in understanding the genetic basis of Parkinson's disease and pulmonary arterial hypertension (PAH). In conjunction with investigators of the REVEAL registry, we have established the National Biological Sample and Data Repository for pulmonary arterial hypertension. This international collaborative effort will provide basic and clinical data for analyzing the pathogenic mechanisms of and developing treatments for PAH.

Immunobiology

Asthma is the leading cause of hospitalization in children. Although existing therapies can control mild forms, severe asthma is not well controlled. Marsha Wills-Karp, PhD, and colleagues have identified a novel pathway by which severe asthma may develop. Specifically, they showed that overproduction of an innate immune mediator, complement factor C3, leads to aberrant Th17 cell responses, which induce severe asthma. This recognition may lead to the development of novel therapies for difficult-to-treat asthma.

Unexplained anemia and other low-blood counts are often found in patients who develop sudden and severe inflammation. Patients with these conditions, such as sepsis, can also look quite similar to children with the immune disorder hemophagocytic lymphohistiocytosis (HLH). Michael B. Jordan, MD, and his colleagues have found that the inflammatory molecule interferon gamma (IFN-γ), which is found in excess in children with HLH, is a critical driver of the acute anemia observed during diverse microbial infections via a unique mechanism called hemophagocytosis. In a related study, Jordan launched a multicenter clinical trial, called "Hybrid Immunotherapy for Hemophagocytic Lymphohistiocytosis" (HIT-HLH), to test a unique combination of therapies that arrest damaging immune responses. As significant numbers of HLH patients die during the initial phases of therapy, this approach should improve survival.

Fatal anaphylactic responses have been associated with allergic people ingesting certain foods such as peanuts. Fred Finkelman, MD, and colleagues have recently demonstrated that producing IgG antibodies, rather than IgE antibodies, protects against food allergens, and delivering IgG antibodies systemically can suppress the induction of shock by food allergens. Moreover, they identified new markers to distinguish whether an individual develops a deleterious IgE or a protective IgG antibody response. Identifying the underlying antibody response may help develop therapies to prevent fatal anaphylactic shock.

Infectious Diseases

Jason Jiang, PhD, and Ming Tan, PhD, have extended their work on the norovirus P particle and its adaptability as a vaccine platform. Their studies in mice have shown that the P particle platform can protect against rotavirus and influenza virus by inserting the M2e epitope of influenza virus and the VP8 epitope of rotavirus into the three surface loops of each P domain.

The Rotarix vaccine, invented by David Bernstein, MD, and Richard Ward, PhD, was recently associated with a 42 percent decrease in deaths among children aged 11 months or younger in Mexico. A study published in the *New England Journal of Medicine* also reported that diarrhea-related mortality was 29 percent lower for children between the ages of 12 and 23 months.

Nancy Sawtell, PhD, has continued her work on the herpes simplex virus type 1 (HSV-1) virion protein VP16 as a central mediator of latency and reactivation from latency in sensory neurons. Sawtell plans to use innovative animal models to identify transcription factors or protein-modifying enzymes that regulate VP16 as potential targets for therapies to prevent HSV reactivation.

Rhonda Cardin, PhD, has developed a guinea pig model that accurately reflects transmission of cytomegalovirus (CMV) from mother to fetus and resulting hearing loss. Since CMV infection in humans is the major cause of nonhereditary deafness, this animal model will serve as an important tool for testing new therapies.

The International Adoption Center, led by Mary Staat, MD, has added mental health services and family counseling to help adopted children and their new families overcome abusive backgrounds.

Robert Frenck, MD, has become Chief of the Clinical Service after the departure of Michael Gerber, MD. Under Frenck's leadership, divisional revenues from inpatient consults have increased by 37 percent, and patient encounters in the outpatient antibiotic service have grown more than 40 percent. Plans call for opening a travel clinic at the Burnet Campus and a general infectious disease clinic at the Liberty Campus within the next year.

Mayerson Center for Safe and Healthy Children

In October 2010, the Mayerson Center for Safe and Healthy Children celebrated its 10-year anniversary as a local and national leader in protecting children from abuse. Our specialty services include forensic interviewing, medical-legal examinations, evidence collection and testimony. Our physicians are among the first doctors in the country to be board-certified in the new field of child abuse pediatrics.

Each week, we evaluate more than 30 children for concerns of child abuse or neglect. These evaluations are conducted in an environment designed to minimize child and family stress.

In the past year, we began employing a statewide maternal depression screening and referral program that was established for the Ohio Department of Health's Help Me Grow home visiting program. We also continued to collaborate with area physicians, nurses, social workers, researchers, caseworkers, law enforcement officers and prosecutors.

Our center is widely recognized for its role in developing educational networks, which include on-site instruction and innovative telemedicine services. We provide various programs for pediatric sexual assault nurse examiners, child forensic interviewers and pediatric child abuse fellows. Our Trauma Treatment Training Program serves community mental health providers while our Stewards of Children Sexual Abuse Prevention Program provides trainings for parents and other community groups.

Molecular Immunology

Edith Janssen, PhD, has made major strides defining the unique capabilities and potential therapeutic utility of merocytic dendritic cells, a novel cell population that she discovered. In two recent, high-profile papers, Janssen and colleagues report that harnessing merocytic dendritic cells significantly increases the efficacy of antitumor vaccines in mice. These cells also can play an important pathogenic role in autoimmune disease – breaking T-cell tolerance to beta cell antigens and driving type 1 diabetes in mice.

Avoiding immune-mediated pathology demands tight regulation of the amplitude, duration and class immune responses – something provided by diverse mechanisms of immune counter-regulation. The research of Claire Chougnet, PhD, on regulatory T cells, which play important counter-regulatory roles across the immune system, continues to bear important fruit. Work published last year in *Blood* demonstrated that regulatory T cells restrain HIV replication in activated T cells. Another paper, published in *The Journal of Immunology*, reports that the pro-apoptotic molecule, Bim, plays a major role in regulatory T-cell homeostasis. Meanwhile, a study in *PLoS One* (work done with Suhas Kallapur, MD, Alan Jobe, MD, PhD, and investigators from Maastricht University) reports that chorioamnionitis, which leads to inflammation that interferes with gut maturation, is associated with depleted intestinal regulatory T cells in sheep.

Mice have triumphed as the ***in vivo*** model of choice in biomedical research. However, there are clear limitations to mouse models. The literature is full of therapeutic approaches that worked in mice but failed in humans. Christopher Karp, MD, is addressing the novel hypothesis that the cold stress laboratory mice are subjected to (largely for the comfort of their human handlers) profoundly affects mice in ways that directly impair modeling of human immunology and immune-mediated disease. This research program seeks to develop better, more humanized models of immune-mediated disease.

Nephrology and Hypertension

This year we launched the Center for Acute Care Nephrology (CACN), a collaboration with the Heart Institute and Critical Care. The center began in-house consultative acute pheresis service early this year and implemented early, proactive peritoneal dialysis in children at risk of acute kidney injury after cardiac surgery. These initiatives dramatically improved outcomes. Additionally, the CACN worked with the Anderson Center on a hospital-wide initiative to reduce nephrotoxic medication-associated kidney injury. Our funded research continues, including studying the biomarker NGAL to identify early kidney failure in critically ill children.

Our Kidney Transplant Center performed its 500th transplant this year. The center has seen a surge in cases of children with complex malformations, antibody-mediated rejection and BK virus nephropathy. Despite the complexity, our patient and graft survivals are at or above national benchmarks, with shorter lengths of stay for the initial transplant surgery. These successes have made us one of the top five busiest pediatric kidney transplant centers in the country. Ongoing funded research aimed at improving these outcomes even further continues, focusing on immunology, adherence and quality improvement.

Our Dialysis Unit, second largest in the Midwest and among the 10 largest in the country, has seen an unprecedented number of infants needing dialysis. Infants are by far the most challenging dialysis patients; we now care for seven infants on home dialysis. Most come from outside the Cincinnati area. Because we coordinate the child's care across many disciplines and implement policies for aggressive feeding, hormonal and dialytic treatments, the infants show improved physical and mental development and are able to have earlier kidney transplantation. Such initiatives set best practice care standards for this unique dialysis population.

Neurology

Our Magnetoencephalography (MEG) Center provides highly detailed information about functional brain activity and has become one of the leading clinical MEG sites in the world. We use MEG routinely for evaluation before epilepsy surgery. Our researchers have developed 17 collaborative projects, including the study of language function in the developing brain, identifying neuromagnetic abnormalities in migraine and localizing epileptic foci with high-frequency oscillations. We have published 26 papers on MEG research in peer-reviewed journals and have trained 10 MEG scientists, six of whom now direct departments or MEG/EEG labs at their hospitals or institutions.

In our Tuberous Sclerosis program, we follow hundreds of patients with the disorder, in addition to patients with related disorders such as lymphangioleiomyomatosis (LAM). This past year, our researchers published findings in the *New England Journal of Medicine* that led to FDA approval of everolimus for subependymal giant-cell astrocytomas and continues to build on the use of agents involved in mTor pathways to treat neurological conditions.

Our Comprehensive Neuromuscular Care Center provides comprehensive interdisciplinary care for patients from around the world, specializing in the treatment of children with Duchenne muscular dystrophy. Our doctors have an active program of translational and clinical neuromuscular research, collaborating with other specialties on research and clinical trials in Duchenne muscular dystrophy. Additionally, we train pediatric and neurology resident staff as well as pediatric neuromuscular specialists.

Neurosurgery

A new program in deep brain stimulation, headed by Ellen Air, MD, PhD, will focus on children with complex movement disorders and pain. Cincinnati Children's will be the first to offer this treatment.

Our Surgical Epilepsy Program has grown and published highly favorable outcomes. Francesco Mangano, DO, program Director, uses diffusion tensor imaging (DTI) to predict outcomes for children with hydrocephalus. A NINDS-funded investigation into hydrocephalus earned Mangano and his research team a National Student Research Forum Neuroscience Award and The Ohio State Neurosurgical Society Resident Award. The team also worked with a visiting neurosurgeon from China to help him implement an epilepsy program in his home country.

Todd Maugans, MD, directs the neurosurgical craniofacial team and is helping form a Craniofacial Center. He has presented experience with minimally invasive craniosynostosis techniques and intraoperative use of medications to limit blood loss at national and international meetings, as well as in publications including the *Journal of Craniofacial Surgery*. His manuscript describing cutaneous anomalies of spina bifida was named Editors' Choice in *Neurosurgery*.

Charles Stevenson, MD, has expanded surgical treatment options for children with debilitating spasticity. He uses intrathecal baclofen therapy or selective dorsal rhizotomy (SDR), in which malfunctioning nerve roots are identified and sectioned to reduce spasticity in the legs.

Stevenson and colleagues in the Fetal Care Program began performing *in utero* repair of myelomeningocele defects, with highly favorable outcomes. This followed data from the NIH-sponsored Management of Myelomeningocele Study demonstrating that fetal repair of spina bifida substantially reduces the chance that these children will require a shunt for hydrocephalus.

Stevenson is researching ways to make tumors "glow" in the operating room, making it easier for surgeons to safely remove tumors in their entirety while sparing healthy brain matter. The doctors use a novel fluorescent compound engineered to bind and label brain tumor cells.

Oncology

We are a national center for research in new anticancer therapies with designer small molecules targeting tumor signaling pathways, engineered viruses, tumor-targeting antibodies, and targeted radiopharmaceuticals.

Brian Weiss, MD, leads a national clinical trial treating neurofibromatosis tumors. For pediatric brain tumors and other malignancies, Maryam Fouladi, MD, MSc, identifies molecular markers predictive of tumor response. She presented early results at the American Society of Clinical Oncology annual meeting. Lars Wagner, MD, leads a phase 2 trial of IMC-A12 and temsirolimus (CCI-779) for children and adolescents with relapsed cancers.

Denise Adams, MD, developed a phase 2 study to assess the mTOR inhibitor sirolimus for complex vascular anomalies. It is the first prospective clinical trial of a new treatment for these conditions.

This year we focused on epigenetic therapies targeting chromatin structure and pathologic gene and micro-RNA expression to kill malignant cells. Christine Philips, MD, presented work at the 2010 American Society for Hematology meeting demonstrating complete remissions in children with highly treatment-resistant forms of acute myeloid leukemia using decitabine. This provided the foundation for a new study combining a related drug, azacytadine, with a chromatin-targeting drug, vorinostat. Trent Hummel, MD, leads a phase 1 study of vorinostat with temozolomide to treat relapsed or refractory brain or spinal tumors.

In cancer stem cell research, James Geller, MD, leads a phase 1 trial of the small molecule c-Met inhibitor ARQ-197 in children with relapsed malignancies. In parallel work, Fouladi leads a phase 1 study of the AKT inhibitor, MK2206, in recurrent or refractory solid tumors and leukemias, as well as a Pediatric Brain Tumor Consortium phase 1 study of the Notch inhibitor, MK0751. The Notch signaling pathway holds particular promise for brain tumor therapy. Timothy Cripe, MD, explores new ways to identify and develop therapies against neuroblastoma stem cells. Rachid Drissi, PhD, studies the role of telomerase in malignant stem cells, particularly brain tumors.

Our faculty continue to lead the national clinical research agenda for childhood and young adult cancers. John Perentesis, MD, FAAP, Division Director, was elected to the executive committee of the Children's Oncology Group and serves as chair for relapsed leukemia clinical trials and vice-chair for young adult cancer initiatives. He serves on the Investigational Drug Steering Committee of the National Cancer Institute. Fouladi, Medical Director of the Neuro-Oncology Program, chairs the CNS tumor new agents/relapse committee for the Children's Oncology Group. She also is a member of the national steering committee for the Collaborative Ependymoma Research Network (CERN).

Ophthalmology

Our Division continues to research ways to improve clinical outcomes. Retinopathy of prematurity (ROP) is caused by overgrowth of capillaries in the eye, which can lead to scarring and eventual detachment of the retina if left untreated. Michael Yang, MD, has received internal funding to study the efficacy of national screening criteria for ROP when applied to a subset of heavier, older premature infants. The hypothesis is that very few from this subset of infants develop severe ROP or require surgery, and may not require screening exams at all. The objective is to decrease the number of screenings performed on infants, reducing time and cost for families and enhancing quality of care.

Our Visual Systems Group has completed recruitment efforts to build its research team. Our mission is to study the development of the visual system and understand the disease processes that affect vision. With recruitment completed, we expect to see increasing and significant research contributions from our group.

COMPLETING THE CIRCUIT

FROM ANXIETY TO CEREBRAL PALSY, OUR SCIENTISTS EXPLORE THE WIDE-RANGING CONSEQUENCES OF DISRUPTIONS IN BRAIN DEVELOPMENT

Some birth defects such as cardiac problems, airway malformations and liver and gut disorders are so extensive that survival depends on immediate medical intervention.

Other defects that occur are more subtle.

Prenatal defects in how the brain is assembled can lead to cognitive defects, emotional and behavioral disorders and deficiencies in motor skills and language development. However, these problems often do not reveal themselves until a child begins growing up.

At Cincinnati Children's, as investigators gain new understanding of the molecular pathways that guide brain development *in utero*, they are beginning to pinpoint precisely when, where and how the process can go wrong.

These insights eventually could lead to life-altering treatments for conditions ranging from post-traumatic stress disorder and ADHD to cerebral palsy and learning disabilities.

"HOW WE RESPOND TO FEAR IS A CRUCIAL ASPECT OF NORMAL HUMAN BEHAVIOR. WHAT HOLDS US BACK? WHAT ALLOWS US TO TAKE RISKS?

AS WE CHARACTERIZE HOW THE AMYGDALA FORMS, WE WILL GAIN NEW UNDERSTANDING OF WHAT COMPRISES A NORMAL FEAR CIRCUIT, AND WHAT COMPRISES AN UNHEALTHY ONE."

The roots of fear

Much of what makes us human comes from the telencephalon, or the forebrain — the region that controls cognition, emotion and purposeful movements.

Kenneth Campbell, PhD, a researcher in the Division of Developmental Biology, has been studying the molecular mechanisms that guide the formation of the mouse telencephalon during embryonic development.

His work focuses on understanding how disruptions in the formation of basal ganglia within the subcortical telencephalon may contribute to ADHD, Tourette syndrome and obsessive-compulsive disorder (OCD).

Dr. Kenneth Campbell studies the roots of fear.

In the past year, Campbell's research also has delved into the realm of emotional control. Campbell is studying the formation of the amygdala, a portion of the limbic brain that plays a major role in controlling emotions. Specifically, Campbell and colleagues are mapping out the brain circuitry involved in fear and anxiety.

Early results from this work were published in the May 19, 2010, edition of the *Journal of Neuroscience*. The paper, by Campbell and lead author Ronald Waclaw, MS, PhD, Division of Experimental Hematology and Cancer Biology, describes the origins of neurons that later connect to form the fear circuit of the developing mouse.

They reported a novel origin of the progenitor cells that migrate and differentiate into intercalated cells (ITCs), which are fundamental for the control of fear responses. Campbell's work has focused on identifying the transcription factors that mark distinct amygdalar progenitors and regulate their differentiation.

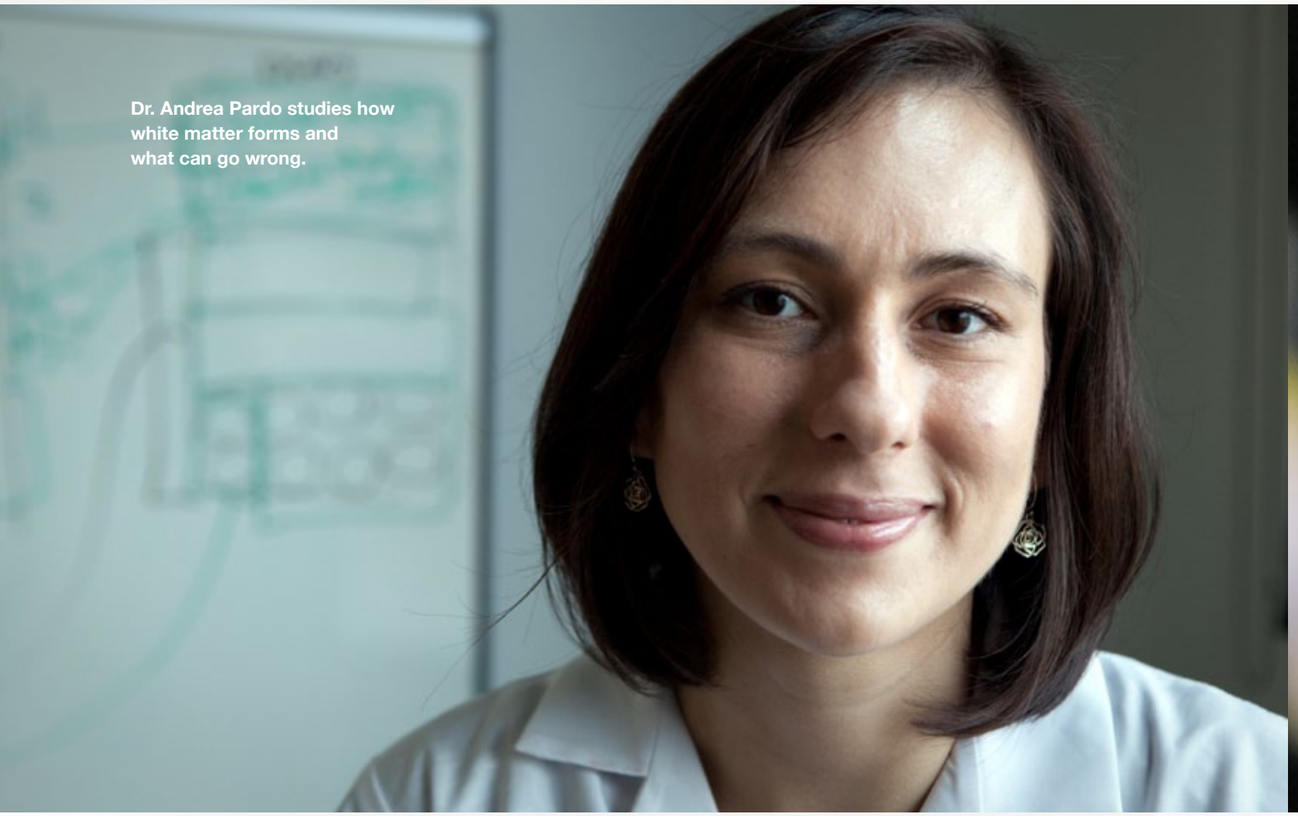
He and Waclaw have developed mouse models that produce far fewer ITCs than normal. His team is studying these mice (Gsx2 and Sp8 mutants) to determine how their fear response varies from normal.

"How we respond to fear is a crucial aspect of normal human behavior," Campbell says. "What holds us back? What allows us to take risks?

"The structure of the amygdala is one of the least well-understood areas within the telencephalon," he continues. "As we characterize how the amygdala forms, we will gain new understanding of what comprises a normal fear circuit and what comprises an unhealthy one."

Such understanding could shed new light on many conditions. Fear is linked to post-traumatic stress syndrome, which affects many children who survive disasters, injuries and physical or sexual abuse. Fear-and-anxiety-related stress also helps trigger unusual behaviors in OCD and Tourette syndrome.

Eventually, Campbell's research will help untangle which aspects of fear response are innate, and which are learned. Once the circuit of fear is better understood, improved therapies might be developed to hit more specific targets in the brain – potentially helping control unhealthy fear responses without causing other unwanted impacts on the brain.



Dr. Andrea Pardo studies how white matter forms and what can go wrong.

Connections that matter

The brain's white matter consists mainly of long, myelin-coated axons that relay motor and sensory information from the brain to the body and vice versa.

Defects in white matter can result in a wide variety of neurological deficits, including cerebral palsy, learning disabilities and behavior disorders. However, little is known about how healthy white matter forms.

Understanding this process is especially important because a rising number of infants are surviving extremely premature birth, only to grow up with a range of disabilities later in life.

As many as 50 percent of very low birthweight preterm babies (those born weighing less than 1,500 grams) suffer neurological deficits and developmental disabilities. These brain-related problems have many causes: lack of oxygen, lack of blood flow, infections and drug exposures. But MRI studies reveal a common thread – many of these deficits can be traced to disruptions in the healthy formation of white matter.

At Cincinnati Children's, Andrea Pardo, MD, a resident in the Division of Neurology, is working with Masato Nakafuku, MD, PhD, a researcher in Developmental Biology, to describe in detail how white matter forms, how defects can occur, and at which critical points developmental problems might happen.

During development, brain stem cells begin dividing to generate three key types of brain cells: neurons, astrocytes and oligodendrocytes. The oligodendrocytes go on to form white matter.

Crucial steps in white matter development occur between 23 and 32 weeks of gestation — the same time when many preterm births occur. Most premature infants avoid brain complications. However, extremely premature babies often suffer neurological consequences, even with the advent of surfactant to help infants survive until their under-formed lungs mature. Late preterm infants are also at risk for developmental delays, as oligodendrocytes continue to form well after 32 weeks of gestation.

"NICUs are getting better at maintaining healthy oxygen levels. However, some hypoxia is almost inevitable, and, these white matter-forming cells are very susceptible to damage at this crucial stage of development," Pardo says.

The Children's team is working to more fully describe the stages of oligodendrocyte development at the molecular level, from brain stem cells all the way to fully mature, myelin-coating cells. Investigators are going beyond known descriptions of critical proteins that are active during various stages of development to describe transcription factors that control those proteins.

So far, this research has identified three key transcription factors, each of which is active only during brief windows of time. If hypoxia occurs during one of those windows, these transcription factors do not function properly and white matter formation gets thrown off-track.

As a result, surviving premature infants can wind up with white matter injury. The more extreme the damage, the more extreme the symptoms.

This line of research remains in very early stages. Eventually, the researchers believe it might be possible to up-regulate those critical transcription factors, thus providing a form of protection against hypoxia that could give preterm infants better odds of achieving normal brain development.

The ultimate goal, Nakafuku says, is to develop treatments that can protect and enhance white matter formation while the brain is still developing in the weeks and months after a premature birth, similar to how artificial surfactant supports immature lungs.

"We do not want to wait until the child grows old enough to detect the problem. Then, it would be too late," Nakafuku says. "We want to find a treatment that can prevent the damage from occurring in the first place." ■

Orthopaedics

For the second consecutive year, we were ranked among the top five pediatric orthopaedic programs in the country by *U.S. News & World Report* magazine. Our Division continues to lead the field in podium and poster presentations at annual meetings of the Pediatric Orthopedic Society of North America (POSNA) and the American Academy of Orthopaedic Surgeons (AAOS).

This year marked the successful recruitment of James McCarthy, MD, and Peter Sturm, MD. McCarthy is from the University of Wisconsin School of Medicine and Rehabilitation and is the new Director of the Division of Pediatric Orthopaedic Surgery. He was awarded the Alvin H. Crawford Chair in Pediatric Orthopaedics.

Peter Sturm, MD, joined us from the Shriners' Hospital for Children in Chicago to direct the Alvin H. Crawford Spine Center. Sturm was awarded the Alvin H. Crawford Chair of Spine Surgery and is working with Crawford to develop a global center of basic science and clinical investigation to improve outcomes for spine conditions.

The Division has worked closely with the Physical Therapy department, the Perlman Center and Physical Medicine and Rehabilitation to develop a new Cerebral Palsy Center and to launch a state-of-the-art motion analysis laboratory, headed by Jason Long.

We also finalized an agreement with SpineForm, LLC, and received IRB approval to begin clinical testing of the HemiBridge Spine Clip. Developed by Eric Wall, MD, and our orthopaedic biomechanics research team, the HemiBridge clip is the first vertebral stapling device to receive an FDA investigational device exemption. The study will involve placing the spine clip via a minimally invasive surgical technique to redirect spine growth, a procedure that could revolutionize scoliosis treatment.

Otolaryngology

Our "Oto-gen" project, the first next-generation platform to rapidly sequence genes involved in pediatric hearing loss, became a reality in 2011. Developed through a collaboration of the Ear and Hearing Center and the Molecular Genetics Laboratory at Cincinnati Children's, this technology will allow rapid, cost-effective gene screening to diagnose and treat hearing loss.

The auditory genetics lab of Saima Riazuddin, PhD, made large strides toward unlocking the mystery of hereditary deafness. Her lab recently identified the MSRB3 gene that is responsible for autosomal recessively inherited deafness (DFNB74) in eight Pakistani families. In addition, her lab recently discovered a new locus for recessively inherited deafness (DFNB86) in another family. These discoveries could lead to diagnostic screening tools and treatments.

Otolaryngology was part of a collaborative, multidisciplinary project that won NIH funding to create and validate anatomical and physiological computational models of children with Down syndrome who have obstructive sleep apnea. Our goal is to use these models to predict the likelihood of success for surgical intervention.

Pathology and Laboratory Medicine

Kathryn Wikenheiser-Brokamp, MD, PhD, studies the molecular underpinnings of lung cancer and pediatric cystic lung disease. She has identified critical functions for the Rb/p16 and p53 tumor suppressive pathways in pulmonary epithelial cell growth in the context of lung development, injury repair and carcinogenesis. These studies are supported by the NIH and the American Cancer Society. Wikenheiser-Brokamp leads a multicenter consortium that seeks to elucidate how DICER1 and the microRNAs it generates control organogenesis and oncogenesis. This team recently discovered DICER1 mutations among families predisposed to develop pleuropulmonary blastoma (PPB). Published in *Science* in 2009, this work represents the first human syndrome associated with DICER1 mutations.

The introduction of Gleevec (imatinib mesylate) has changed the management of chronic myelogenous leukemia (CML) and has inspired efforts to target other oncogenic kinases such as EGFR, c-KIT, PDGFRA, PDGFRB and BRAF. Targeted inhibition of these oncogenic kinases by small molecule inhibitors induces hematologic remission in leukemias and tumor regression in solid tumors. Despite this success, most patients retain molecular evidence of residual disease, and emergence of drug resistance limits the prospects for cure. Mohammad Azam, PhD, is studying oncogene addiction in imatinib-responsive cells, which could lead to therapies targeting the intrinsic resistance of leukemia stem cells. His comparative expression profiling studies are identifying critical mediators of this process.

Cincinnati Children's is a nationally recognized treatment center for children with malignancies of the hematopoietic system. To support this clinical program, we have joined with the Cancer and Blood Disease Institute research under the direction of Yi Zheng, PhD, to build a world-class research program in leukemia and stem cell biology. The focus is to dissect hematopoietic and cancer cell signaling networks at the molecular level. Gang Huang, PhD, has obtained funding from the Ohio Cancer Research Associates to study molecular mechanisms in MLL-mediated leukemia. His investigations of non-Hoxs MLL downstream targets may potentially lead to more precisely targeted therapy for MLL-leukemias.

Pediatric and Adolescent Gynecology

Effective January 2011, Pediatric and Adolescent Gynecology moved from the Division of Adolescent Medicine to become an independent division in the Department of Surgical Services.

The Division, under the direction of Lesley Breech, MD, focuses on medical and surgical management of gynecological problems as well as promoting reproductive health. Faculty members also include Leslie Ayensu-Coker, MD, and Jill Huppert, MD, MPH.

The alignment with Surgical Services was designed to provide more institutional support for new surgical specialty areas, such as the Disorders of Sexual Development Program and the OncoFertility Program. The transition also provides additional support for fellowship training. Our Division offers one of only six Pediatric and Adolescent Gynecology fellowship training programs in North America.

Physical Medicine and Rehabilitation

Our Cerebral Palsy Program is expanding its services for children and their families as well as its research endeavors. Planned developments include forming interdisciplinary clinics, a new motion laboratory for gait analysis, surgical services for dorsal rhizotomy, and research into novel combinations of robotic gait therapy and functional electrical stimulation.

Jilda Vargus-Adams, MD, and Doug Kinnett, MD, lead a working group that is formulating a five-year plan to make this a world-class program in managing children with cerebral palsy. This effort includes input from families and collaboration with the Perlman Center, Occupational and Physical Therapy, Orthopaedics, Neurosurgery and the Anderson Center for Health Systems Excellence.

Team members will be introduced at the upcoming annual Aaron Perlman Conference for Cerebral Palsy at Cincinnati Children's.

Plastic Surgery

Our craniofacial anomalies team is an interdisciplinary clinical group that serves children with cleft lip/palate and other craniofacial abnormalities. The team includes members from Genetics, Plastic Surgery, Physical Therapy, Speech Pathology, Audiology, Dentistry, Psychiatry, Neurosurgery, Otolaryngology and Nursing. As we work to improve patient outcomes, we also are collaborating with Developmental Biology to build a world-class research program.

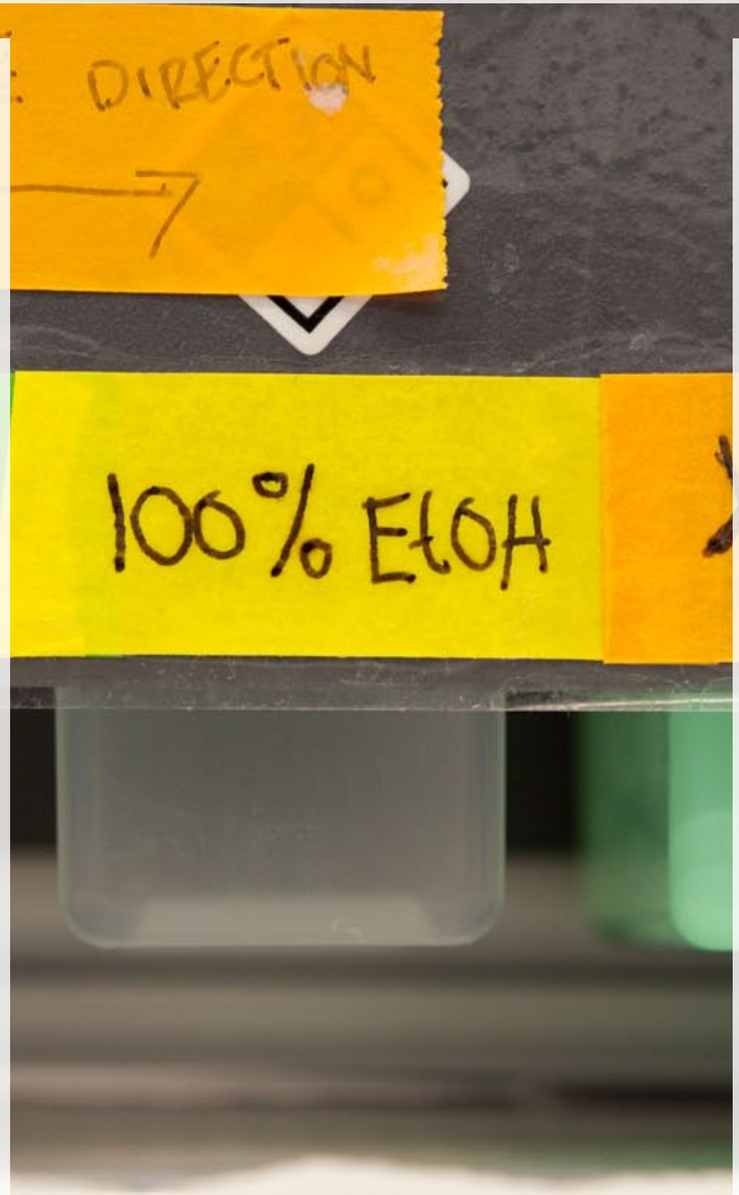
Christopher Gordon, MD, Bruce Aronow, PhD, and a visiting research scientist, Armando Uribe-Rivera, are investigating the role of microRNAs as master controllers of craniofacial development. They have identified several important families of miRs and are characterizing the molecular pathways they control. The ultimate goal is to manipulate these pathways to protect against facial clefts and other malformations.

Donna Jones, PhD, and Chris Runyan, MD, PhD, are researching methods to improve bone allograft revitalization, utilizing stem cells, growth factors and periosteum in a swine model. Runyan and Jones have engineered tissue that replicates the form and function of bone, as well as the capacity to heal. This project could lead to bone revitalization techniques that could sharply reduce the need for follow-up surgeries.

Gordon and Uribe-Rivera are collaborating with Alessandro de Alarcon, MD, and Michael Rutter, MD, from the Division of Otolaryngology on a project in which cadaveric tracheas are reanimated within a muscle flap in the abdomen in a rabbit model. Using a combination of fat-derived stem cells and respiratory epithelial biopsies, these constructs have been successfully used to replace up to two-thirds of the native trachea. This approach may provide an option for tracheal reconstruction in patients who have failed conventional therapy.

Gordon, Aronow and Steven Potter, PhD, have identified a novel human craniofacial syndrome in which a noncoding mutation has been identified, resulting in a unique phenotype. The group is working to producing transgenic mice to validate and express this novel mutation.

Our research team expanded in the past year with the hiring of Samantha Brugmann, PhD, who joined the Division in January 2011 from Stanford University. She studies the molecular and cellular basis of craniofacial patterning in avian and murine models. We also welcomed Marty Visscher, PhD, and the Skin Sciences Program into our Division.



Psychiatry

Child abuse often leads to severe deficits in emotional, physical and cognitive functioning that appear later in childhood and adult life. Our Therapeutic Interagency Preschool Program works with victims of severe abuse at an early age to improve their long-term social and emotional development, school readiness and family stability. This program, led by Jane Sites, EdD, LSW, has demonstrated outcome data showing significant improvements in speech, language development, social skills and self-control as well as a reduction in the number of children in foster care.

More than half of the children in our nation who suffer with psychiatric conditions do not receive adequate care, and the demand for pediatric mental health services continues to grow. Michael Sorter, MD, Division Director, and his team have worked with other Ohio children's hospitals and the Ohio Department of Mental Health to develop the Pediatric Psychiatry Network, a real-time phone consultation service to assist community pediatricians as they encounter patients with psychiatric needs. Consultations have been provided in most Ohio counties, with requests growing continuously.

Intellectual disabilities such as mental retardation are frequently associated with mental health difficulties and often complicate attempts to recover from acute psychiatric illness. To address these concerns, we have developed a specialized 10-bed psychiatric inpatient service to serve the complex needs of these dual diagnosis patients. We are using applied behavioral analysis (ABA) and other advanced psychiatric care to enhance outcomes for these patients. This unique regional service, led by Hilton Rodriguez, MD, and Michael Lind, PhD, served more than 300 children in the past year.

Pulmonary Medicine

John "JP" Clancy, MD, joined our Division in January of 2011. Previously Chief of Pediatric Pulmonology at the University of Alabama at Birmingham, he has been appointed the Thomas Boat Endowed Chair and director of cystic fibrosis clinical and translational research. Clancy oversees the CFF-Therapeutic Development Network Translational Research Center at Cincinnati Children's. His research focuses on airway and epithelial biology, examining novel targets to treat cystic fibrosis. One area of expertise includes developing new agents to restore function to disease-causing mutations in the cystic fibrosis transmembrane conductance regulator (CFTR), which is the root cause of CF. He focuses on developing new preclinical model systems and patient biomarkers to bridge these findings from the lab to the bedside.

Clancy has played international leadership roles in drug development, study design and execution, and data analysis for new cystic fibrosis therapeutics. He recently served as the international lead investigator of two phase 2 studies of new CF treatments. His translational research laboratory brings basic research laboratory personnel and clinical research coordinators together and provides an environment for the training of students, medical professionals and research scientists in translational research.

PREVENTIVE MEDICINE

DETECTING PROBLEMS EARLIER IS HELPING KIDS STAY HEALTHY INTO ADULTHOOD

Dr. Elaine Urbina and sonographer Connie McCoy aim to curb heart disease.

How do you prevent setting a body up for a heart attack later in life?

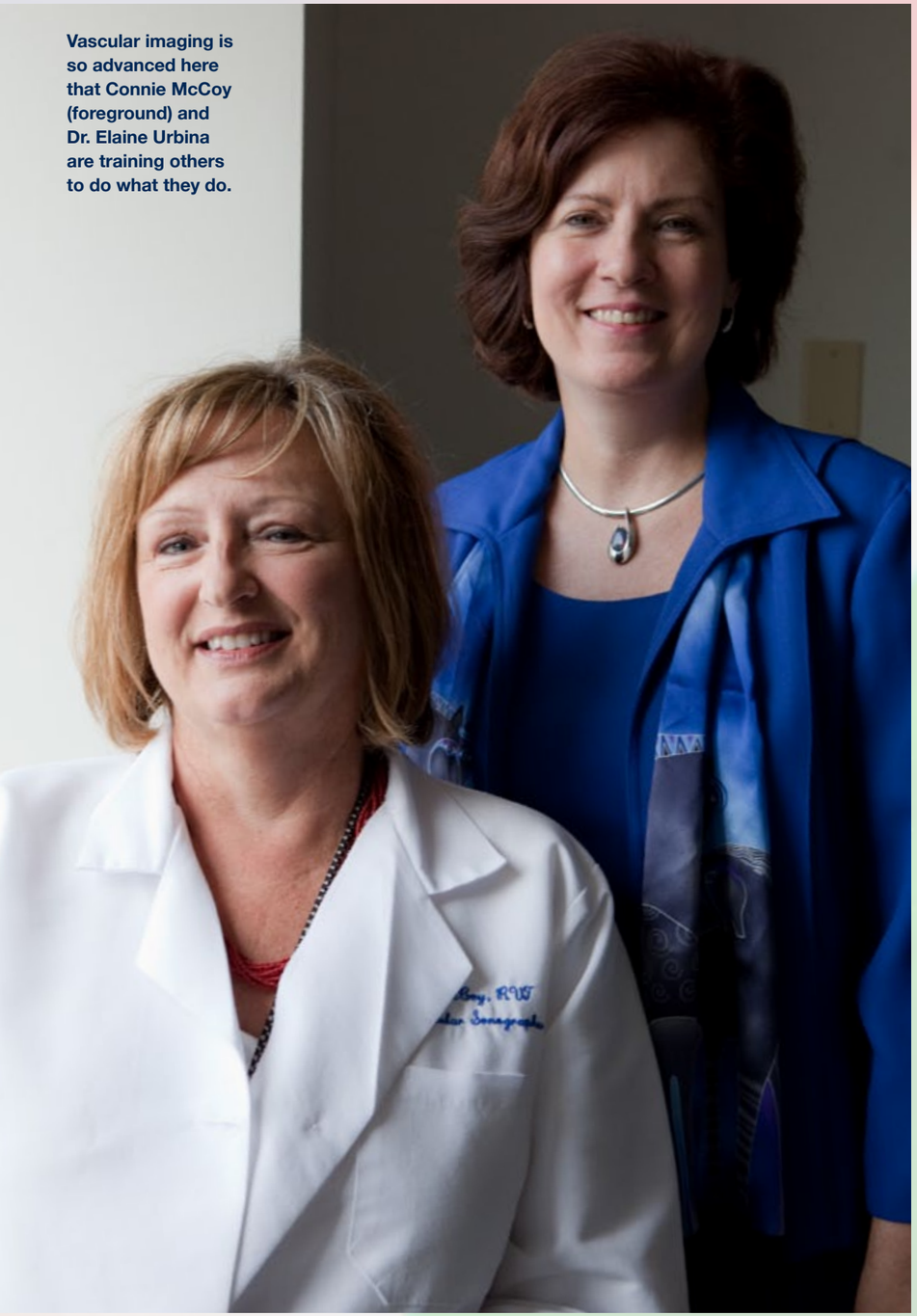
Doctors have known for more than 20 years that some babies are genetically predisposed to heart disease. A low birthweight increases the risk of coronary heart disease in adulthood.

The "developmental origins of disease hypothesis" proposes that coronary heart disease and the diseases related to it originate through responses to undernutrition in the womb and in infancy that permanently change the body's structure, physiology and metabolism.

But a sedentary lifestyle and poor eating habits can also put kids on the wrong course toward heart disease. That is where researchers at Cincinnati Children's are stepping in to come up with strategies to turn things around.

"In our experience, the development of obesity in children and adolescents is a combination of genetic and environmental influences," says Elaine Urbina, MD, Director of Preventive Cardiology in the Heart Institute at Cincinnati Children's.

"More often than not, there is a family history of overweight in many family members. This hereditary tendency is compounded by adverse lifestyles shared by the family."



Vascular imaging is so advanced here that Connie McCoy (foreground) and Dr. Elaine Urbina are training others to do what they do.

The 'v' in cardiovascular

Today's generation of children may be the first to have a shorter life expectancy than their parents, and it may be entirely related to the obesity epidemic, Urbina says.

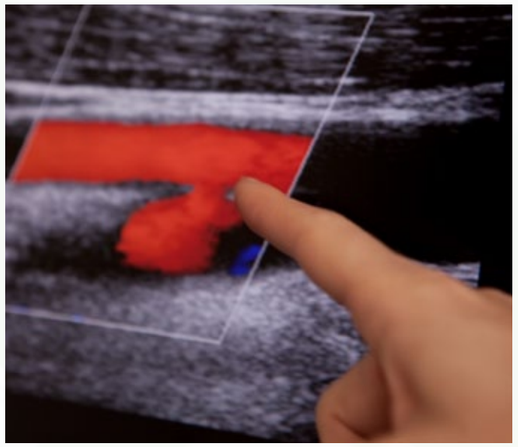
Her job is to research how to keep kids from having a heart attack or stroke when they get older. She is seeing more signs of organ damage in kids as young as 10, who have thick hearts or stiff arteries.

Stiffened arteries make it harder for the heart to relax. In adults, it is called diastolic dysfunction, and it is a precursor of congestive heart failure.

"These changes that we're seeing in high-risk youth in their adolescence really portend a poor cardiovascular future for them," Urbina says.

She is fighting back by trying to prevent childhood obesity and using intensive therapies for kids who already have problems like diabetes or multiple cardiovascular risk factors.

Her work starts in the laboratory, where she concentrates on noninvasive vascular imaging techniques to advance what we know about heart disease in kids. That involves using ultrasound to visualize the veins and arteries, measure blood flow to organs and tissues throughout the body and identify blockages to blood flow, such as plaque build-up.



Imaging kids' vessels shows damage in its earliest stages.

"People forget that cardiovascular disease has a 'v' in it," she says. "There is the vascular part. We're always focusing on the heart, and there have been noninvasive techniques developed in adults that we've now been able to translate down to younger ages."

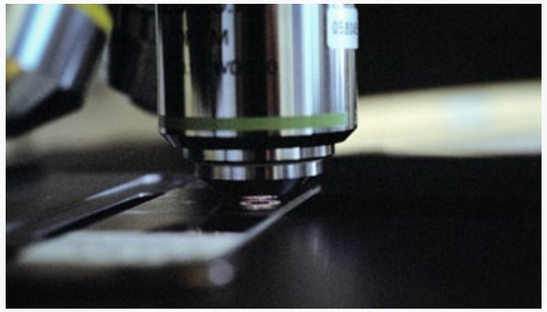
Urbina's interest in preventive cardiology stems from her cardiology fellowship in 1991 at Tulane University in New Orleans, where she joined the world-renowned Bogalusa Heart Study, one of the longest-running epidemiologic studies of cardiovascular risk factors in kids. The study began in 1973 and has tracked the cardiovascular health of the Louisiana town's residents ever since. It confirms that coronary artery disease begins in childhood and that a healthy diet can make for a good heart.

Expanding vascular imaging for children

Cincinnati Children's recruited Urbina in 2003 to expand our capabilities and our research in pediatric vascular imaging.

Imaging a child's vessels involves examining the endothelial cells that line the interior surface of the vessels, looking for signs of damage, such as fatty material that could eventually block the arteries if the problem continues into adulthood.

"We've examined every type of arterial stiffness in endothelial function testing available and have worked with the manufacturers to adapt tests for pediatric use," Urbina says. "This really puts us in the forefront of that particular field."



Detecting problems earlier

Most pediatric heart centers image only hearts, says Connie McCoy, RVT, a senior research vascular sonographer in our Cardiovascular Imaging Core Research Laboratory. But here, she is responsible for advancing what we know about heart disease by imaging of all the arteries and veins outside of the heart.

McCoy was instrumental in developing our Pediatric Vascular Training Institute, where pediatric researchers come from all over the country to develop expertise in vascular structure and function in kids. She also has performed independent research and presented her most recent findings in March to the American Heart Association epidemiology meeting in Atlanta.

"We certainly see functional and structural changes in kids who have risk factors," McCoy says. "They might have type 1 or type 2 diabetes. They might have lupus. They might be obese. We know that as these kids age, they can have early events, whether it is heart attack or stroke. We want to know, when does that damage start? And when can we intervene and reverse it?"

She applies imaging techniques to look at kids who are at risk for cardiovascular complications from a variety of diseases in addition to diabetes and obesity, such as hypertension, HIV, chronic kidney disease, obstructive sleep apnea or Turner syndrome.

"Our goal is to develop new strategies, perhaps new protocols in the way that we image, what we look at or what we measure," she says.

Those strategies likely will involve working with primary care physicians and families earlier, before disease progresses.

"When I first started here, there was an ongoing study about vascular structure of kids with type 2 diabetes," McCoy says. "We just started seeing them again five years later. They're heavier and they're bigger, and their arteries are stiffer and thicker five years later. They're on the course for early cardiovascular events. The question is, what interventions could have been done in those five years to prevent the progression of their cardiovascular disease?"

Dr. Philippe Backeljauw works with the largest group of Turner syndrome patients in North America.

Stepping in to help

The vascular imaging McCoy uses to identify risk in diabetes patients can predict cardiovascular problems in patients with Turner syndrome, a chromosomal condition that affects 1 in 2,000 women.

Girls born with Turner syndrome lack an X chromosome, resulting in short stature or other skeletal anomalies and congenital problems. They are at risk for thyroid disease, high blood pressure and diabetes.

"This condition kills," says Larry Dolan, MD, Medical Director of the Diabetes Center in the Department of Endocrinology. "But Dr. Philippe Backeljauw and his team are on the road to identifying potentially who is going to be at greater risk. If we have a way to predict who would develop aortic dissection (a tear in the inner wall of the aorta that can be fatal), the question becomes: What's an effective intervention?"

Philippe Backeljauw, MD, Medical Director of our Turner Syndrome Clinic, is working with Iris Gutmark-Little, MD, and Sarah Lawson, MD, to further the clinical research that might answer this question.

They follow about 170 patients with Turner syndrome, the largest collection of Turner patients in one center in North America. About 75,000 women in the United States have it, Backeljauw says. Some 90 percent have ovarian failure at a young age, and 30 percent have heart disease. Pediatric endocrinologists treat them because they have hormone deficiencies and short stature. Cincinnati Children's is the only center in this region that cares for Turner women through adulthood, does large studies and offers a support group.

From a research perspective, Backeljauw's team is looking at helping young women with Turner syndrome avoid or lessen cardiovascular complications. They are studying the prevalence of hypertension, problems with the pulmonary veins returning blood to the right atrium instead of the left, and in vasculopathy, a disorder of the blood vessels.

This knowledge helps doctors identify the patients at risk for cardiovascular disease and allows them to intervene by working with weight control and anti-hypertension medicines, he says.

His group will continue to study cardiovascular malformations, airway dysfunction and behavioral aspects of patients with Turner syndrome, he says, and they hope to come up with three-dimensional modeling to guide surgeons.

"We are able to provide optimal care for these patients," he says. "We have the tools and resources to train healthcare professionals and parents in Turner syndrome care. And we have a patient population and manpower to continue to do research studies." ■

Skin tests on kids may tell doctors who is more likely to get asthma, says Dr. Gurjit Khurana Hershey.

UNDERSTANDING ASTHMA

Everything researchers thought they knew about asthma may just be skin deep.

They are now looking at the skin itself in hopes that it can provide more clues about asthma than the lungs.

"People used to think of asthma as only a lung disease," says Gurjit "Neeru" Khurana Hershey, MD, PhD, Director of the Division of Asthma Research at Cincinnati Children's. "And it is, in the sense that it's your lungs that are affected. But what is it in the lungs that is contributing to the development of asthma?"

She is looking at the role of the epithelial cell in allergic inflammation in asthma. Recent studies have highlighted that the epithelial cell is the most important cell initiating the whole process that leads to asthma, she says.

So whether asthma is triggered by diesel exhaust, air pollution, smoke or mold, that trigger comes in contact with the epithelial cell, and the ensuing inflammation leads to asthma. But no current therapy specifically targets the epithelial cell, so that is the goal.

"One thing we've learned is that skin barrier function is an important determinant of asthma," Khurana Hershey says. "The better your skin works, the less likely you are to get asthma. And if your skin barrier is not good early in life, you're more likely to have asthma symptoms."

Researchers have long known eczema is a risk factor for asthma, but they are now learning that some of the genes associated with the development of asthma are actually skin genes.

"It's not just that the eczema is an allergic disease in the skin that often precedes asthma," Khurana Hershey says. "There's something innately wrong with the skin of individuals with eczema. Their skin barrier isn't normal."

Researchers can measure skin barrier function in kids as young as 2 to figure out how much water the skin loses and whether the skin barrier works properly.

"It's not surprising that skin that has eczema on it doesn't work well," Khurana Hershey says. "But it is surprising that normal appearing skin of someone with eczema isn't normal. Even their 'normal' skin does not have good barrier function, compared to a person without eczema."

That, along with genetic studies that indicate that defects in genes important in skin barrier function can promote the development of asthma, tells her that maybe researchers should be thinking about asthma in a different way.

"Maybe the dust and the other things that we're exposed to, in addition to getting in through the lungs like we thought, are also getting in through the skin and sensitizing us," she says.

Doing a skin test on a 2-year-old may tell doctors who may be more likely to get asthma. And maybe researchers can figure out how to improve skin barrier early in life as a way to prevent the development of asthma altogether.

"It's never been tried," she says. "People have been very focused on other things in the lung. But that's why our grant is looking at the role of the epithelial cell. We're not concentrating on epithelial cells in one particular location. We are studying the skin, the gut and the lung."

The best way to make an impact on a disease like asthma is to study the science behind it to try to identify new targets, Khurana Hershey says. If clinical researchers can compare treatments and decide on the best ones, they can develop guidelines that will help more kids stay healthy as long as possible.

Early intervention, she says, can give kids a better fighting chance. ■

Radiology

Our faculty continue to be leaders in clinical, translational, and basic science research in pediatric imaging. Additionally, Radiology faculty are actively involved in education and patient safety from the local to international level.

The Alliance for Radiation Safety in Pediatric Imaging was founded by one of our faculty in 2007. It has grown to include more than 62 organizations worldwide, including the American Academy of Pediatrics, the International Atomic Energy Agency and the World Health Organization. The alliance's "Image Gently" campaign, to ensure radiation safety for children throughout the world, has been recognized by the Food and Drug Administration, the Agency for Healthcare Research and Quality, and other organizations as the leader in pediatric radiation dose minimization and education.

Our imaging scientists have developed a new type of magnetic resonance scanner for premature babies. The scanner is small enough to place inside the Neonatal Intensive Care Unit and overcomes the challenges of transporting fragile babies outside the NICU for imaging. Early results with the prototype were presented at the 2011 meeting of the Joint Societies of Pediatric Radiology in London and won the Caffey award for best basic science paper. The scanner is planned for installation in Cincinnati Children's NICU at the end of this year.

This year we developed a number of initiatives with our Information Technology Department to improve report turnaround times. These include implementing 24/7 overnight faculty coverage and use of standardized reports. Our current average turnaround time for ED and stat films is under 30 minutes.

Reproductive Sciences

Takiko Daikoku, PhD, received a $50,000 pilot and feasibility funding grant from Cincinnati Children's Perinatal Institute for her project, "In pursuit of Lgr5 regulation and function in the uterus."

Satoshi Namekawa, PhD, received a two-year, $150,000 March of Dimes Basil O'Connor starter scholar research award for his project titled, "Regulation of sex chromosome inactivation by the FANC/BRCA Pathway."

S.K. Dey, PhD, received a Bill & Melinda Gates Foundation grant of $100,000 for 18 months for "Targeting mTOR signaling to prevent preterm birth." This pilot funding provides an opportunity to compete for additional research funds.

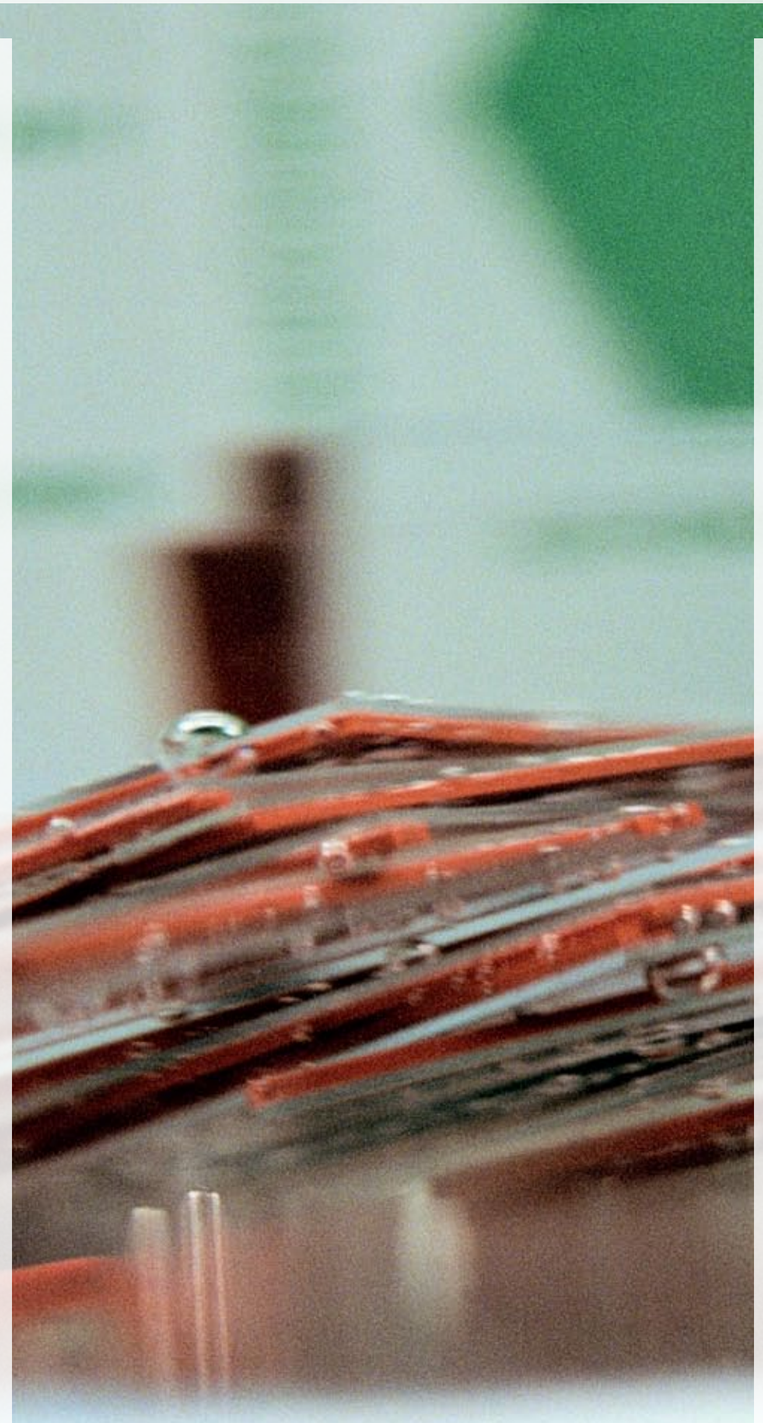
Yuya Ogawa, PhD, received a Cincinnati Children's trustee grant of $60,000 per year for two years for his project, "The mechanism of escape genes on the inactive X-chromosome."

Sanjoy Das, PhD, received funding of $330,000 for an NIEHS R01 grant, "Environmental Toxins and Uterine Gene Expression."

Our Division continued to demonstrate its commitment to training the next generation of reproductive sciences researchers. Xiaofei Sun received his PhD from Vanderbilt University this year and will continue postdoctoral work with Dey's lab. He recently received a Lalor postdoctoral fellowship.

Poornima Chandran, a Fulbright fellow from Osmania University in Hyderabad, India, trained with the Division for the 10 months of her fellowship. Her research will contribute to her PhD requirements.

Mikihiro Yoshie joined us as a visiting research fellow. Yoshie is supported by the Tokyo University of Pharmacy and Life Sciences. We continued to train postdoctoral fellows and graduate students from other institutions in specific laboratory techniques so that these skills will be used to expand the field of reproductive research.



Rheumatology

The Division of Rheumatology and Center for Autoimmune Genomics and Etiology (CAGE) achieved many milestones this past year. Work led by Alexei Grom, MD, identified a pathway important in the development of the sometimes deadly macrophage activation syndrome.

Susan Thompson, PhD, led work that provided genetic insight into the variations of DNA that predispose children to juvenile onset idiopathic arthritis. Dan Lovell, MD, MPH, Ed Gianinni, MD, MSc, and Hermine Brunner, MD, MSc, have shown that new biological therapies are spectacularly successful; their work has become the new standard of therapy and is helping thousands of afflicted children avoid the lifelong disability of chronic destructive arthritis.

Esi Morgan-DeWitt, MD, MSCE, has achieved better compliance and therapeutic outcomes in juvenile onset rheumatoid arthritis by applying quality improvement interventions. DeWitt and Brunner are co-leading efforts to align research, clinical care and quality improvement to provide the highest possible value for care provided at Cincinnati Children's. They are also leading international initiatives to develop quality indicators and benchmarks for pediatric rheumatology care with a focus on systemic lupus erythematosus (SLE) and juvenile idiopathic arthritis.

Biomarker development efforts must be synchronized with developing clinical trial outcome measures to begin testing novel medications for children with SLE. John Harley, MD, PhD, has led an effort to identify the genes that cause SLE, now numbering more than 40, and Brunner is characterizing biomarkers in lupus kidney disease. Harley is discovering the mechanisms and pathways through which the genes cause lupus.

Schmidlapp Center

The Charlotte R. Schmidlapp Foundation of Fifth Third Bank donated $2 million over the past two years to establish the Schmidlapp Women Scholars endowment. Interest from this endowment supports the Schmidlapp Women Scholars Program, which encourages the academic development of women faculty in pediatrics.

Faculty and parents of undergraduates supported by the Schmidlapp fund have donated more than $25,000 to the fund in this fiscal year.

The program provides educational and networking opportunities for faculty. Current projects include designing a department-wide mentoring program and an initiative to broaden the diversity of our faculty.

Section of Neonatology, Perinatal and Pulmonary Biology

Bruce Trapnell, MD, MS, and co-workers are using an NIH grant to develop lung biomarkers and a new gene therapy for pulmonary alveolar proteinosis (PAP). They have found that PAP is caused, in part, by autoimmunity against GM-CSF and by mutations in GM-CSF receptors.

Timothy Weaver, MS, PhD, has received NIH funding to identify the mechanisms associated with mutations in the surfactant protein-C gene, which can result in life-threatening idiopathic pulmonary fibrosis.

Anne Karina Perl, MS, PhD, leads work to identify lung growth factors that eventually may help treat children and adults with emphysema.

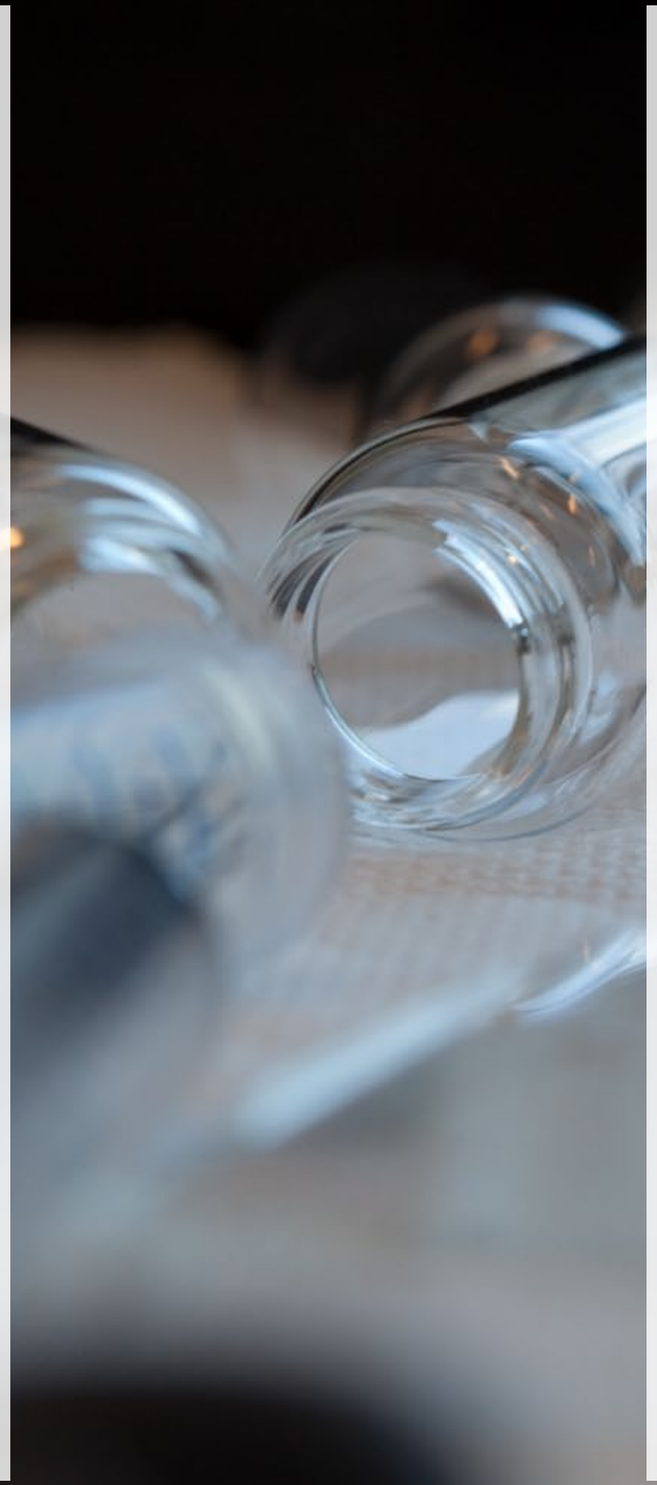
Thomas Korfhagen, MD, PhD, and Jeffrey Whitsett, MD, are leading an NIH-funded study of a novel genetic network found to regulate airway epithelial cell differentiation and mucus production related to cystic fibrosis, asthma and COPD. Targeting this master regulator of mucus production could lead to new therapies.

Beena Kamath, MD, MPH, with colleagues at the University of Cincinnati and Good Samaritan Hospital, reported important findings regarding the limitations of fetal lung maturity testing to predict readiness for postnatal life.

Noah Hillman, MD, Machiko Ikegami, PhD, Alan Jobe, MD, PhD, and Suhas Kallapur, MD, led a pre-clinical study of a novel prototype MRI developed by Charles Dumoulin, PhD, at the Cincinnati Children's Imaging Research Center. An improved device based on these findings is scheduled for installation in our NICU in January 2012.

James Greenberg, MD, Eric Hall, PhD, and Jareen Meinzen-Derr, PhD, are working with the James M. Anderson Center for Health Systems Excellence to target geographic "hot spots" of infant mortality as part of our strategic goal to reduce infant mortality in Hamilton County to the national average of 6.9 per 1,000 live births by 2015.

Heather Kaplan, MD, Edward Donovan, MD, and Carole Lannon, PhD, recently demonstrated the efficacy of the Ohio Perinatal Quality Collaborative as a key resource for reducing NICU infections. The team continues to develop quality improvement protocols in this field.



Sports Medicine

Teri Metcalf McCambridge, MD, was hired to serve as Division and Medical Director for Sports Medicine. McCambridge completed her medical school and residency training at the Johns Hopkins School of Medicine and her sports medicine training at the University of Wisconsin-Madison

Nicholas Edwards, MD, MPH, received a research scholars mentored career development award to research the "Effects of physical activity on cardiovascular risk factors in youth." Edwards' study will help determine the best methods for preventing children from developing heart problems as they mature.

Mark Paterno, PhD, won the 2010 NCAA research award from the American Orthopaedic Society for Sports Medicine for his work, "Biomechanical Measures During Landing and Postural Stability Predict Second Anterior Cruciate Ligament Injury after ACL Reconstruction and Return to Sport."

Carmen Quatman, MD, and co-author Laura Schmitt received the AJSM Systematic Review Award. Sam Wordeman received the American College of Sports Medicine Biomechanics interest group student research award.

This year, several division staff members received advanced degrees. Mark Paterno received a PhD in Orthopaedic and Sports Science from Rocky Mountain University of Healthcare Professions. Greg Myer received a PhD in athletic training from Rocky Mountain University and was promoted to research instructor. Carmen Quatman received her medical degree from the University of Toledo College of Medicine.

Urology

The Division ranked fourth in this year's *U.S. News & World Report* survey in recognition of our clinical and research activities. Our services include the Disorders of Sexual Development Clinic and the Urogenital Center, providing world-class care for children with complex genitourinary conditions. Our faculty also lead several significant research projects and serve in a variety of national leadership roles.

Pramod Reddy, MD, studies the relationship between the central nervous system and the lower urinary tract and how stress can induce changes in bladder function and morphology. Reddy headed a phase 3 clinical trial to evaluate darifenacin as a treatment for neurogenic detrusor overactivity.

William Robert DeFoor Jr., MD, is the principal investigator on a subcontract for the NIH clinical trial "Randomized intervention for children with vesicoureteral reflux (RIVUR)." DeFoor also led an Oceana Therapeutics study to evaluate the use of Deflux for VUR patients receiving endoscopic correction.

Paul Noh, MD, was awarded a National Kidney Foundation grant to study urinary NGAL as a noninvasive biomarker of obstruction in unilateral hydronephrosis.

Eugene Minevich, MD, served as president of the American Association of Pediatric Urologists (AAPU). Minevich also served on the clinical research committee of the AAP section of pediatric urology in October and as program chairman of the Society of Pediatric Urology, AUA annual meeting, in May. DeFoor was named secretary-treasurer of the AAPU.

Reddy was honored during the AAP meeting in October for his clinical research presentation on "The impact of the Alexander technique" on improving surgical ergonomics. Reddy also moderated clinical scientific sessions in India, Turkey and Washington, D.C.

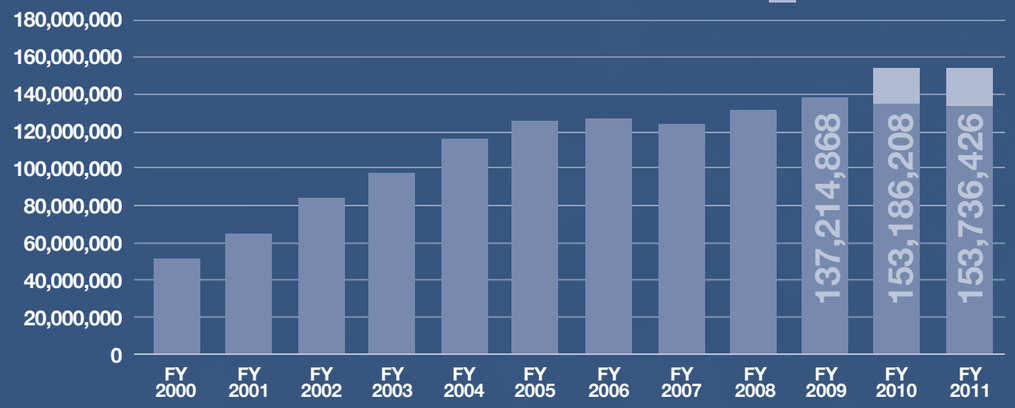
Shumyle Alam, MD, was a visiting Professor at the anorectal malformations workshop in Rotterdam. Noh was invited in January to present at the Arab Health Congress in Dubai.

Our Division completed the final year of our three-year affiliation with Arkansas Children's Hospital. This highly successful collaboration resulted in recruiting three pediatric urology faculty for the Arkansas hospital.

AWARDS & FUNDING

Overall Sponsored Program Awards

Total Costs (Prime and Sub-awards)

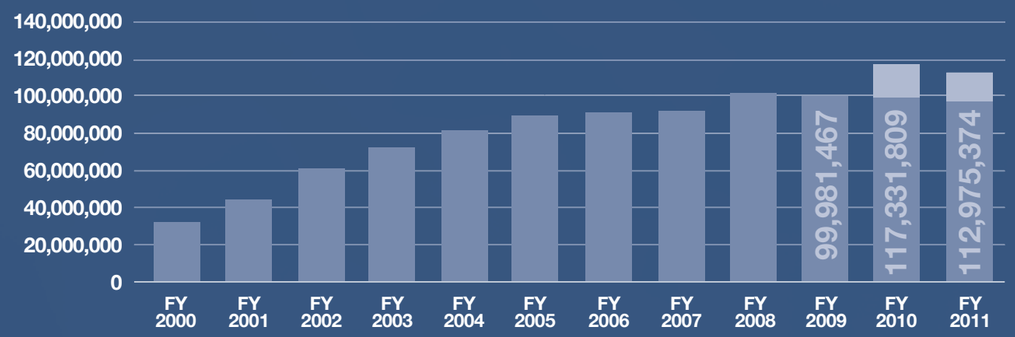


Approximately $6.8 million of ARRA awards received in FY10 were awarded for a two-year period. Half is reflected in FY10, and half is reflected in FY11.

Approximately $13.7 million of ARRA awards received in FY11 were awarded for a three-year period. One third is reflected in each of FY11, FY12, and FY13.

National Institutes of Health Awards

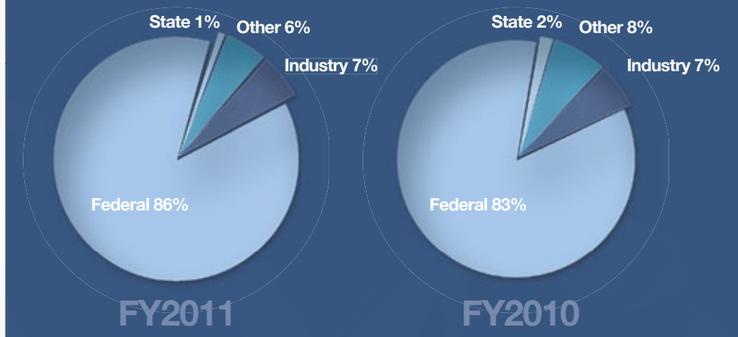
Total Costs (Prime and Sub-awards)



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

Approximately $1.8 million of NIH ARRA awards received in FY11 were awarded for a three-year period. One third is reflected in each of FY11, FY12, and FY13.

Distribution of Funding



Sources of Federal Funding

National Institutes of Health (NIH)	112,975,374
Agency for Healthcare Research and Quality (AHRQ)	5,804,616
Health Resources & Services Administration (HRSA)	5,133,213
Centers for Disease Control (CDC)	3,458,165
Department of Defense Army (DOD)	2,286,752
Substance Abuse & Mental Health Service Admin (SAMHSA)	686,229
Food & Drug Administration (FDA)	538,853
Administration on Developmental Disabilities (ADD)	502,327
Department of Education (DOED)	189,241
Department of Health and Human Services (DHHS)	157,626
Department of Labor (DOL)	94,190
National Science Foundation (NSF)	37,542
Total	**131,864,128**

Foundation and Other Agency Awards

Cystic Fibrosis Foundation	744,660
Charley's Fund	664,148
American Heart Association	546,500
Hamilton County Public Health	459,088
March of Dimes	402,954
Crohn's & Colitis Foundation of America	355,887
The Hospital for Sick Children	266,882
Robert Wood Johnson Foundation	265,299
American Cancer Society	230,000
The American Bd. of Med. Spec. Research & Educ. Fdn.	219,654
The Leukemia and Lymphoma Society	218,271
Cancer Free Kids	215,000
Miscellaneous Other (88)	5,193,270
Total	**9,781,613**

FACULTY & CLINICAL STATISTICS

Department of Pediatrics and Research Foundation Faculty

Total Faculty Members

Full-time/primary appointments in Pediatrics	543
Part-time/primary appointments in Pediatrics	50
During fiscal year 2011	71 new faculty members were appointed
During fiscal year 2011	25 departed (including retirement)

Pediatric Faculty by Rank and Track

	Clinical	Part-time	Research	Field Service	Tenure Track	Tenured
Instructor	8	5	17	3	0	0
Assistant Professor	117	22	62	8	41	0
Associate Professor	75	13	23	8	10	25
Professor	41	10	3	3	0	99

Instructors: 33 • Assistant Professors: 250 • Associate Professors: 154 • Professors: 156

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

	Full-Time	Part-Time	Total
Males	324	20	344
Females	219	30	249

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

	Black	Hispanic	Asian	Total
Full-Time Males	5	6	60	71
Full-Time Females	6	4	31	41
Part-Time Males	0	0	2	2
Part-Time Females	0	0	3	3

Clinical Activity

Admissions
(Excludes Short Stay Admits)

Type	Number
Medical	11,703
Surgical (I/P Surgeries)	6,141
23-Hour Admissions	13,107

Outpatient Visits

Type	Number
Surgical procedures	26,168
Emergency Room Visits	121,875
Primary Care (PPC)	65,444
• **Burnet, Hopple & Batesville**	
Subspecialty care Burnet	403,472
All neighborhood outpatient locations	411,222

Training

Students

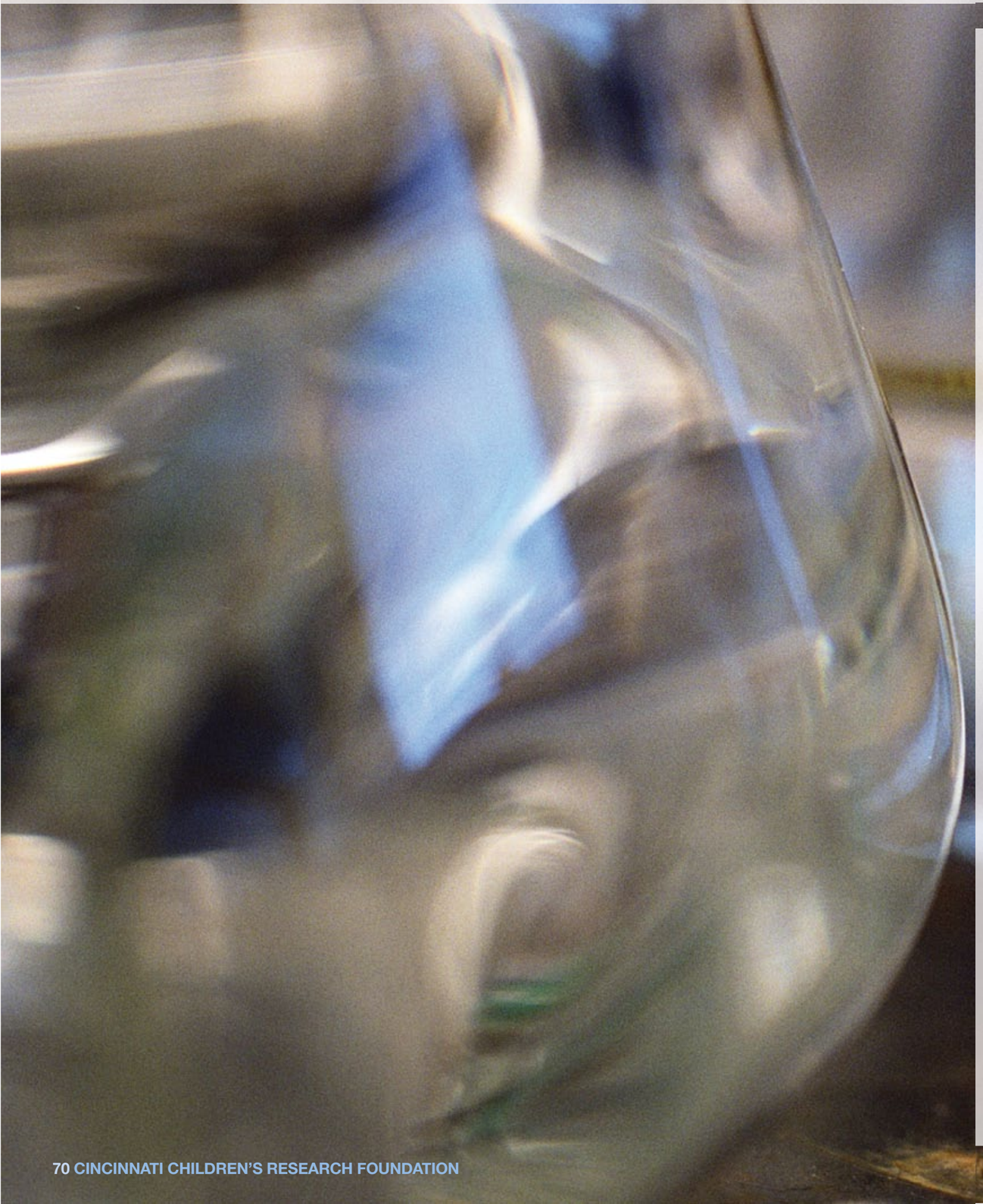
Junior Medical Students in the Pediatric Clerkship	168
Senior Medical Students in Pediatric Training	19
Senior Medical Students in Medicine/Pediatric Training	6

Residents

Pediatrics	116
Medicine/Pediatrics	28
Pediatric Physical Medicine and Rehabilitation	5
Dental	10
Psychology	6
Psychiatry/Child Psychiatry/Pediatrics	14
Human Genetics/Pediatrics	4
Neuro/Pediatrics	18
Dermatology	9 rotating
Anesthesia	11
Surgery (includes General Surgery, Cardiothoracic, Neurosurgery, Otolaryngology, Ophthalmology, Plastic, Orthopaedic & Urology)	110 rotating
Radiology	33 rotating

Pediatric House Staff Recruitment 2010

Pediatric Candidates Interviewed	289
Medicine/Pediatric Candidates Interviewed	80
PM&R Candidates Interviewed	5
Psychiatry/Child Psychiatry/Pediatrics Interviewed	16
HG Pediatrics Interviewed	7
Neuro/Pediatrics Interviewed	30



Fellows

Adolescent Medicine	4
• **Pediatric/Adolescent Gynecology**	2
Allergy/Immunology	7
Anesthesia	10
Cardiology	10
• **Cardiac Electrophysiology**	1
• **Cardiac Imaging**	1
Child Abuse	2
Critical Care	12
Developmental Disabilities	6
Emergency Medicine	11
Endocrinology	9
Gastroenterology	11
• **Pediatric Transplant Hepatology**	1
General Pediatrics	3
• **Pediatric Hospitalist Medicine**	1
Hematology/Oncology	13
• **BMT**	1
Infectious Disease	3
Medical Genetics	1
• **Clinical Cytogenetics**	1
• **Clinical Molecular Genetics**	2
Neonatology	13
Nephrology	6
Neurology	
• **Pediatric Epilepsy**	1
Neurosurgery	1
Ophthalmology	1
Orthopaedics	2
• **Hand & Upper Extremity Surgery**	1
• **Surgery of the Spine**	1
Otolaryngology	6
Pathology	2
Plastic Surgery	1
Psychiatry	4
Psychology	16
Pulmonary	7
Quality Scholars in Transforming Health Care	1
Radiology	9
• **Body MRI**	1
Rehabilitation Medicine	2
Rheumatology	6
Sleep Disorder Medicine	1
Sports Medicine	2
Surgery	2
• **Colorectal Surgery**	2
• **ECMO**	1
• **Pediatric International Surgical Fellow**	1
• **Trauma Surgery**	1
• **Vascular Anomalies**	2
Urology	2
Total Clinical Fellows	**207**
Total Research Postdoctoral Fellows	**137**

Publications

Peer Reviewed Articles	1,242
Non Peer Reviewed Articles	115
Books	3
Chapters of Books	104
Online Site Contributions	3
Total, FY 2011	**1,467**

Procter Scholars

Third Year

Alan Kenny, MD Neonatology
Molecular analysis of foregut organ specification in xenopus

Second Year

Eric Mullins, MD Hematology/Oncology
Project: Mechanisms linking hemostatic factors to neuroinflammatory disease

Ajay Perumbeti, MD, FAAP Hematology/Oncology
Project: Genetic approaches to correct human sickle cell anemia

Charles Samson, MD Gastroenterology/Hepatology & Nutrition
Project: Homeostatic responses to gut injury in inflammatory bowel disease

Sundeep Keswani, MD Pediatric General & Thoracic Surgery
Project: Molecular mechanisms of regenerative wound repair

First Year

Tanya Mullins, MD Adolescent Medicine
Project: Adolescent sexual behavior and incidence of sexually transmitted infections

Kasiani Myers, MD BMT & Immune Deficiency
Project: Leukemogenesis and genomic instability in Fanconi Anemia

Stephanie Merhar, MD Neonatology
Project: Safety, tolerability and efficacy of levetiracetam as initial monotherapy for the treatment of neonatal seizures

Elizabeth Schlaudecker, MD Infectious Diseases
Project: Influenza infection and immunization in pregnancy

Summer Research Programs

High School Interns	17
Undergraduate Students	113
Medical Students	20

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