



CINCINNATI CHILDREN'S  
RESEARCH FOUNDATION

2009 ANNUAL REPORT

*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.*



This report features highlights of our research activities of the past year. For a detailed look at our research, publications and faculty, go to [www.cincinnatichildrens.org/research09](http://www.cincinnatichildrens.org/research09).

You can also go there to request a CD of our detailed research activities.

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## Dear Colleagues,

2009 was a year of change and invigoration for the Cincinnati Children's Research Foundation (CCRF) and for all of us in American academic medicine and the biomedical research community. We witnessed a dramatic switch in the national focus and support for ongoing scientific investigation, resulting in huge increases in federal funding for biomedical and patient-related outcomes research and innovation.

At the CCRF and Cincinnati Children's, this year of change was incredibly positive, as described in the following pages of data, feature stories and summaries, the past year's highlights of discovery in each of our 52 research divisions, centers and departments.

In each of the feature stories about our research teams, you will meet a young patient whose health was transformed or whose life was saved by research and clinical advances. You will read about breakthroughs that span every area of child health, from exploring the mechanisms underlying asthma and autoimmune disorders (*When Good Systems Go Bad*, page 16) to developing a reliable biomarker to prospectively diagnose kidney injury (*Staying Ahead of Kidney Disease*, page 28); from understanding how and why liver tumors grow to better nourishing children whose intestines fail (*Gut Instinct*, page 10); and from saving children with acute leukemia to using genetics to predict and customize treatments (*Outsmarting a Killer*, page 23).

### Funding for Discovery and Innovation

In this year of change, CCRF-sponsored research increased by 4.4 percent to more than \$137 million, despite a \$1.6 million decrease in NIH funding. Funding from other federal agencies whose focus is epidemiology, outcomes and health services, such as the Centers for Disease Control, the Health Services and Research Administration and the Agency for Healthcare Research and Quality, also declined slightly. But substantial increases (\$6 million) in support from industry and foundations, including the Gates Foundation, the American Heart Association and the Cystic Fibrosis Foundation, broadened the portfolio and pushed our total research funding to a record high.

During the fiscal year transition from June to September, we received an influx of nearly \$29 million in NIH funds, the result of the American Recovery and Reinvestment Act of 2009. This support, spread over the next two years, represents a 14 percent annualized increase in our NIH funding that will revitalize our research efforts. Of special note was a Clinical and Translational Sciences Award (CTSA) led by Jim Heubi, more than \$20 million over 5 years, an accomplishment featured in *Kick-Starting Science* (page 33).

### The Faculty — Our Foundation for Change

Of course, our talented community of faculty, fellows, research nurses and staff forms the foundation for our continued leadership in discovery and innovation and for our outstanding efforts in clinical care. In this year of change, we recruited 64 new faculty, resulting in a total of 504 faculty in the Department of Pediatrics and an expansion of faculty conducting

research in the Departments of Radiology, Anesthesia and Surgery. Jeff Towbin, executive co-director of the Heart Institute, Chuck Dumoulin, director of Imaging Research, and Daniel von Allmen, chief of General and Thoracic Surgery, were among our key recruits.

The faculty's research and clinical outcomes studies resulted in 1,147 publications, including 979 peer-reviewed articles, many in high-impact journals such as *Nature*, *Cell*, *New England Journal of Medicine* and *Journal of Clinical Investigation*. These publications generate visibility for our discoveries and increase their potential to improve outcomes more broadly.

We initiated three Institutes focused on pediatric heart disorders, cancer and blood diseases and perinatology, including fetal care, developmental biology and reproductive sciences. A goal of this effort is to accelerate translation of basic discoveries into improved patient care.

### Talent Development and Education

Our future depends on developing talented young physicians and scientists. This year, we trained 178 fellows in 50 different clinical specialties and subspecialties. In addition, 181 medical students, nearly 60 doctoral students, 194 full-time residents in 10 specialties, 130 rotating surgical and radiology residents, 118 post-doctoral research fellows, and hundreds of nursing, pharmacy and allied health students were training here. CCRF internal grant support of Procter scholars, trustee grants, translational research awards and the newly announced Geoffrey Place outcomes awards facilitated development of physician and PhD scientists.

### Leadership Transition

This year of change encompassed a transition in leadership as well. 2009 was our final year under the leadership of president and CEO Jim Anderson, who is retiring. Geoffrey Place, who has chaired the research committee of the Board of Trustees for more than 30 years, also retires this year. The leadership of these two icons has transformed CCRF over the years to our status as an internationally-recognized leader in pediatric biomedical research. We thank Mr. Anderson and Mr. Place greatly and know that their legacy will last for generations.

I congratulate and thank all of our CCRF administrative leadership, faculty, trainees and staff who, working with all of Cincinnati Children's, generated the changes documented in this report through their hard work, innovation, discovery and collaboration.

Sincerely,



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



In each of the feature stories  
about our research teams,  
you will meet a young patient  
whose health was transformed  
or whose life was saved by our  
research and clinical advances.

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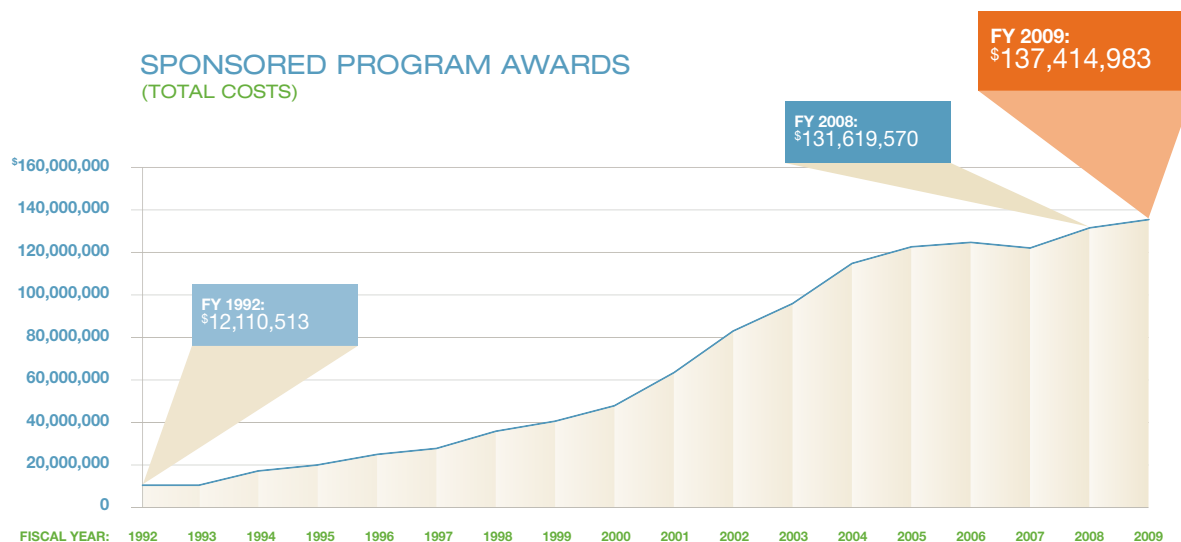
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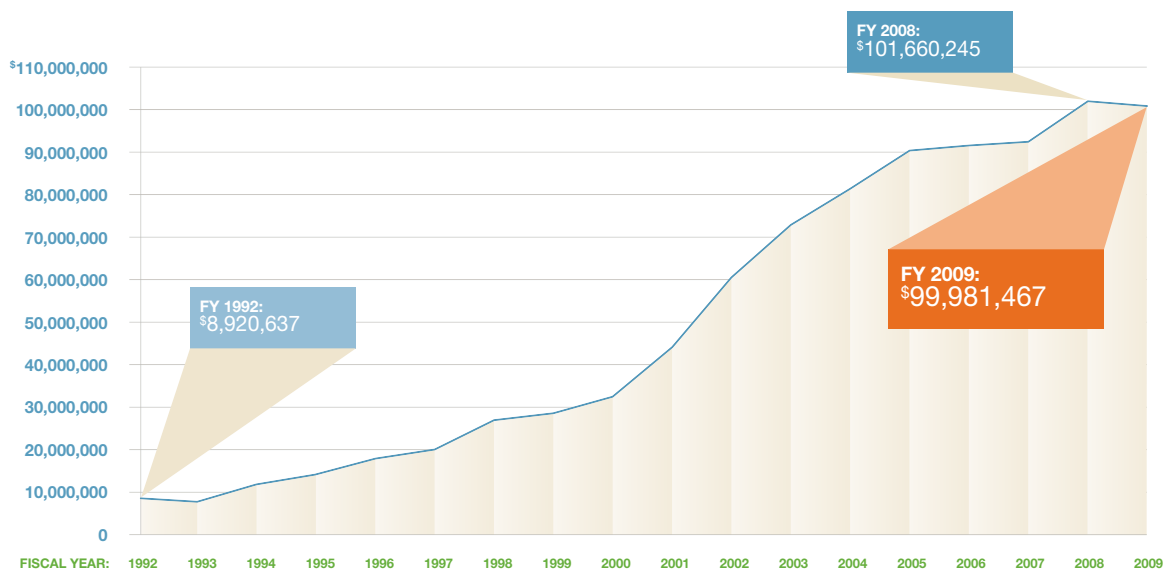
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# Awards & Funding

## SPONSORED PROGRAM AWARDS (TOTAL COSTS)

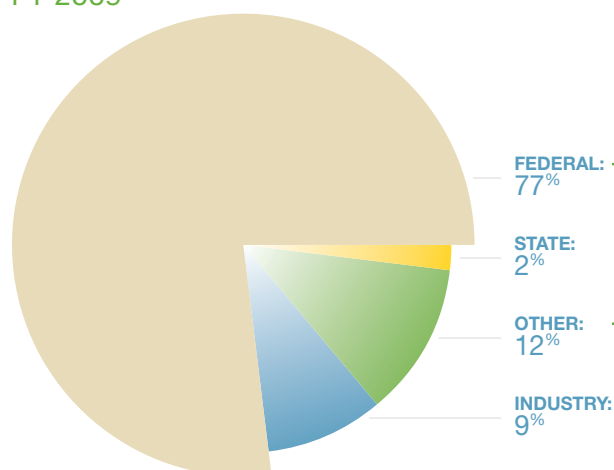


## NATIONAL INSTITUTES OF HEALTH AWARDS (TOTAL COSTS)



## SOURCES OF EXTERNAL FUNDING

FY 2009

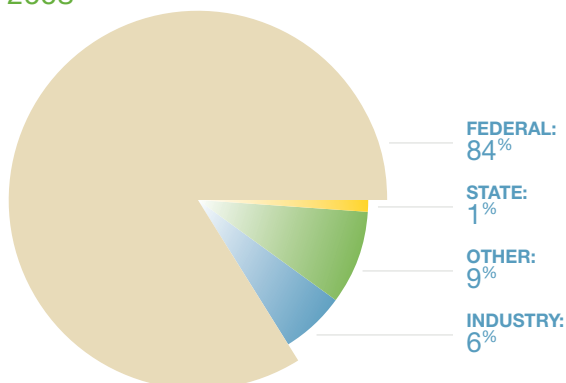


## SOURCES OF FEDERAL FUNDING

(FY 2009)

National Institutes of Health (NIH)	99,981,467
Health Resources and Services Administration (HRSA)	1,704,665
Centers for Disease Control (CDC)	1,621,069
Department of Defense (DoD)	1,142,414
Agency for Healthcare Research and Quality (AHRQ)	999,821
Administration on Developmental Disabilities (ADD)	417,231
National Science Foundation (NSF)	314,328
Department of Education (DoE)	146,762
Substance Abuse & Mental Health Service Administration (SAMHSA)	123,330
Department of Labor (DoL)	94,820
Environmental Protection Agency (EPA)	46,200
Social Security Administration (SSA)	25,000
<b>TOTAL</b>	<b>106,617,107</b>

FY 2008



## SOURCES OF OTHER AGENCY FUNDING

(FY 2009)

Gates Foundation	1,813,359
American Heart Association	1,119,700
Cystic Fibrosis Foundation	882,488
University of Cincinnati	793,260
The American Board of Medical Specialties Research & Education Foundation	522,805
Robert Wood Johnson Foundation	448,606
Juvenile Diabetes Research Foundation	432,296
American Cancer Society	410,707
Crohn's & Colitis Foundation of America	333,000
March of Dimes	329,748
Foundation LeDucq	326,242
Charlotte R. Schmidlapp Fund	300,000
First 5 LA Commission	300,000
Miscellaneous Other (92)	7,806,901
<b>TOTAL</b>	<b>15,819,112</b>



# Faculty/Clinical Statistics

## DEPARTMENT OF PEDIATRICS AND RESEARCH FOUNDATION FACULTY

### TOTAL FACULTY MEMBERS

**462**

Full-time/primary  
appointment in Pediatrics

**42**

Part-time/primary  
appointment in Pediatrics

During fiscal year 2009:

**64** new faculty members  
were appointed

**27** departed  
(including retirement)

### PEDIATRIC FACULTY BY RANK AND TRACK

	CLINICAL	ADJUNCT (PART-TIME)	RESEARCH	FIELD SERVICE	TENURE TRACK	TENURED
<b>INSTRUCTOR</b>	9	1	18	4	0	0
<b>ASST. PROFESSOR</b>	92	12	65	6	24	0
<b>ASSOC. PROFESSOR</b>	60	15	19	4	8	29
<b>PROFESSOR</b>	29	14	2	3	0	90
<b>TOTAL</b>	<b>190</b>	<b>42</b>	<b>104</b>	<b>17</b>	<b>32</b>	<b>119</b>

### GENDER DISTRIBUTION (INCLUDES FULL-TIME AND PART-TIME FACULTY)

	FULL-TIME	PART-TIME	TOTAL
<b>MEN</b>	273	25	<b>298</b>
<b>WOMEN</b>	189	17	<b>206</b>

### MINORITY DISTRIBUTION

(INCLUDES FULL-TIME AND PART-TIME FACULTY)

	MEN		WOMEN	
	FULL-TIME	PART-TIME	FULL-TIME	PART-TIME
<b>BLACK</b>	4	0	4	0
<b>HISPANIC</b>	5	0	2	0
<b>ASIAN</b>	33	1	16	1
<b>TOTAL</b>	<b>42</b>	<b>1</b>	<b>22</b>	<b>1</b>



## CLINICAL ACTIVITY

### ADMISSIONS

(EXCLUDES SHORT STAY ADMITS)

Medical	12,673
Surgical (I/P Surgeries)	5,667
23-Hour Admissions	12,877

### OUTPATIENT VISITS

Surgical procedures	24,669
Emergency Room Visits	114,985
Primary Care (PPC) Burnet, Hopple & Batesville	58,944
Sub-specialty Care Burnet	381,347
Outpatient Liberty	83,887
Outpatient Mason	92,000
Outpatient Anderson	53,045
Outpatient Eastgate	22,882
Outpatient Harrison	16,580
Outpatient Fairfield	53,766
Outpatient Kentucky	45,684
Outpatient West Chester	1,364
Outpatient Kenwood	1,070
Outpatient Drake	15,235

## TRAINING

### STUDENTS

Junior Medical Students in the Pediatric Clerkship	156
Senior Medical Students in Pediatric Training	20
Senior Medical Students in Medicine/Pediatric Training	4
Triple Board	0
Pediatrics/Physical Medicine and Rehabilitation	0
Pediatrics/Neurology	0
Pediatrics/Genetics	1

### RESIDENTS

Pediatrics	106
Medicine/Pediatrics	28
Pediatric Physical Medicine and Rehabilitation	6
Dental	10
Psychology	4
Psychiatry/Child Psychiatry/Pediatrics	13
Human Genetics/Pediatrics	3
Neuro/Pediatrics	17
Dermatology	1
Anesthesia	6
Surgery (includes General Surgery, Cardiothoracic, Neurosurgery, Otolaryngology, Ophthalmology, Plastic, Orthopedic & Urology)	87 rotating
Radiology	43 rotating

### PEDIATRIC HOUSE STAFF RECRUITMENT 2008

Pediatric Candidates Interviewed	306
Medicine/Pediatric Candidates Interviewed	54
PM&R Candidates Interviewed	11
Psychiatry/Child Psychiatry/Pediatrics Interviewed	21
HG Pediatrics Interviewed	6
Neuro/Pediatrics Interviewed	16

## Faculty/Clinical Statistics

TRAINING *continued*

## FELLOWS

Adolescent Medicine	4	Neurophysiology	0
+ Pediatric/Adolescent Gynecology	1	Neurosurgery	1
Allergy/Immunology	3	Ophthalmology	1
Anesthesia	8	Orthopedics	2
Cardiology	9	+ Orthopedic Spine Surgery	2
+ Fetal Cardiology	1	Otolaryngology	6
Child Abuse	1	Pathology	2
Critical Care	11	Pharmacology	0
Dental	0	Psychiatry	6
Developmental Disabilities	3	Psychology	14
Emergency Medicine	9	Pulmonary	3
Endocrinology	7	Quality Scholars in Transforming Health Care	2
Gastroenterology	12	Radiology	7
+ Pediatric Transplant Hepatology	1	+ Body MRI	2
General Pediatrics	0	+ Neuroradiology	1
Hematology/Oncology	12	Rehabilitation Medicine	2
Infectious Disease	3	Rheumatology	6
Medical Biochemical Genetics	1	Sleep Disorder Medicine	2
Medical Genetics	1	Sports Medicine	2
Neonatology	12	Surgery	2
Nephrology	6	+ Colorectal Surgery	1
Neurology	0	+ Fetal Surgery	0
+ Movement Disorders	1	+ Trauma Surgery	1
+ Pediatric Epilepsy	2	+ Vascular Anomalies	1
+ Pediatric Neuromuscular	1	Urology	3

TOTAL, CLINICAL FELLOWS: **178**TOTAL, RESEARCH POSTDOCTORAL FELLOWS: **118**

## PUBLICATIONS

Peer-reviewed articles	979
Other articles	85
Books (edited or authored)	6
Chapters of books	72
Online site contributions	4
Pamphlets	1
<b>TOTAL, FY 2009</b>	<b>1147</b>

## SUMMER RESEARCH PROGRAMS

High school interns	17
Undergraduate students	91
Medical students	24

## PROCTER SCHOLARS

	NAME	DISCIPLINE	PROJECT
THIRD YEAR	<b>Brad Dixon, MD</b>	Nephrology	Study genomic instability, DNA damage response, and cell cycle regulation in the hyperosmolar conditions of urine
	<b>Adam Spanier, MD</b>	General Pediatrics	Determine longitudinal relationship of environmental exposures with eNO levels
SECOND YEAR	<b>Noah Hillman, MD</b>	Neonatology	Lung development and lung injury with the goal of understanding components of neonatal resuscitation
	<b>Trent Hummel, MD</b>	Hematology/Oncology	Correlate serum proteins with tumor burden in NF1 patients
FIRST YEAR	<b>Kimberly Czech, MD, PhD</b>	Nephrology	Altered gene expression in pediatric patients with focal segmental glomerulosclerosis (FSGS)
	<b>Alan Kenny, MD, PhD</b>	Neonatology	Characterize mechanisms regulating foregut organ induction and identify genes induced in the endoderm in response to mesodermal signaling

# Gut Instinct

*Research and clinical achievements demonstrate how this division earned its top national ranking*

Chase Del Ferraro shows no signs of ever having faced life-threatening illness. The lively, curious 3-year-old holds his own as one of triplet brothers. But just one year into his life, his fate hung in the balance while he waited for a liver. He had a condition known as biliary atresia, where the ducts that drain bile from the liver to the intestine are obstructed. A Kasai procedure at 6 weeks of age postponed his need for a liver transplant for a while, but when his condition started to deteriorate, Chase was brought to Cincinnati Children's for evaluation. He entered our pre-transplant clinic and went on the liver transplant list at the age of 5 months. He received a new liver at 13 months, and he hasn't stopped since.

Ensuring happy endings like Chase's is the goal of the research and clinical advances being made in the Division of Gastroenterology, Hepatology and Nutrition. The work being done here earned the division its number one ranking in the *U.S. News & World Report* 2009 edition of America's Best Children's Hospitals.

The Liver Transplant program is a critical component of the division's comprehensive clinical and research efforts. Ours is one of just a few pediatric centers nationally that performs a high volume of liver transplants – 25 to 30 a year. The program's successful track record attracts referrals from around the country and the world, says Kathleen Campbell, MD, its medical director. She credits that in large part to the science behind our clinical approaches.

"A core of our mission is to identify gaps in knowledge and to conduct research to close those gaps," Campbell says.

## Good Starts, Better Finish

One gap that children needing liver transplants have experienced has been rapid deterioration in their health while they await a liver. Our program has addressed that with a pre-transplant clinic that involves specialists in a variety of disciplines, says Jorge Bezerra, MD, a researcher and gastroenterologist in the division.

"I don't know of any other hospital with a pre-transplant clinic devoted exclusively to children with liver disease," he says. "While children are waiting for a transplant, they are seen by a team of specialists who aggressively manage all aspects of their health in a coordinated way. The team works to optimize the nutritional state and to diagnose and treat promptly any complication of the liver disease. Keeping children as healthy as possible before transplant positively affects their entire transplant course."



## Understanding Biliary Atresia

Bezerra has a special interest in biliary atresia, a condition where the bile ducts don't form or work properly. Although a rare condition, it is the number one reason why children need liver transplants, and it continues to perplex scientists.

"No one knows what causes it," Bezerra says. "We are trying to discover the mechanisms that destroy the bile ducts so we can identify treatments and rescue patients before they need liver transplantation."

Bezerra and his team are also trying to identify how to analyze a child's liver at the time of diagnosis to more accurately predict the course of the disease and response to treatment.

## Probing the Cause of Liver Tumors

Another category of children who may require liver transplants are those who have liver tumors. Hepatoblastomas are the most commonly occurring liver tumors in children, but they are not well understood. Researcher Mike Leonis, MD, PhD, is working to change that.

The tumors usually show up in children before age 4 or 5, but when and how they actually start is a mystery, he says.

"We don't know whether the tumor starts a couple months before presentation or whether it's present at birth and grows to the point where it is eventually detected," Leonis says.

Once it is detected, the tumor must be treated aggressively. Children undergo multiple courses of chemotherapy followed by surgical resection of the tumor. In cases where the tumor can't be safely operated on, the child must have a liver transplant.

Leonis wants to know what causes these tumors to grow in the first place. He is studying the involvement of a receptor tyrosine kinase named RON (recepteur d'origine nantais) in that process.

After examining 45 tumor specimens from children with hepatoblastoma, he found that more than half had an excess of RON receptor expression. The next question was whether a surplus of the receptor actually caused the tumor, or was it simply a byproduct of having the tumor. So Leonis and his team developed a transgenic mouse model and over-expressed the RON receptor in the mice livers.

"The mice spontaneously generated liver microtumors, tiny tumor nodules with the histologic features of hepatoblastoma," Leonis says. "Our hypothesis is that over-expression or activation of the receptor leads to or contributes to liver tumor formation or progression."

Leonis hopes now to identify the signaling pathways activated in human hepatoblastomas so that they can tailor drug treatments to block the pathways and halt the growth of liver tumors in their tracks.

## No More Anti-Rejection Drugs?

While liver transplants are life-saving, children who have them must take immunosuppressive drugs for the rest of their lives, and many suffer troubling side effects. But there is research under way that could change that for some kids, says Campbell.

"There is the possibility that we might be able to wean some children from these medications in the future," she says. "Data from centers in the U.S. and other countries suggests that a subset of children can have immunosuppressive medications discontinued and live with their transplanted liver without rejection."

Cincinnati Children's is one of a group of centers recently funded by the NIH to prepare a clinical trial to investigate this. John Bucuvalas, MD, a pediatric hepatologist and researcher, is a co-principal investigator of the study, which aims to identify the children for whom withdrawal from immunosuppressive medication is a possibility. Beyond that, the study will include investigations into the molecular reasons for why one child can live without the medication and another can't.

## Care and Feeding When Intestines Fail

Most of our nutrients are absorbed through the intestines. So when the intestines fail, the body can't grow and thrive. Adam Mezoff, MD, is investigating the best ways to get nutrition to children whose intestines don't work properly.

Mezoff, a pediatric gastroenterologist, is focusing on children with gastroschisis, in which a baby's bowel develops outside the abdominal cavity, and with necrotizing enterocolitis (NEC), a condition seen most often in premature infants.





*From left: Drs. Jorge Bezerra, Mike Leonis, Kathleen Campbell and Adam Mezoff.*

In both instances, surgery may be needed to correct the abnormality or to remove the portion of bowel that is affected, resulting in “short gut” syndrome. The children typically need intravenous nutritional supplementation, which, while it helps them survive and grow, is not without problems, Mezoff says.

“The parenteral nutrition we use is a double-edged sword. While it is life-sustaining, it can be life-threatening because the longer you’re on it, the greater likelihood you’ll get liver damage,” he says.

Premature infants seem particularly susceptible to the harmful effects of intravenous (IV) feedings, he says, and IV nutrition is one of the most common reasons these children require a liver transplant. Some researchers suspect that the byproducts of the nutritional formula may be causing the problem.

“To make nutrition in a form that your body can accept by vein, you can’t just grind up potatoes and put them in there,” Mezoff says. “These are chemical things, and because of that, they affect the body in different ways.”

One of the components of the formula is derived from soy and could be contributing to the problem, he says. Other centers in the U.S. are investigating options in use in Europe that might alleviate the problem.

The goal, Mezoff says, is to use parenteral nutrition for as short a time as possible. His group is about to start a research project to help define where that point is.

“We’re looking at clinical factors that help us decide when we’ve made enough progress in feeding. We don’t know exactly at what point that happens, but let’s say that once you get somebody taking in 50 percent of their calories by their intestine, their liver disease will slowly stop. And if you get them above there, it will start repairing itself.”

## Simple Test Diagnoses Liver Disease



A simple blood test can quickly diagnose the five most common causes of inheritable liver diseases, thanks to a method developed by Jorge Bezerra, MD, of the Division of Gastroenterology, Hepatology and Nutrition. Bezerra developed the “jaundice chip” test in conjunction with the National Institutes of Health. The test is now available for clinical use.





*From left: Drs. Lee “Ted” Denson and Bruce Trapnell.*

### What Stays In, What Comes Out

Another component of Mezoff’s research will measure the intestine’s ability to absorb the nutrients in food. Called “bomb calorimetry,” it involves literally blowing up a sample of a child’s stool to measure heat and calories, thereby learning how much nutrition they are absorbing. Right now, Mezoff says, the only way doctors can measure this is to wait and watch if the child grows.

“We think this will offer us a much better way to design a child’s nutrition,” he says. “Based on how many calories are coming out, we can say ‘you’re absorbing this percentage of nutrients,’” Mezoff says. “So we may be able to say that with this formula, you’re absorbing 70 percent, with this formula, you’re absorbing 90 percent – you’ll do better on the 90 percent formula.”

### Predicting the Future

For children with inflammatory bowel disease – Crohn’s disease and ulcerative colitis – the course of treatment is often a guessing game. Doctors struggle to match the right medication to the illness as early as possible to avoid making a difficult condition even more troublesome.

Lee “Ted” Denson, MD, sees every day what children who suffer from these diseases go through, both as a result of their illness and from the effects of treatment. With the help of a recent NIH grant, he may be able to ease the way.

Cincinnati Children’s is one of two pediatric centers in the multi-center study looking at whether patients with IBD create antibodies that neutralize one of the body’s immune proteins, GM-CSF. GM-CSF is critical to controlling bacteria in the intestines and to managing bacterial infections.

Denson is collaborating with Cincinnati Children’s pulmonary biologist Bruce Trapnell, PhD, in the study. The two have patented the idea that IBD patients with higher levels of GM-CSF-blocking antibodies may be less able to control bacteria. They are also developing a blood test to measure the level of the antibody in patients in order to determine the best course of treatment.

“If patients have a level of this antibody above a certain point, they are much more likely to have a more aggressive form of disease that does not respond to our standard medicines and that will be more likely to require early surgery and frequent hospitalizations,” Denson says. “We think we can use a predictive blood test to help doctors determine whether patients are going to have a more complicated course. It may also ultimately point to a different type of therapy for those patients.”

One therapy option they are looking at, says Denson, is whether GM-CSF itself could be given as a medication to help patients with more of the antibody.

“We’re working with the pharmaceutical company that currently has the rights to GM-CSF to collaborate on whether we should give it as a medication to patients with high levels of this antibody,” he says. “It would be a more personalized type of medicine.”

Denson and Trapnell published their findings in *Gastroenterology* this year, and have already started receiving blood samples from doctors at other institutions who are interested in the level of antibodies their patients have.

### The More Information, the Better

Because the total number of children needing liver transplants remains relatively small, the division has joined with other liver transplantation centers to collect and share data on these patients. The Studies in Pediatric Liver Transplantation (SPLIT) study group is a collaboration among 40 centers throughout the United States and Canada that collects and shares data on children from the time that they are listed for liver transplant through their post-transplant course up to 18 years or older. The registry has been capturing data on children who have had liver transplants for the past 15 years.

We also participate as one of the centers involved in a functional outcome study in pediatric liver transplant, an ancillary study of SPLIT, which has information on more than 500 children who've received liver transplants.

"This study will help us define what are the complications when we give a child like Chase Del Ferraro a liver at an early age," Campbell says. "Does this have implications for how he's going to do in school or what kind of job he's going to be able to get, or how he's going to feel about himself? I think it will provide us with much-needed information on how we can help these kids 10 years after transplant to have normal, healthy lives and excellent functional outcomes."

"When we give a child...a liver at an early age, does this have implications for how he's going to do in school or what kind of job he's going to be able to get, or how he's going to feel about himself?"



# When Good Systems Go Bad

## *The Tricky Science of Immunology*

Simply catching her breath has never come easily to Vantrese Siler. As a newborn, she was in and out of the hospital because of coughing, wheezing and sluggishness that worried her mother. Her family and doctors first thought she had pneumonia. But her symptoms persisted.

Vantrese was diagnosed with asthma before she could even pronounce it. Ever since she can remember, it has been a part of her life. Grass, dust or even a change in the weather can trigger shortness of breath and tightness in her chest. Severe flare-ups often send the 17-year-old and her family back to Cincinnati Children's, where she gets help managing the condition she expects will follow her through adulthood.

She carries an inhaler wherever she goes. Lately, that's to track and basketball practices at her high school, where Vantrese is a senior. Her experience at Cincinnati Children's has made a lasting impression. It's part of the reason she's focused on becoming a nurse. "I want to deliver babies," she says. And she wants to help find a cure for kids who have asthma.

### **Investigating Immunology**

Although the immune system has long been recognized for protecting us from infections with viruses such as the flu and HIV, when it does not work properly, it can actually cause diseases such as asthma, diabetes, arthritis, cancer and Crohn's disease.

In these conditions, the immune system views an individual's cells and tissues as foreign invaders or mounts abnormal responses to harmless substances we encounter every day, such as pollens and certain foods.

Cincinnati Children's studies what causes these diseases in several divisions devoted to the study of the immune system, including Molecular Immunology, Immunobiology, and more recently, Asthma Research.

### **Advancing Asthma Research**

Gurjit "Neeru" Khurana Hershey, MD, PhD, does research every day to help kids like Vantrese Siler live normal lives despite severe asthma.

There is a great need for advanced asthma research. It's the most common chronic disease in childhood and the most common reason for pediatric hospital admission.

"One in eight kids has asthma," says Khurana Hershey, director of the Division of Asthma Research. "The public health burden is huge. Two-thirds of all children with asthma report an attack in the last year, so there is a lot of room for improvement in managing this disease. We are very







*Dr. Gurjit Khurana Hershey*

interested in asthma, and we research all aspects of it.”

Khurana Hershey and other investigators have been keeping tabs on nearly 800 Cincinnati kids since birth to identify what leads some children to have asthma. The children in that study are now 7 years old and have given investigators clues about the connection between asthma and childhood allergies and eczema.

Khurana Hershey is also the lead investigator in one of only a few asthma centers in the country funded by the National Institutes of Health. As part of this center, she is working to identify which genes in the epithelium promote asthma and allergic inflammation.

Asthma is caused by both genetic and environmental factors. Epithelial cells are the first cells in the body to encounter an environmental exposure.

“Epithelial cells are the first cells exposed to environmental triggers at the surface,” she says. “Whether the allergic process is affecting the lung, the skin or the gut, the epithelial cell is really important.”

Although epithelial cells are critical to developing asthma and asthma symptoms, there are no therapies that specifically target them.

“Despite the fact that asthma’s been around for so long, we have very few medications to treat it, and none of them is focused on the epithelial cells, which is where it starts,” Khurana Hershey says.

In fact, she says, the epithelial genes and factors that promote asthma are largely unknown.

This year, her research team identified a new pathway in the epithelial cells that plays a critical role in regulating mucus production in asthma. Many children who have asthma

produce too much mucus and their airways get plugged, Khurana Hershey says. Identifying genes that regulate mucus may provide a new target for intervention in asthma.

“We’re hoping that our research will identify pathways in the epithelium that can be targeted to help combat asthma and allergic disease.”

### **Driven by Dust Mites**

Marsha Wills-Karp, PhD, director of the Division of Immunobiology, has earned international recognition for her asthma research. She and her colleagues were among the first to report in the early 1990s that T cells were important drivers of inflammatory response that cause difficulty in breathing in asthmatics.

They went on to identify the factor made by these T cells that causes these changes in asthmatics’ ability to breathe, called IL-13, in a landmark paper reported in *Science* in December 1998.

More recently, Wills-Karp’s lab studied the most common triggers of asthma – house dust mites, which live in bedding and carpets in our homes. They identified a specific component of the house dust mite that is recognized by epithelial cells.

Their work, published in the March issue of *The Journal of Allergy and Clinical Immunology*, describes a novel pattern-recognition pathway through which the dust mite triggers immune responses.

They found that dust mites stimulate the respiratory epithelium, which causes a rapid secretion of CCL20, a protein that specifically recruits dendritic cells to the lung, which directly activate T cells. That kind of response doesn’t happen with

other aeroallergens such as ragweed or cockroaches. Wills-Karp's group found the response is dependent on a novel carbohydrate referred to as a  $\beta$ -glucan found in dust mites.

This is the first evidence that allergens elicit innate immune responses via activation of specific receptor pathways at the surface of the airways, Wills-Karp says.

The finding is significant because it could lead to a better understanding of the way the airway epithelium recognizes dust mites and could help determine how to target therapies to decrease immune allergic responses.

"The most important implication of this study is that we might be able to stop the process before it progresses by inhibiting recognition of the dust mite early in life," Wills-Karp says. "This could prevent immune responses that cause Vantrese's asthma."

### Tricky Triggers

Christopher Karp, MD, director of the Division of Molecular Immunology, knew household dust mites could trigger asthma attacks. Now he and other researchers know why the allergic response to dust mites is so strong.

Karp was the lead author in research published in the January issue of *Nature* that explained the main allergen in house dust mite feces, called Der p 2, caused the immune system to mount a response similar to that caused by a bacterial infection. The overly active immune system response to the lipid-binding protein Der p 2 caused asthma-like attacks in tests on mice that were susceptible to the respiratory condition.

Before this study, it was unclear why the immune system recognized some proteins as allergens and ignored others,

They identified  
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epithelial cells.



*Drs. Marsha Wills-Karp  
and Christopher Karp.*



*Drs. Daniel Lovell and Kimberly Risma.*

Karp says. But finding the mechanism underlying immune recognition of Der p 2 helps explain what activates the immune system.

“Finding why a particular protein is recognized as an allergen gives both insight into how the allergic process comes about and also potential ways to intervene.”

### Attacking Arthritis

The same immune system overactivity that can cause Vantrese Siler’s asthma can flare up in the form of Juvenile Idiopathic Arthritis (JIA), the most common form of chronic arthritis in childhood.

Advances made in clinical trials led by investigators at Cincinnati Children’s this year led to two new FDA-approved drugs – abatacept and adalimumab – to treat JIA, says Daniel J. Lovell, MD, MPH, the Joseph E. Levinson professor of pediatrics and the interim director of the Division of Rheumatology.

“In 2009, we had the results of two large international pivotal trials published in leading journals – the *New England Journal of Medicine* and *Lancet*,” Lovell says. “These clinical trials demonstrated the efficacy and safety of these biologic treatments for children with JIA.”

Abatacept (Orencia™) blocks the activation of T cells, which are critical to the development of the inflammation seen in arthritis. So abatacept has the potential to minimize or prevent the development of the arthritis in the first place, Lovell says. “In this trial, it was also shown to be very

effective and safe in controlling the inflammation in children with longstanding arthritis.”

Adalimumab (Humira™) works by blocking tumor necrosis (TNF). TNF is known to be a major factor in the inflammation of arthritis. Several other biologics that block TNF have been approved for treatment. However, adalimumab may be better for some patients, Lovell says. “It can very effectively suppress the inflammation in JIA with patients getting a subcutaneous injection only once every two weeks instead of twice a week, or intravenous infusions as is required with other TNF inhibitors,” he says.

“The drugs represent a unique treatment option that show benefit in kids who had failed the other treatments,” Lovell says. As a result of these studies, both treatments have been approved by the FDA for use in children with JIA and are in widespread use.

### Balancing Act

The body’s immune system has to strike the right balance to function properly. If the immune system is overactive, it can result in inflammatory diseases. If it’s not active enough, the body ends up with infections. That’s where Kimberly A. Risma, MD, PhD, steps in. She studies immunodeficiencies.

Risma focuses on a group of patients who have an immunodeficiency called hemophagocytic lymphohistiocytosis (HLH), a life-threatening disease caused by immune cells that accumulate to fight infection but in reality can’t kill anything.



“Despite the fact that asthma’s been around for so long, we have very few medications to treat it, and none of them is focused on the epithelial cells, which is where it starts.”

A genetic defect in children who have HLH keeps their immune systems from returning to a resting state. Instead, their inflammatory reaction to germs never gets turned off. Their uncontrolled cells go around swallowing everything, but they can’t kill anything. A child could go from having a prolonged fever to needing a bone marrow transplant.

While HLH is rare, Cincinnati Children’s treats a large population of children with HLH, Risma says, and is on the forefront of research. Risma credits that to the leadership of Alexandra “Lisa” H. Filipovich, MD, director of the Immune Deficiency and Histiocytosis Program. Filipovich has recruited several researchers to study HLH and related disorders.

“We have a real niche here,” says Risma, who won this year’s Charlotte R. Schmidlapp Women Scholars award.

“My role is determining how defective killing by immune cells causes HLH,” she says. She wants to understand if milder defects in the genes associated with HLH lead to the development of cancer or other inflammatory conditions.

Although immune deficiencies are rare diseases, Risma says, the knowledge gained from studying “holes” in the immune system often leads to insight into common immune-based diseases. That inability to regulate immune responses can lead to everything from severe allergic conditions like Vantrese Siler’s asthma to autoimmune conditions like arthritis. The more investigators understand, the better they can improve the outcomes, whether in the rarest or most common of cases.







# Outsmarting a Killer

## *Breakthroughs in Cancer Research*

In February 2007, Hannah Rumping's mother took her to the doctor because she thought her 2-year-old had a cold. Hannah was running a fever and had a rash on her legs. The pediatrician sent her to Cincinnati Children's for a blood test. That same day, the results came back: Hannah had leukemia. A week after her initial diagnosis, the news was even worse. Genetic testing confirmed it was a rare type, near-haploid acute lymphocytic leukemia.

Her only hope for survival was a bone marrow transplant. But given her racial makeup (her mom is half Chinese and her dad is Caucasian), her pool of potential matches was limited. Hannah's parents, Mei Ling and Tom Rumping, organized donor drives and prayed for a miracle. Three months later, a match came through and Hannah had her transplant. After more than 170 nights in the hospital and countless visits for check-ups and physical therapy, the Rumpings took Hannah home with a success story. Their 4-year-old daughter remains cancer-free.

Researchers in the Division of Bone Marrow Transplantation and Immunodeficiency at Cincinnati Children's are delighted by outcomes like Hannah Rumping's. But their joy is tempered by the nagging reality that there is still much to learn.

### **Genes and Outcome**

For example, asks Stella Davies, MBBS, PhD, MRCP, what role does genetic makeup play in the outcome of treatment? Davies cares for children with acute myeloid leukemia (AML), and she wants to know why some children do well on drug therapy and others don't.

The fact that there are treatments at all for these children is a major advance. As recently as 30 years ago, the diagnosis of AML was a death sentence.

"Every child with myeloid leukemia would die - no question about it," says Davies, who directs the Division of Bone Marrow Transplantation and Immunodeficiency at Cincinnati Children's. "Parents were recommended to take their children home, and the children were lost."

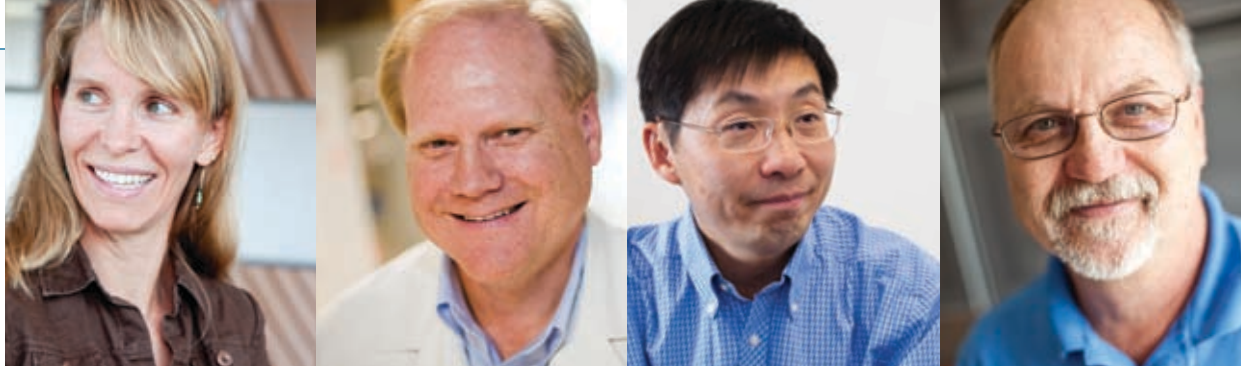
In the rush to find treatments, Davies says, doctors tried "a little bit of this and a little bit of that," with less than satisfactory results. It wasn't until they developed organized clinical trials of drug treatments that things started to turn around.

### **A Good Start**

Those clinical trials have provided what Davies sees as some major advances in treatments. "It's been a triumph of discipline and organization," she says. "When every child receives the same treatment, you start to figure out what works and what doesn't."

What works is that many more children survive AML. But Davies says science is still a long way from where it should be.





From left: Drs. Susanne Wells, Timothy Cripe, Yi Zheng and Clinton Joiner.

"We've figured it out so that 60 percent of children are cured, 25 percent will relapse, and about 10 to 15 percent will die of the toxicity of their therapy," she says. What puzzles researchers, Davies says, is that the disease is the same, the treatment the same, yet the outcomes are vastly different. Why?

"What's different are the children," Davies says. "So my lab is trying to figure out genetically what's different in the children in how they handle the drugs – what makes the difference between just right, too much and too little."

Her hope is that research leads to better screening before starting treatment and to appropriate adjustments instead of giving every child the same dose of drugs and chemotherapy.

### Miracle Matches

In a related area of research, Davies is exploring the role of donor genes in how children fare after bone marrow transplant. To do this, she is focusing on her sickest patients, children with AML who are unlikely prospects for cure.

"We can pick them out by looking at the genetics of the leukemia cells before we start," she says. She is participating in a study with St. Jude Children's Research Hospital looking at donors who have a special genotype for killer immunoglobulin-like receptor (KIR), which might improve their ability to fight the leukemia.

"We think KIR genotyping might allow us to pick out the donors that allow refractory AML to clear after transplant and stay away," Davies says. "It's a miracle when this happens."

She witnessed that miracle in a patient recently, a teenage boy whose AML had been unresponsive to treatment.

"In such a case, you can go home and say, 'I'm going to live out my last days in peace,' or you can go for the Hail Mary pass," she says. "We decided to go for the Hail Mary

pass, got a donor ready in two weeks and went straight to transplant. And he never looked back."

The boy's leukemia went away. Nearly three years later, he's still doing well. Davies attributes the outcome to the boy's donor having the KIR genotype, which heightened the donor cells' ability to suppress the leukemia.

"Before, we just were picking randomly because we didn't know if it mattered," she says. "This is a study to figure out if it does matter."

### How Do Tumors Form?

Susanne Wells, PhD, may be one of the few people at Cincinnati Children's trying to get tumors to grow instead of shrink.

Wells, a researcher in the Division of Hematology/Oncology, generates tumor models in her laboratory and makes them multiply. Such research could help patients like Hannah Rumping by figuring out how cancers form and progress.

Wells' research focuses on the human papillomavirus (HPV) – a sexually transmitted infection that remains the leading cancer killer in women in non-industrialized nations. Wells wants to know how HPV can amplify itself in an infected cell, how it makes more of its own DNA and proteins, how it can drive particles to then infect neighboring cells and how it drives tumor development.

She also is interested in studying the devastating disease Fanconi anemia (FA), an inherited anemia that leads to bone marrow failure and cancer susceptibility. Wells is using skin samples that have mutations in Fanconi anemia genes to try to figure out why those patients have up to an 800-fold increased rate of head and neck cancer.

"This is really looming over them all throughout life," she says. "We don't really know why these cancers appear so early in life, why they're so frequent or why they're so aggressive."

She does know that these patients have fragile chromosomes and don't do well with conventional chemotherapy and radiation.

"So it's very important to find new, non-conventional ways of treating these patients," Wells says. "We're interested in how we can form a tumor that best mimics the patient's."

To do that, she takes patient skin samples to the laboratory to analyze their genetic make-up and then their ability to grow out of control. Her lab generates three-dimensional laboratory tumor systems both in plastic dishes and in animals. Then they use the resulting laboratory tumors to test new drugs that can safely and effectively kill the cancer cells.

Eventually, she says, finding those answers could lead to cures.

"Each patient is different, and each tumor is different," she says. "In the end, these models might help us tailor treatments for those patients who donated the skin samples in the first place."

### Killing Tumors with Viruses

Other researchers in the Division of Hematology/Oncology collaborate to better understand the biology of cancer. Not only do they want to know how cancer forms and spreads, but they also want to find out how to stop it.

Timothy P. Cripe, MD, PhD, tries to kill tumors with viruses that seem to be drawn to tumor cells. The viruses replicate and amplify in the tumor cells, destroying them.

"My primary research effort is in developing the use of viruses as a new cancer therapy," says Cripe, a clinician and researcher in the division and co-medical director of the Office for Clinical and Translational Research. "To do that, we need to understand the biology of cancer and how viruses infect those cancers. We also need to understand effects of other treatments, such as small-molecule drugs and other inhibitors that might be useful in combination with the virus therapy."

### Putting the Findings to Work

This year, Cincinnati Children's plans to open two clinical trials of virus therapies.

"We'd be the first pediatric hospital using this to target pediatric diseases," Cripe says. "It's been known for a long time that tumors are a rich culture media for viruses to grow, and part of what viruses do is destroy cells. So it's a way to utilize their cell-destroying capability to kill the tumor cells."

Investigators have been doing this kind of research in mice, but the Food and Drug Administration recently gave Cincinnati Children's the go-ahead for the clinical trials in humans. Once the funding is in place, researchers will launch the research, Cripe says.

"Translating things to the clinic is really where we're at," he says. "Getting this approved was our biggest highlight this year."

### New Ways of Targeting Cancer

To save the lives of children such as Hannah Rumping, researchers are working on devising new ways of targeting cancer, says Yi Zheng, PhD, director of the Division of Experimental Hematology and Cancer Biology.

Finding a small pool of "bad apple" cancer cells and surgically removing them is like cutting grass, says Zheng, associate director of the Cancer and Blood Diseases Institute. "It does not remove the roots."

To get at cancer's underlying causes, Zheng's lab is trying to find the unique features of cancer stem cells and effective ways to target them.

"The hope is, if you target this unique population, you will someday be able to eradicate it," he says. "So that's revolutionary."

His lab has identified a small-molecule inhibitor that targets a key signaling pathway shared by cancer stem cells in leukemia and lung cancer. Researchers have been working with mouse models to grow human cancer, suppress and kill cancer stem cells and test therapies that might someday be used in people.

The goal is close to Zheng's heart. His mother died of lung cancer two years ago. In addition to leukemia and brain



“It’s been a triumph of discipline and organization.  
When every child receives the same treatment, you  
start to figure out what works and what doesn’t.”

tumors, his lab has embarked on a project to identify, characterize and target the possible lung cancer-initiating cells. Not only is lung cancer deadly and still much of a mystery, but it’s closely associated with lung development, he says.

“It’s like the chicken and the egg,” he says. “Which cells will make up the healthy organs and which ones will develop cancer? Without knowing the first answer, we can’t know the second. So far in the preliminary study, we think there are certain cell types we find in human lung cancer, leukemia and brain tumors that are more potent in causing cancer than others.”

Although researchers would like to find a quick cure, Zheng says he doesn’t want to rush science.

“Eventually, we may know which children are more susceptible to cancer,” he says. “First, we must figure out what’s normal. Then we can begin to sort out how to avoid and attack what’s not.”

### Understanding Sickle Cell Disease

When researchers can identify when a “normal” function of the body fails, they can begin to figure out how to prevent it from happening.

That’s one aspect of the work of Clinton H. Joiner, MD, PhD, director of the Comprehensive Sickle Cell Center in the Division of Hematology/Oncology’s Blood Disease Center. Joiner, who was a red blood cell physiologist before he became a pediatrician, got interested in studying sickle cell disease because of his interest in red cell physiology. And that has led to research into what happens when “normal” goes haywire.

“It turns out, one of the pathological processes that goes on in sickle cell disease is a failure of the normal mechanism of volume regulation in cells,” he says.

It’s not something people often think about, Joiner says, but mammals have to regulate their cell volume, or they would swell up and burst. A sickle cell mutation interrupts that fundamental biological process. Instead of maintaining the correct volume, it gets dehydrated and shrinks.

“We’re focused specifically on a particular transport protein that is part of the whole volume regulation system in red cells,” Joiner says. “It’s called the potassium chloride cotransporter.”

It is responsible for regulating the cell’s salt and water content. In sickle cell disease, “it’s overly active,” Joiner says, “and we think that’s one of the reasons that the cells become dehydrated.”

His lab is trying to understand why that happens and whether they can do anything genetically to modify it. They’re also interested in exploring whether variations in these transport proteins could explain variations in the severity of the disease.

The major advancement so far is defining the abnormal regulation of the transporter in sickle red blood cells, he says. The next step will be to incorporate those findings into gene therapy approaches that could spur the development of drug treatment for sickle cell patients.

“We had to go back to the ‘normal’ situation to understand what ‘normal’ was before we could move forward,” Joiner says. “That’s what we’re working on right now – making sure we understand how the expression of these transporters is regulated in the normal cells.”



# Staying Ahead of Kidney Disease

## *Earlier Diagnosis, Better Treatment Spare Damage*

On a family trip when he was just a toddler, Preston Henson, now 3 years old, was infected with the *E. coli* bacterium. Difficult to diagnose, the infection quickly progressed to hemolytic uremic syndrome (HUS), a disease that destroys the red blood cells. Preston came to Cincinnati Children's in July 2008, where he underwent hemodialysis for a period of time. But the disease had caused so much damage to his kidneys that he will need a transplant. The family is preparing for Preston to receive one of his father's kidneys early next year.

As researchers at Cincinnati Children's discover more about the kidney's role as a powerful chemical factory, they're finding new ways to prevent kidney failure and the often life-threatening effects of kidney disease.

That's good news for the 5,000 to 7,000 children nationwide on dialysis and the more than 26 million Americans — one in nine adults — with chronic kidney disease.

### **Breakthrough Test Saves Kidney Function**

Using just a drop of blood or urine, a new bedside test developed at Cincinnati Children's can diagnose kidney failure in a few minutes. The compact, portable test kit can have a huge impact for newborns to senior citizens, says Prasad Devarajan, MD, lead investigator and director, Division of Nephrology and Hypertension.

"The current test for acute kidney injury requires one to three days after an injury to become positive. Even in that short timeframe, you can lose more than 50 percent of your kidney function," he says. "The new test measures an early diagnostic

biomarker to predict kidney dysfunction and its devastating clinical consequences within two hours of an injury."

Devarajan discovered that when the kidney is injured, it over-expresses the protein neutrophil gelatinase-associated lipocalin, or NGAL, as a normal stress response. When the new test detects high levels of NGAL, physicians can begin treatment immediately. They'll know the treatment is working if a retest shows NGAL levels decreasing.

With this information, Devarajan explains, doctors can better plan the patient's care — with better outcomes.

"For instance, we can start dialysis early, instead of waiting until it's too late. Or we may be able to prevent a patient from needing dialysis at all."

With the test that's currently in use, once kidney injury shows up, there is little more doctors can offer beyond supportive care and dialysis, Devarajan says, adding that the outcome from dialysis is poor. "That's why we still have the same number of people dying from kidney failure today as we did 50 years ago."





“If we can make the diagnosis early enough, we hope to reduce mortality from kidney disease significantly over the next 10 years.”

He is optimistic that the new method can change that. “If we can make the diagnosis early enough, we hope to reduce mortality from kidney disease significantly over the next 10 years.”

Another breakthrough use for the test will be to monitor side effects of new drugs in development.

“A large number of drugs approved by the Food and Drug Administration (FDA) in the past have turned out to cause kidney damage after we started using them on a community-wide basis,” says Devarajan. “Because this test is so sensitive, it can be used during the drug development process both by the pharmaceutical industry and the FDA to make sure new products don’t cause kidney damage.”

The test is already in use in Europe, Asia and Australia; FDA approval for use in the U.S. is expected within the coming year.

### Connections of the Heart

One of the side effects of Preston Henson’s kidney disease was severe hypertension and an enlarged heart. His doctors were able to diagnose and treat the hypertension quickly to prevent the progression of heart disease. But not all children with kidney disease are so fortunate, says nephrologist Mark Mitsnefes, MD.

“Most kids on dialysis survive into adulthood, but they often die in their 20s or 30s, apparently from accelerated heart disease,” Mitsnefes says. “Our goal is to discover how to delay and prevent heart disease in kids with chronic kidney disease by identifying abnormalities early, and finding and treating their risk factors.”

His team discovered that many children with mild kidney disease already have left ventricular hypertrophy, a known indicator of heart disease in adults. As a result, at diagnosis, children with kidney disease now routinely undergo echocardiography to see if the heart is enlarged.

As in adults, changes in the carotid artery also may indicate heart disease in these children. “Ultrasound of the carotid artery can reveal if there’s increased intima-media thickness, even in children with mild renal insufficiency,” Mitsnefes says.

He leads the cardiovascular arm of a National Institutes of Health multi-center study of 600 children with chronic kidney disease. Recently the group identified masked hypertension as a possible cause for heart enlargement. “When patients wore a blood pressure cuff for 24 hours — in addition to in-office measurement — many more were diagnosed with hypertension. This shows that we’re missing and undertreating high blood pressure,” Mitsnefes explains. “This research can make a real impact on children by improving treatment and prolonging their lives.”

A report on the study, “Masked Hypertension and Associated Left Ventricular Hypertrophy in Children with Chronic Kidney Disease (CKD),” has been accepted for publication in the *Journal of the American Society of Nephrology*.

### The End is Just the Beginning

Beginning with the end in mind drives the research of nephrologist Larry Patterson, MD. He is studying how kidney development ends, a brand new area of embryonic

*From left: Drs. Prasad Devarajan, Mark Mitsnefes, Jens Goebel and Larry Patterson.*



development research. “If we understand how and why the kidney stops developing, eventually we will find ways to control its growth when development goes awry,” he explains.

A mature kidney can have 250,000 to 1 million nephrons, or filtering units. “Within this range there is a relationship between the number of nephrons and blood pressure, with hypertension developing in people who have a lower number. Also, people who have a low number are more susceptible to kidney diseases. To help prevent these conditions, we hope to be able to intervene early and promote kidney growth in those who have poor growth or poor potential for growth,” Patterson says.

His work in animal models will use genetic and chemical studies to dissect what controls growth of a particular cell type, what determines the organ’s size and proportion, and why growth stops. “By understanding the end, we’ll learn more about earlier events in development. We hope our findings can also be applied to other organ systems.”

### **Making Anti-Rejection Drugs Easier to Swallow**

If anti-rejection medications make a child feel bad, it’s likely the drugs won’t be taken as directed long-term, after a kidney transplant. Nephrologist Jens Goebel, MD, medical director of kidney transplantation, and his team have figured out a way to predict a child’s negative reaction to a commonly used anti-rejection medication, mycophenolate mofetil (MMF). The next step will be to use the information to prevent or minimize such reactions.

Goebel has already talked with Preston Henson’s mother about using the predictive method on Preston after his kidney transplant. “We would draw blood monthly and look at his genetic makeup so we can get the MMF dose at a level that reduces the risks of side effects without increasing the risk of rejection,” Goebel says.

MMF is associated with gastrointestinal and hematological toxicity. Reducing the dosage may minimize toxicity but can also increase the risk of rejection. Cincinnati Children’s already has adjusted protocols for administering MMF to reflect the latest findings on dosage and metabolism.

To understand how to use MMF more effectively, Goebel and fellow David Hooper, MD, together with the Cincinnati Children’s Division of Clinical Pharmacology directed by Alexander Vinks, PhD, PharmD, are leading a multi-center collaborative project through the Midwest Pediatric Nephrology Consortium.

“It’s clear now that the same size dose affects each body differently. As long as a child still needs anti-rejection medications long-term, our dream is to take a drop of blood before treatment begins, analyze it and produce an individualized prediction on the correct dose, rather than trying to minimize side effects later,” Goebel says. “We’re not there yet, but we’re getting there.”







# Kick-Starting Science

*Research flourishes at Cincinnati Children's thanks to programs that connect scientists with needed resources*

When Jennifer Patchell saw the X-rays of her daughter's spine, she thought the doctors had a mix-up. Surely her daughter's back couldn't be as bad as the X-ray. But there it was in black and white: Her daughter, Rachel Tracy, had severe scoliosis, an abnormal curvature of the spine that affects about 3 percent of children ages 10 to 16. Patchell wasn't sure what the diagnosis would mean for her daughter, now a 13-year-old high school freshman. Would Rachel need to wear a brace for years? Would scoliosis ruin her chances of living an active life? Could doctors fix the problem?

Patchell agreed to let Rachel become part of a research study that seeks to determine the best treatment for scoliosis. The five-year study, a \$5 million project that includes Cincinnati Children's, is the largest pediatric orthopaedic trial ever funded by the National Institutes of Health. It will evaluate the effectiveness of using a corset-like brace, standard scoliosis treatment since the 1940s, versus a watch-and-wait approach to treatment, in the first randomized, controlled trial of its kind.

Rachel is part of the randomized "watchful waiting" control group, monitored by doctors who watch to see how her scoliosis progresses instead of treating it with a brace or surgery. Rachel visits doctors and researchers at Cincinnati Children's every six months for clinical exams and X-rays. She still plays her favorite sports. But she lives with a twist in her spine and wants to become part of finding a better solution for scoliosis. She will continue to be part of the research for the next four years in the hopes of improving outcomes for others for years to come.

Studies like the one Rachel Tracy is participating in are part of everyday life at Cincinnati Children's.

Whether researching the best treatment for scoliosis or trying to figure out what triggers childhood cancer, our scientists work every day to turn discoveries into cures.

One of the strengths of our research program is the support we give young scientists, says James E. Heubi, MD. With the help of a \$23 million Clinical and Translational Science and Training Award (CTSA) from the National Institutes of Health, that support will be even greater.

As co-director of the Center for Clinical and Translational Science and Training, Heubi will use the award funding to help new researchers establish their programs.

The goal is to connect the investigators with experts who guide them as they find ways to improve care, find relief for patients' symptoms and cures for diseases.

For Heubi, an established researcher who began his career at Cincinnati Children's in 1975 as a gastroenterology fellow, it's about leaving a legacy. He wants to help the



*From left:  
Drs. James Heubi and Scott Powers.*

next generation of scientists find their way at a time when research is all about collaboration.

“Research is no longer one guy working in the laboratory night and day trying to find a discovery,” he says. “The way that people actually are being successful in medicine now, in terms of research, is to have a group of investigators with a variety of backgrounds bring their separate and disparate expertise to bear on a single problem.”

Cincinnati Children’s has one of the largest and best-rated pediatric research programs in the country – with 1,300 investigators, more than 450 pediatric faculty and nearly 1 million square feet of research space.

We rank second nationally among all pediatric centers in research grants from the National Institutes of Health, which amounted to more than \$99 million in 2009.

And we are one of only a handful of NIH-funded centers in the nation devoted to pediatric research.

This is where researchers come to foster relationships that can end up improving patients’ lives, Heubi says. “We’re breaking down silos so people can interact better.”

### Picking Up the Pace

Cincinnati Children’s is a place where junior researchers find advisers and where senior scientists become leaders in their field.

For Cassie L. Kirby, a clinical research coordinator in pediatric orthopaedic surgery, having the right resources readily available makes doing research easier. She’s participating in the scoliosis research with patients such as Rachel Tracy.

Her mentors have allowed her to launch her research career with other projects as well. What began as a curiosity about clavicle fractures led to doing a study and publishing results within the span of a year.

“As a clinical research coordinator, it’s my job to find the tools needed to get the job done,” Kirby says. “Without those resources, like being able to connect with expert statisticians, research ideas can get lost in the process and delayed.”

Proper planning makes for more meaningful research, she says. “The research services available here make getting started like one-stop shopping.”

The goal is to connect investigators with experts, Heubi says. “We’re sort of a concierge service for people who want to do research.”

### Thinking Outside the Lab

The same collaborative concept is changing the way research works throughout Cincinnati Children’s Research Foundation, says Scott W. Powers, PhD, ABPP, director of the Office for Clinical and Translational Research.

His office provides clinical investigators, scientists and sponsors with a centralized core of research support. It also offers a connection to regulatory experts who offer help from the start of a project all the way through the end phases of clinical trials.

Their support includes help in developing study protocols, assistance in writing investigational new drug applications, recruiting subjects and developing and monitoring data.



“We’re broadening the way we look at problems and going after bigger advances.”

“Scientists are finding success by teaming with business-minded colleagues and writing clearer, more targeted proposals that lead to more grants, partnerships with industries – and ultimately, better outcomes for patients,” Powers says.

“Our job is to help the investigators feel comfortable about being creative and to give them the support necessary so that they have the business and execution model to succeed.”

### **Making Bigger Advances**

Research success stories at Cincinnati Children’s range from Albert Sabin’s oral polio vaccine 50 years ago to the recent discovery and testing of a vaccine (Rotarix) that prevents rotavirus infection, a disease that kills half a million children worldwide each year.

More recent discoveries include an innovative treatment for eosinophilic disease that avoids the side effects of steroids; a chip that diagnoses liver disease with a mere drop of blood; a test that identifies kidney failure in record time; and a test of the sugar in a premature infant’s saliva to predict risk of NEC and other problems.

Gains like these can happen only in a place that truly fosters research, says Heubi, who wants to recruit and encourage the next generation of scientists here.

“This type of environment at Cincinnati Children’s makes a difference,” he says. “We’re broadening the way we look at problems and going after bigger advances.”



CINCINNATI CHILDREN'S RESEARCH FOUNDATION 2009

# Division Reports



## Adolescent Medicine

In the past year, we increased asthma control among teens and raised awareness of adoption as an option for unplanned pregnancies.

The Center for Innovation in Chronic Disease Care, directed by Maria Britto, MD, MPH, runs an asthma innovation lab located in the Teen Health Center. This year, the lab focused on translating recommendations from the Cincinnati Children's evidence-based practice guideline for asthma self-management into usable clinical tools. Prototyped, tested and incorporated into our technology system, the tools are now in use in six medical center clinics. This work and other efforts led to a 25 percent increase in the proportion of teens who achieved optimal asthma control.

The Sexual Health and Adoption Education Project team developed guidelines for comprehensive sexual health and adoption education. Leaders were Paula Braverman, MD,

and Christopher Kraus, JD, MTS, both from our division, and Keith King, PhD, CHES, from the University of Cincinnati. We held four training sessions for Ohio teachers, followed by a pilot program in spring 2009 in seven urban, suburban and rural schools. An initial data review reveals that most students were very satisfied with what they learned about adoption and making healthy decisions about sexual behavior. Most teachers planned to continue using the program.

Lea Widdice, MD, and Jennifer Hillman, MD, MS, participate in Building Interdisciplinary Research Careers in Women's Health, a program of the National Institutes of Health. Widdice's research explores the transmission of HPV between sexually active couples and the reasons for the development of persistent infections. Hillman studies the relationship between anxiety and depressive disorders and obesity among school-age and adolescent girls.

## Allergy and Immunology

Food allergy research, a key focus area for our division, got a boost from the Food Allergy and Anaphylaxis Network (FAAN). Director Marc Rothenberg, MD, PhD, and associate professor Simon P. Hogan, PhD, are two of six scientists to share in a \$1.1 million grant, the largest since FAAN's research grant program began in 2004.

Rothenberg is developing new diagnostic and treatment approaches to eosinophilic esophagitis (EE), an emerging food allergy and disorder characterized by the infiltration of a large number of eosinophils (a type of white blood cell) in the esophagus. He hopes to uncover the molecular basis for EE.

Hogan is studying anaphylaxis by comparing the levels of IL-9, possibly associated with anaphylaxis, in children who are at risk for this life-threatening reaction against levels in children not at risk. This information could help diagnose food-triggered, life-threatening anaphylaxis.

Nives Zimmermann, MD, and graduate student Leah Kottyan, along with UCLA collaborators, identified a new cellular pathway in eosinophils triggered by pH. Their findings, published in *Blood*, show that eosinophil viability is increased in acidic environments, such as those found in asthma. They identified the mechanistic pathway, including a novel receptor that senses acidity and transmits the survival signal in eosinophils. In models of asthma, they identified that this receptor (GPC65) was important for accumulation of eosinophils in the lungs.

Kimberly Risma, MD, PhD, received a \$100,000 award from the Fifth Third Bank/Charlotte R. Schmidlapp Women Scholars Program. Risma researches how lymphocytes kill target cells by secreting toxic proteins.

## Anesthesiology

Pediatricians and family practitioners have a new resource to help their patients: *Pain in Children: A Practical Guide for Primary Care*, recently published by our Division of Pain Management. The book gives primary care practitioners information and practical approaches to pain and specific pain problems.

Three NIH grants to Steve Danzer, PhD, strengthened neurobiology research, a key department focus. Danzer received a five-year grant to study the impact of deleting the phosphatase and tensin homolog gene (PTEN) on the development of epilepsy and autism, a grant to examine the role of adult-generated hippocampal granule cells in epilepsy and a grant to research the impact of neonatal seizures on hippocampal development.

Andreas Loeckel, MD, PhD, and George Istaphanous, MD, continue to explore the role of anesthesia in inducing neuroapoptosis in the developing brain. David Richards, PhD,

joined the department to further his NIH-funded research on synaptic mechanisms. Senthilkumar Sadhasivam, MD, won a two-year outcome research award to study responses of children to morphine in an effort to personalize perioperative pain management based on genotype.

Clinically, assessing sedation became part of routine pain assessment for patient-on-patient-controlled analgesia and epidurals. Perioperative soft tissue injuries dropped significantly when we implemented a preventive clinical protocol. Coordination of care for complex patients improved using the new Epic surgical scheduling system. More first cases and subsequent cases started on time.

We presented our quality scorecard to a national meeting of pediatric pain practitioners in preparation for expanding our quality improvement efforts into a nationwide, collaborative process.

The Department of Pediatric Anesthesia performed more than

33,000 anesthetic procedures  
+ 14,000 consultations  
in 2009.



## Asthma Research

Gurjit Khurana Hershey, MD, PhD, director, Division of Asthma Research, received one of only 14 National Institutes of Health Asthma and Allergic Diseases Cooperative Research Center grants. The primary goal of our Asthma and Allergic Diseases Center is to identify epithelial genes important in allergic inflammation.

Epithelial cells are critical initiators of allergic inflammation and asthma. We developed a novel method that uses data on nasal epithelial RNA expression arrays from a variety of sources to identify novel potential epithelial candidate genes. We tested these candidate genes for associations with childhood asthma phenotypes in a large cohort of children with asthma. The results validated our gene selection approach and identified *KIF3A* as a new gene determining susceptibility to childhood asthma and allergic disease.

Melinda Butsch Kovacic, MPH, PhD, received an NIH grant to identify biomarkers of diesel exhaust particle (DEP)-induced oxidative stress in asthma. We recently reported a dose response relationship with DEP exposure and wheeze in a birth cohort. To date, no established biomarkers distinguish between DEP exposure in one child and biologically relevant exposure in another. Preliminary data suggest that fluorescent plasma oxidation products (FPOP) may be most relevant. We will determine whether high levels of DEP exposure are associated with a significant increase in FPOP and whether this measurement better predicts risk of childhood asthma.

Excessive mucus production and mucus plugging is a key pathologic feature of asthma, yet its mechanisms are largely unknown and therapies to target it are lacking. We found that genes for serpin (serine protease inhibitor) family members were significantly up-regulated in childhood asthma and the serine protease inhibitor SERPINB4 is strongly induced in respiratory epithelial cells of children with asthma. Our studies reveal that SERPINB4 contributes to mucus production in asthma and may be a target for therapeutic intervention.

one in  
eight

children in this  
country has asthma.

It is the number one  
reason for pediatric  
hospital admissions.





## Behavioral Medicine and Clinical Psychology

Our division's community research program, INNOVATIONS in Community Research and Program Evaluation, led by Monica Mitchell, PhD, and Lori Crosby, PsyD, played an instrumental role in the University of Cincinnati and Cincinnati Children's successful application for a National Institutes of Health Clinical and Translational Science Award.

We are part of the Community Engagement Core, which will bring clinical and translational researchers together with the community to optimize health outcomes across the region and the nation. Mitchell will promote the development of pilot grants that engage community members around health education, promotion or improvement activities. The core also is training students from high school through fellowship in translational research. Our first three high school students completed their first round of training and summer research projects in July.

Our division is a leader in quality improvement within pediatric psychology. Under the leadership of Anne Lynch-Jordan, PhD, the clinicians and researchers who work with children and adolescents referred for treatment of pain created a system to define and collect patient outcomes at 97 percent of all treatment visits. They demonstrated improvement in functional disability in 67 percent of the patients seen. The pain team is using this data to refine our treatment procedures to improve outcomes.

Michelle Ernst, PhD, partnered with the Division of Pulmonary Medicine to improve the delivery of airway clearance therapy (ACT) to adolescents with cystic fibrosis who are patients at Cincinnati Children's. Using behavioral interventions to motivate young people to partner with their respiratory therapists, the percentage of patients receiving ACT four times per day increased by 23 percent.

The data from both efforts are firsts in pediatric psychology and were accepted for publication in a special quality improvement issue of the *Journal of Pediatric Psychology*.

## Biomedical Informatics

Our division studies human diseases using computational approaches. A unique one-stop suite of online software tools linked to a disease-centered gene knowledge datamine is being developed by programmers and graduate students working with Bruce Aronow, PhD, and Anil Jegga, DVM, MRCS. Use of this system permits researchers to develop new insights into specific genes, pathways, and mechanisms that regulate biological processes and alter susceptibility, severity, and resistance to disease. We're focusing on helping researchers identify candidate therapeutics for a wide variety of diseases, including cancers, immunological, neurologic and infectious diseases

Jason Lu, PhD, developed a novel computational algorithm to identify a compendium of essential genes in a pathogen that causes chronic lung infection in more than 80 percent of cystic fibrosis patients. These genes are the most obvious targets for new drugs designed to kill the organism and treat infection.

The Clinical Linguistic Group, led by John Pestian, PhD, MBA, focuses on analyzing neurological and psychiatric free-text and is developing a suicide risk index with faculty from the Divisions of Psychiatry and Emergency Medicine. It combines biomarkers and thought markers to measure the likelihood of repeated suicide attempts.

Jun Ma, PhD, uses a mix of computational tools and experimental observations to study embryo development using *Drosophila* as a model system. His group performed quantitative studies to evaluate a *Drosophila* protein called Bicoid, a maternally-deposited master control protein that instructs the development of anterior structures, including the head. His analyses traced the origin of proportionate development of body parts in early embryos to scaling properties of the Bicoid gradient. These results demonstrate that developmental proportionality, an ability to correct embryo-to-embryo differences in size, can be understood at a molecular level.

Human milk can  
protect infants  
from norovirus,  
which causes about  
**90%** of  
non-bacterial  
outbreaks of  
gastroenteritis  
worldwide.

## Biostatistics and Epidemiology

Our statistical genetics program, in collaboration with a diverse group of medical center investigators, studies genetic risk factors and modifiers for disease and drug metabolism. In the past year, Jessica Woo, MHSA, PhD, and Lisa Martin, PhD, received a substantial NIH subcontract for genome-wide association analysis for ischemic stroke. Martin, along with Robert Hinton, Jr., MD, and Woodrow Benson, MD, PhD, published the first report localizing genomic regions responsible for hypoplastic left heart syndrome, a critical step in identifying the genes responsible for this condition.

Our major collaboration on human milk and perinatal epidemiology continued to grow with several important implications for child health. We are developing novel strategies to improve child health based on the protective components of human milk. The Human Milk Program Project was approved by the National Institute for Child Health and Human Development Council. New knowledge emerged about how human milk protects against norovirus infection and the relationship between human milk and necrotizing enterocolitis.

A new perinatal epidemiology faculty member, Laurie Nommsen-Rivers, PhD, RD, joined the division as a secondary appointment, strengthening lactation research. This unique program is internationally known for research on the bioactive components of human milk and factors affecting mothers' ability to breastfeed.

Mekibib Altaye, PhD, published a study with Scott Holland, PhD, providing the first infant brain templates for magnetic resonance imaging — fundamental to important studies of brain imaging in infancy.

Additional research focuses on child growth, development and obesity.

## Cardiology

To help combat the alarming rise in childhood obesity, the Heart Institute has opened the Center for Better Health and Nutrition. It includes obesity management, clinical obesity research and education, and clinical services for health and activity. The Center, directed by Rober Siegel, MD, unites a variety of existing programs and will have satellites at Cincinnati Children's suburban locations. Each location will offer the services of a physician or nurse practitioner, dietitian and exercise physiologist specializing in obesity.

We also started a pediatric cardiomyopathy and heart failure service, directed by Jeffrey Towbin, MD, and a cardiovascular genetics service, co-directed by Towbin

and Stephanie Ware, MD, PhD. The new Cardiovascular Diagnostic Laboratory will provide genetic testing for cardiovascular disease, as well as viral genome testing of heart tissue for myocarditis and transplant rejection. Cong Liu, PhD, has been recruited as associate scientific director of this laboratory.

The new Heart Institute Research Core supports innovative clinical and translational science. Our goals include increasing the productivity of high-quality, innovative research and encouraging collaboration among specialties within the Heart Institute, as well as across the medical center and pediatric community worldwide.

## Cardiothoracic Surgery

Improving outcomes for open-heart surgery in newborns and in the womb is the goal of the cardiothoracic surgery research of Jodie Duffy, PhD, and Pirooz Eghtesady, MD.

Their collaboration focuses on understanding the cellular processes of fetal bypass. The National Institutes of Health funds a collaborative grant examining the role of vasopressin in the placental dysfunction associated with fetal cardiac bypass. They also are investigating a novel, non-invasive procedure called periodic acceleration as a therapy for pediatric surgery patients.

Duffy's lab studies reoxygenation and reperfusion injury during repair of congenital heart disease and cardiac transplantation. The program includes studies using proteomics, gene therapy, protein and gene expression arrays, and novel *in vitro* models of reperfusion injury. The lab has an NIH grant to study the role of the calpain/calpastatin pathway in reperfusion injury, using large animals, with *in vitro* characterization of the cellular pathways.

Eghtesady's group recently pioneered an experimental model of fetal intracardiac surgery that may facilitate *in utero* repair of select pathologies. Other efforts investigate the role of nitric oxide/cGMP signaling and natriuretic peptides in vascular dysfunction, suggesting the novel role for vasopressin.

Research continues into the pathogenesis of hypoplastic left heart syndrome (HLHS), which causes significant neonatal mortality and morbidity. A recent epidemiologic analysis of the Pediatric Hospital Information Systems database demonstrated that HLHS occurs as "mini-epidemics" with a seasonal distribution. This supports the lab's novel hypothesis that HLHS is an expression of rheumatic heart disease in the fetus, caused by the maternal antibodies to strep throat that cross the placenta and alter fetal heart valve development. To test this hypothesis, the research team is conducting studies in pregnant women recruited from the Fetal Care Center at Cincinnati Children's.

## Clinical Pharmacology

The goal of the Division of Clinical Pharmacology and the Pediatric Pharmacology Research Unit (PPRU) is to produce new knowledge that leads to optimal use of medications in infants, children and teens. Under the direction of Alexander Vinks, PharmD, PhD, the PPRU unit is one of just 13 in the United States established by the National Institute of Child Health and Human Development to develop appropriate drug therapy for children.

Our research funded by the National Institutes of Health and other agencies focuses on differences in clinical response and adverse events in transplant patients linked to specific, identifiable genetic factors. Using newly discovered genetic polymorphisms, we start to better understand how children with renal transplants and those with childhood systemic lupus erythematosus respond to mycophenolic acid (MMF, CellCept®) therapy. In collaboration with the Divisions of Nephrology and Rheumatology, these studies are helping develop algorithms to allow personalized dosing tailored to each patient's needs.

Our PPRU unit is the lead site for several investigator initiated studies, including drug class evaluations for anti-epileptic drugs in a study sponsored by the National Institute of Neurological Disorders and Stroke, with the Division of Neurology. We also study pharmacokinetics-pharmacodynamics safety and efficacy studies of propofol (Diprivan®) dose optimization in morbidly obese patients, with the Departments of Anesthesia and Surgery and sponsored through CCHMC's Translational Research Initiative (TRI).

We participate in the first genetic pharmacology service in a pediatric institution, helping reduce adverse effects of commonly used medications for multiple diseases and disorders. The GPS is a multidisciplinary collaborative of the Divisions of Neurology, Human Genetics and Biomedical Informatics. We identify genetically determined variations in drug metabolism, providing patient-specific dosing recommendations and delineating clinically significant drug interactions. This is a first step toward personalized medicine for neuropsychiatric and anticoagulation drug therapy.

## Clinical Translational Research Center

The Clinical Translational Research Center (formerly the General Clinical Research Center) provides resources including nursing, bionutrition, body composition, behavioral psychology, informatics and biostatistics for protocols that apply novel ideas derived from the laboratory to the bedside.

The Center's services will be complemented by programs developed with the Center for Clinical and Translational Science and Training and supported by the Clinical and Translational Science Award received by the University of Cincinnati, Cincinnati Children's and the Cincinnati Veterans Affairs Medical Center in April 2009, with funding for the next five years.

Type 2 diabetes in obese teens is a key focus. In a study published in *Pediatrics*, researchers found that gastric bypass surgery significantly improved weight loss and overall

health in adolescents, with decreased cardiovascular risks, insulin resistance, and  $\beta$ -cell function. They determined that gastric bypass is a potentially effective option for treating extremely obese adolescents with type 2 diabetes.

In a study published in the *Journal of Inherited Metabolic Disease*, investigators collaborated with the Kennedy-Kreiger Institute, McGill University and Great Ormond Street Hospital to describe the clinical, biochemical, histopathological and genetic characteristics and response to cholic acid in a patient with a peroxisomal defect caused by mutations in PEX10. This case emphasizes the heterogeneity of the phenotypes of peroxisomal disorders, the challenges of accurate diagnoses and the value of genetic analysis.



The new  
pediatric  
intensive care  
unit has  
a capacity of  
**36 beds,**  
up from 25  
in 2008.

## Critical Care Medicine

This year, we opened a renovated pediatric intensive care unit (PICU) with a 36-bed capacity, an increase from 25 beds. We cared for a record number of admissions to the PICU.

We changed coverage in the PICU this year to a two-team system, which includes coverage by two attending-level faculty per day. This new coverage system, along with the larger capacity PICU, should serve us well in meeting the needs of all critically ill children admitted to Cincinnati Children's.

Derek Wheeler, MD, FAAP, became medical director of the division and of the Pediatric Intensive Care Unit and was promoted to associate professor.

Basilia Zingarelli, MD, PhD, became a standing member of the SAT study section at the NIH; Lesley Doughty, MD, successfully transitioned her K-level funding to a first time R01; and Ranjit Chima, MD, and Jennifer Kaplan, MD, received K-level funding for their respective research programs.



Research and clinical activity continues to expand in the areas of autism, Down syndrome, spina bifida and Rubinstein-Taybi syndrome.

## Dentistry

Over the past year, our division adopted and began using an electronic patient management system that has helped us improve our operational efficiency and patient safety.

We have also undertaken several clinical research projects, including developing an improved appliance to correct unilateral cleft lip and palate; investigating the dental implications of tuberous sclerosis; looking at the effects of growth hormone therapy on dental development and facial growth in Larion dwarfs; evaluating bacteremia in surgical patients who have had their oral cavities swabbed with chlorhexidine; and collaborating with the National Institute of Occupational Safety and Health on ambient nitrous oxide in the dental office.

Our residents presented five posters at the American Academy of Pediatric Dentistry. We have five peer-reviewed papers accepted or in press at this time. We also plan to collaborate with other disciplines to investigate the interaction of oral with general health research.

Of the five residents who graduated a year ago, four have already passed the American Board of Pediatric Dentistry exam, the fastest time that our residents have ever become boarded.

## Developmental and Behavioral Pediatrics

Our programs will be united this year in a new building designed to meet the specific needs of our patients and programs. The building will allow for major expansion and upgrading of our clinical, research, training and community outreach initiatives and will house the Rubinstein Library.

In anticipation of this growth, we recruited new faculty. Karen Summar, MD, is the new director of the Jane and Richard Thomas Center for Down Syndrome, replacing Bonnie Patterson, MD, who retired in March. Julia Anixt, MD, is a new pediatric faculty member with research interest in ADHD.

A number of psychology research faculty were also recruited, including Ryan Adams, PhD, statistician and developmental psychologist; Somer Bishop, PhD, whose research focus is in autism spectrum disorder; Anna Esbensen, PhD, research associate; and Robin Gurwitch, PhD, coordinator of the National Center for School Crisis and Bereavement.

Our training programs in Developmental-Behavioral Pediatrics continue to attract a broad range of disciplines and trainees from throughout the United States and abroad. During the year, we hosted or co-hosted extended visits by trainees from Australia, China, Greece and Turkey.

## Developmental Biology

How do tissues differentiate into specific lineages, and how do they become patterned? We addressed these central development issues in two major papers in *Developmental Cell*. Brian Gebelein, PhD, and colleagues describe how the Hox genes control tissue patterning by forming a molecular switch with the transcription factor Senseless in the *Drosophila* embryo. Jim Wells, PhD, and his group define the role played by the transcription factor Sox17 in forming different organs in the mammalian foregut.

A basic tenet of stem cell biology is that the pluripotency and proliferation of stem cells are controlled by cells that surround them, their “niches.” However, the migration of some stem cell populations during embryogenesis raises the question of how these properties are controlled. Graduate student Ying Gu showed in *Development* that essential signals are released progressively by tissues along the migratory route of primordial germ cells in the mouse embryo, thus providing a “traveling niche” for these essential pluripotent cells. During spinal cord development, sensory neuron processes that enter the cord dorsally migrate ventrally and form synapses on their target motor neurons in the ventral spinal cord.

In *Nature*, Yutaka Yoshida, PhD, showed that recognition of the target neurons by the sensory neuron processes requires the semaphorin/plexin family of ligands and receptors. The concentration and localization of signaling ligands must be tightly controlled. Excess Wnt signaling, for example, causes cancer. In a paper in *Development*, Janet Heasman, PhD, and her group show that the amount of Wnt signaling is controlled in the early embryo both by the specific inhibitor Dkk and by dimerization of two different Wnts. This finding offers novel translational opportunities to control Wnt signaling in disease.

Since 2000, the  
Developmental  
Biology Division  
has grown  
to **25** faculty  
members, making  
it one of the largest  
developmental  
biology centers in  
the country.

## Drug and Poison Information Center

With 25 American Association of Poison Control Center certified specialists in poison information and 51 staff certified in national incident management systems, the Drug and Poison Information Center (DPIC) is one of the largest in the country. We serve 3.7 million people in 20 Ohio counties.

World events have continued to reinforce and define our community and public health services. The DPIC continued its collaborations with regional medical response systems, county disaster committees and the Ohio Department of Health's disaster preparedness and response program. With the help of a health alert network, we send alerts to 60 regional hospitals on subjects such as H1N1 flu, blue-green algae in the river and contaminated heroin.

This year, the Centers for Disease Control Real Time Disease Detection Grant allowed the DPIC to further

contribute to how poison control data may potentially provide toxico-surveillance on a variety of public health problems such as food poisoning, water quality, substance abuse patterns and terrorism preparedness.

Our Prevention Research Unit (PRU) promotes healthy, drug-free lifestyles and involves youth, parents and community members. The staff includes prevention specialists and other professionals (health educators, pharmacists, other health care professionals, military personnel and law enforcement officers) who also serve as role models. More than 500,000 people in Hamilton County, Ohio, have benefited from PRU services. About 3,500 residents also have received intense substance abuse prevention and education services. The PRU also provides programming on preventing delinquency and violence among African-American youth.

## Emergency Medicine

Outcomes for emergency patients with painful fractures have improved because of quality research led by Scott Reeves, MD, and Mike Buncher, MBA. Reeves and Buncher also developed measures and interventions to handle emergency department overcrowding, a national issue.

Jackie Grupp-Phelan, MD, MPH, and Mike Gittelman, MD, lead our prevention research team. They focus on key national priorities, including screening for mental health issues (Grupp-Phelan), smoking prevention in children (Melinda Mahabee-Gittens, MD, MS), and injury control (Gittelman and Wendy Pomerantz, MD, MS) through interventions that cut across the larger health care system.

The first free-standing Cincinnati Children's emergency department opened last year at our Liberty Campus, in a suburb north of Cincinnati. With 24-hour pediatric emergency medicine attending coverage, this ED offers extended

pediatrician coverage, accepts all acuities and life squads, integrates pediatric transport to ensure rapid transfer for tertiary care, and integrates direct transfer to observation beds at the Liberty Campus and to higher level subspecialty care at the main hospital. Over 11 months, the new ED treated nearly 25,000 children.

Clinical systems improvement at the Cincinnati Children's main campus ED focused on evidence-based care for treating the spectrum of painful conditions, led by Reeves and Eric Mailloux, RN. The work of Rima Rusnak, MD, and Sharon Foreman, RN, strengthened the culture of safety, with zero serious safety events in the last year. Partnership with the resuscitation/simulation team has resulted in consistent use of communication tools to dramatically improve communications about high risk patients.

# Cincinnati Children's ranked #4

in the nation for Diabetes and Endocrine Disorders,  
according to *U.S. News & World Report*.

## Endocrinology

In the past year, clinical research in our division resulted in FDA approval of human insulin-like IGF-1 (mecasermin). Since the early 1990s, Philippe Backeljauw, MD, has been a principal investigator in clinical studies for this agent that joins growth hormone (GH) as a means to promote growth.

IGF-1 therapy is now approved to treat patients with short stature resulting from severe primary IGF-1 deficiency. These patients have normal or increased GH concentrations, but low IGF-1, because of defects of the GH receptor or post-GH receptor signaling pathway. Long-term clinical research, in collaboration with investigators at the University of North Carolina, led to important advances in understanding the physiology of the GH-IGF-1 axis, and opened the door for the therapeutic use of IGF-1. Final height data for initial study patients were presented at the combined Lawson Wilkins Pediatric Endocrine Society/European Society for Pediatric Endocrinology global meeting in New York in September.

As the director of the Turner Syndrome Center, Backeljauw follows more than 100 patients in a multi-disciplinary clinic staffed by physicians in the divisions of Pediatric Cardiology and Developmental and Behavioral Pediatrics, among others. Original research using the clinical/research database of Turner Syndrome patients includes evaluating the prevalence of ADHD and the frequency of partial anomalous venous return evaluated by cardiac MRI, accepted for oral presentation at the 2009 endocrine global meeting.

Research continues in the study of aortic root dilatation by cardiac MRI, as well as arteriopathy using non-invasive imaging techniques.

## Every Child Succeeds

Every Child Succeeds works with first-time, at-risk mothers and their babies, providing regular home visits, support and care to more than 3,000 young women annually who meet one or more of these criteria: unmarried, low income, 18 or younger, and little or no prenatal care. Young women enter the program during pregnancy, and home visits continue for two to three years.

To serve children better and more cost-effectively, Every Child Succeeds is conducting two clinical trials addressing prevention and home visitation. Funded by the National Institute of Mental Health, one study examines an innovative home-based psychological treatment for first-time mothers in our program who have postpartum depression. Preliminary findings from this trial, recently presented at the annual meeting of the Pediatric Academic Societies, show substantial reductions in depressive symptoms and improvements in parenting and child functioning. The second study, funded by the Maternal and Child Health Bureau, examines motivational interviewing to increase program adherence and retention.

We have a well-developed quality improvement strategy that directs program changes and enhanced program implementation in 15 sites in seven counties and two states. The Every Child Succeeds medical home committee, led by Charles Schubert, MD, enhances child health outcomes by improving access to care and optimizing the partnership among families, home visitors and pediatricians.

During the past year, we have received growing national recognition for our innovative approach, with numerous requests for information.

## Experimental Hematology

Researchers advanced the understanding of neurofibromatosis and Bloom's syndrome in the past year. Neurofibromatosis is a common inherited disease characterized by nerve tumors called neurofibromas, whose cellular origin had not been known. A team led by Nancy Ratner, PhD, reported in *Cell Stem Cell* that Nf1 gene mutation expands a peripheral nerve progenitor, which confers tumor potential. In the normal mouse, the nervous system requires signaling from the EGFR tyrosine kinase. Loss of Nf1 function makes the nervous system hypersensitive to growth factors and allows tumor growth.

Mouse neurofibromas, but not normal nerve, contain a progenitor population with similar growth requirements, potential and marker expression. Following the mouse model studies, the team identified cells in human neurofibroma cells with progenitor properties. This study suggests that expansion of an EGFR-expressing early glial progenitor contributes to neurofibroma formation, and provides new insights to therapeutic strategies targeting this tumor-initiating cell population.

Mutations in the BLM gene (Bloom syndrome protein) give rise to Bloom's syndrome, a rare genetic disorder with severe growth retardation, immunodeficiency, anemia, reduced fertility and often cancer at an early age. BLM encodes a DNA helicase that associates with Topo III $\alpha$  and BLAP75/RMI1 to form a large molecular complex that prevents chromosomal aberrations and rearrangements.

Ruhikanta Meetei, PhD, and colleagues reported in *Genes & Development* the discovery of a new component of this complex called BLAP18/RMI2. This molecule represents a new protein important for DNA complex stabilization and checkpoint response required to maintain a stable genome in cells. This discovery illustrates the intricacies of molecular mechanisms that ensure genomic stability and reveals how a destabilized genome may be associated with developmental defects such as growth retardation, immunodeficiency and infertility, as well as cancer.

The Division of  
Experimental Hematology  
and Cancer Biology  
receives more than  
**\$6.3 million**  
in direct annual  
grant support.





U.S. News & World Report ranked our  
Division of Gastroenterology, Hepatology and Nutrition

#1 in the treatment of digestive disorders,  
among all children's hospitals in the nation.

## Gastroenterology, Hepatology and Nutrition

The number of patients receiving medical and surgical care for inflammatory bowel disease (IBD), both regionally and nationally, continues to grow. Investigators at the Schubert Martin Inflammatory Bowel Disease Center completed the first randomized, controlled trial of human growth hormone in children with Crohn's disease and have contributed to the first genome-wide association study to identify susceptibility genes specifically for pediatric-onset IBD. Research is supported by the National Institutes of Health, Crohn's and Colitis Foundation of America and the Pediatric Research Organization for Kids with Intestinal Inflammatory Disorders.

The IBD center plays a leading role in ImproveCareNow, the national pediatric IBD quality improvement network. In 2009, the network achieved a 20 percent improvement in patient remission rates by implementing patient care guidelines and practices.

Members of the Pediatric Liver Transplant Program continue to advance science by leading multi-center clinical and translational studies, including the NIH-sponsored Studies in Pediatric Liver Transplantation (SPLIT) and the Pediatric Acute Liver Failure Study Group (PALF). Under the leadership of John Bucuvalas, MD, SPLIT successfully competed for an NIH planning grant to design a clinical and translational study focused on withdrawal of immunosuppression and the biological mechanisms underlying tolerance.

The PALF group collaborates with Alexandra "Lisa" Filipovich, MD, in preliminary studies investigating the role of natural killer cell dysfunction in acute liver failure. With an increase in referrals for hepatoblastoma resection and/or transplantation and collaboration with James Geller, MD, in the Division of Hematology/Oncology, we now have the infrastructure and patient population to take a lead in patient-based research in this field.

## General and Community Pediatrics

The research of developmental psychologist Kimberly Yolton, PhD, examines how a child's pre- and perinatal environment affects development. She studies factors that may alter the typical trajectory of a child's development, behaviors and mood, including exposures to toxicants (such as tobacco, drugs, and environmental chemicals) and events such as preterm birth or prenatal complications.

Yolton recently published results demonstrating links among exposure to second-hand smoke (SHS), decreased cognitive performance and increased behavior problems in children, with more boys showing behavior problems. New findings also link SHS exposure with more frequent sleep disturbances and increased daytime sleepiness in children. Yolton recently reported significant associations between prenatal tobacco smoke exposure and neurobehavioral performance in infancy, with effects varying by race.

The new Child Health-Law Partnership, a collaboration between the Pediatric Primary Care Clinic (PPCC) and the Legal Aid Society of Greater Cincinnati, seeks to assist low-income families with health-related legal needs. Co-led by Robert Kahn, MD, and Elaine Fink, Esq., from Legal Aid, the program addresses social issues often at the root of poor child health. For example, medical care alone is rarely the best answer for a child with asthma when the landlord refuses to eliminate mold or rodents. More than 400 children have been referred for help.

The program also trains residents in social and legal issues that affect health, in an effort led by Melissa Klein, MD. Though it is less than a year old, the partnership already has been recognized as an emerging national model for medical-legal partnerships.

## General and Thoracic Surgery

Members of the General and Thoracic Surgery Division provide a range of general and specialized surgical treatments, including kidney, liver and small bowel transplants, a surgical weight loss program for children, laser surgery, minimally invasive surgery and Greater Cincinnati's only level-1 pediatric trauma program.

Our research includes participation in multi-center clinical trials, developing guidelines for surgical care, and studies ranging from evaluating injury prevention programs to exploring the molecular biology of neuroblastoma.

In our molecular fetal lab, Timothy Crombleholme, MD, FACS, FAAP, director of the Fetal Care Center of Cincinnati, pursues wound-healing research funded by the National Institutes of Health and Shriners' Hospital. He also is the primary investigator of an NIH-funded clinical trial focusing on the care of twin-twin transfusion syndrome. This year, Crombleholme was named director of surgical research and associate chairman of the Children's Hospital Research Foundation.

The Center for Bariatric Research and Innovation, directed by Thomas Inge, MD, PhD, FACS, FAAP, leads a national effort to evaluate the use of weight loss surgery in adolescents. The team is in the fourth year of the six-year Teen LABS Study, the largest multicenter study in the U.S. to document outcomes of weight loss surgery. The center welcomed Todd Jenkins, MPH, PhD, as associate director.

Gregory Tiao, MD, continues to develop his research in biliary atresia. He was appointed surgical director for liver and intestinal transplantation.

Jason Frischer, MD, is setting up a basic science laboratory to study solid organ cancers. He also has been awarded a grant from Cancer Free Kids to study neuroblastomas.

In June, Richard Falcone, MD, was named director of the division's trauma and injury prevention program. Falcone has received funding for a clinical trial evaluating the safest dose of Tigecycline for pediatric patients and for his work in trauma epidemiology, education and prevention.

## Global Child Health

Vaccine research in the Mother's Gift project based in Bangladesh, led by director Mark Steinhoff, MD, shows that birth weight increases in infants when their mothers have received the influenza vaccine during pregnancy. This suggests that influenza may be more important in pregnancy than previously realized. Another key finding is that the pneumococcal vaccine given to Bangladesh infants results in greater weight and height gain. These results were reported at the National Foundation for Infectious Diseases annual meeting, the Pediatric Academic Societies annual meeting, and the Bangkok meeting of Respiratory Virology.

In December 2008, Steinhoff received a substantial grant from the Bill and Melinda Gates Foundation for a large field trial of maternal immunization with influenza vaccine in Bhaktapur, Nepal. We expect to begin immunizing pregnant women in 2010. Steven Black, MD, and Steinhoff, with colleagues in Suzhou, China, showed that influenza is an important cause of hospital admission and is active year-round in parts of China. This preliminary data will be presented to the Centers for Disease Control and Prevention in China.

The research of Adekunle Dawodu, MBBS, on vitamin D deficiency in mothers and infants is in its second year in the United Arab Emirates. So far, results indicate that 98 percent of subjects with available vitamin D results were vitamin D deficient on enrollment. This extraordinarily high prevalence of vitamin D deficiency during pregnancy could have significant adverse effects on the mother and the growing fetus.

In April, Dawodu received a Qatar National Research Fund award to investigate low- and high-dose Vitamin D supplementation to prevent childhood Vitamin D deficiency in Qatar.

NICU-associated bacterial infections in  
premature infants of 22 to 29 weeks gestation  
are down  
**75 percent,**  
from 20 percent to  
5 percent

## Health Policy and Clinical Effectiveness

The Ohio Perinatal Quality Collaborative (OPQC), led by Edward Donovan, MD, and funded by the Centers for Medicare and Medicaid Services, focuses on applying evidence to improve perinatal care. OPQC represents a unique partnership with the Ohio Department of Job and Family Services, Ohio Department of Health, and 45 teams at 25 Ohio sites that deliver care for premature children.

OPQC is nationally recognized as a unique effort that goes across the continuum of perinatal care to improve quality and reduce costs statewide. The collaborative has achieved a 30 percent reduction, from 12 percent to 8 percent, in scheduled elective deliveries performed in women without appropriate indications in the targeted gestational age (36.1 to 38.6 weeks). OPQC is also working to reduce NICU-associated bacterial infections in premature infants of 22 to 29 weeks gestation. A cost-effectiveness study is part of the research effort.

We also use innovation labs to improve care. In the high reliability unit, we tested a pediatric early warning system linking abnormal vital signs to an action algorithm based on a numeric score. A greater than 90 percent reduction in codes was achieved and spread throughout Ohio and nationally with similar results.

In the chronic care lab, we used cell phones to improve adherence in teens with chronic disease. This successful intervention is now studied in an NIH-funded, randomized trial by Michael Seid, PhD, and Maria Britto, MD, and internally with diabetes patients.

We are now creating a patient-provider collaborative clinical care network using social networking technology to improve clinical practice, patient self-management and disease outcomes for patients with pediatric inflammatory bowel disease.



## Hematology/Oncology

To better understand how to help patients with brain tumors, Maryam Fouladi, MD, MSc, and Trent Hummel, MD, are conducting a pilot study for patients with newly diagnosed high-grade gliomas and diffuse intrinsic brain stem gliomas. Incorporating a promising antiangiogenic agent with standard therapy, this protocol also poses several important questions about tumor biology, quality of life and functional outcome for patients with these poor-prognosis tumors.

Clinton H. Joiner, MD, PhD, was appointed director of Hematology. He continues as director of the Comprehensive Sickle Cell Center, which he has led since 1995. The center received a grant from the National Heart, Lung and Blood Institute to participate in the Sickle Cell Disease Clinical Research Network. Cincinnati Children's leads a consortium that includes the University of Cincinnati, Ohio State University and Nationwide Children's

Hospital of Columbus in conducting clinical trials of new treatments for sickle cell disease.

Researchers in the bone and marrow transplantation program are the first in the U.S. to investigate the clinical consequences of mutation in the gene BIRC4. Children with this genetic, lymphoproliferative disorder have a markedly increased risk of lymphoma and a defective immune system. Many children with the BIRC4 gene defect come to Cincinnati Children's for a bone marrow transplant. Led by Alexandra "Lisa" Filipovich, MD, and Rebecca Marsh, MD, our investigators described a new diagnostic test for this disorder and are describing its clinical and immunological changes. Marsh received an NIH grant for more mechanistic studies to determine why the gene abnormalities lead to mal-function in the immune system.

## The Human Genetics

Division houses one of

about **23** RRC-approved

sites for residency training

in Medical Genetics.

## Human Genetics

To advance understanding of Gaucher disease and its treatment, Gregory Grabowski, MD, and Ying Sun, PhD, used a new neuronopathic model of the disease to evaluate, for the first time, small molecules called pharmacological chaperones for the treatment of malformed lysosomal enzymes *in vivo*. The results show that selected chaperones increased the Gaucher disease protein and activity, suppressed the proinflammation, and extended life span, but had no effect on substrate accumulation.

William Nichols, PhD, extended the association of variants in the Gaucher disease gene and susceptibility to Parkinson's disease. Two polymorphism variants lower the age of disease onset in Parkinson's patients heterozygous for such variants. Additional associations of parkin gene variant heterozygosity were shown to increase susceptibility to Parkinson's.

Derek Neilson, MD, a new junior faculty member, established the first genetic cause for acute necrotizing encephalopathy (ANE), a disorder in which children are predisposed to a devastating neurologic injury following common infections. He identified mutations in the RANBP2 in more than a dozen families with ANE. This finding may offer insights into other neurodegenerative diseases.

Our medical genetics residency program successfully recruited for three residency positions (one in medical genetics and two in combined pediatrics/medical genetics) in a year when nationally, only one other combined pediatric/medical genetics residency program matched a single resident.

## Immunobiology

An exciting discovery in our exploration of the immunologic and genetic basis of immune-driven diseases is that aberrant immune responses to the most common allergen, the house dust mite, are initiated at the airway surface.

Marsha Wills-Karp, PhD, and her group identified the first evidence that allergens elicit innate immune responses via a specific pattern recognition receptor in the  $\beta$ -glycan receptor family. This discovery, published in the *Journal of Allergy and Clinical Immunology*, helps create a better understanding of asthma's pathogenesis and may lead to new therapies for this common disease.

Leighton Grimes, PhD, a Leukemia and Lymphoma Society scholar, illustrated an ancient transcriptional circuit underlying myeloid progenitor transformation. His lab described the deregulation of microRNA in mice and humans with growth factor independent-1 (Gfi1) loss of function. Moreover, Grimes' group has described a novel transcriptional circuit underlying the accumulation of arrested myeloid progenitors in Gfi1-mutant severe congenital neutropenia (SCN) patients. As patients with SCN are at greater risk for developing myeloid leukemia, this pathway may underlie the development of their leukemia. Grimes was invited to give the plenary session on this important work at the American Society of Hematology annual meeting.

Jochen Mattner, MD, discovered a novel association between bacterial infections and the development of autoimmune diseases, in particular primary biliary cirrhosis (PBC). He provided evidence in a mouse model that infection with a specific bacterial species, *Novosphingobium*, is sufficient to induce a liver disease that mimics that seen in human PBC patients. Because patients with PBC demonstrate evidence of chronic infection of the liver with *Novosphingobium*, these results suggest that an infectious trigger may drive the development of autoimmunity. These studies may revolutionize our thinking of the etiology of autoimmunity and lead to new treatments for these debilitating diseases.



## Infectious Diseases

Last April, the World Health Organization recommended worldwide vaccination of children with the Rotarix vaccine, developed in our division. An efficacy trial of Rotarix completed in Malawi and South Africa in 2008 showed that the vaccine prevented more than 60 percent of severe rotavirus illnesses in developing countries, sufficient to save many lives each year. The universal recommendation will allow funding for vaccine use in the world's poorest countries.

We tested the pentavalent rotavirus vaccine (RV5) for effectiveness using the Centers for Disease Control and Prevention's vaccine surveillance network. We identified children under 3 years of age in three US counties who

were seen in the emergency department or hospitalized for rotavirus acute gastroenteritis from January 2006 through June 2008. Rates of rotavirus hospitalizations and ED visits declined more than 80 percent as a result of RV5 vaccination, even after fewer than three doses. Rotavirus rates in 2008 declined far more than expected based on vaccine coverage, suggesting indirect benefits for non-vaccinated children.

Investigators from our division uncovered a critical piece of the herpes simplex virus latency and reactivation puzzle. Their exploration has revealed the role that a key protein, VP16, plays in this process. The findings will provide a basis for developing new antiviral therapeutic and vaccine strategies.

## Mayerson Center for Safe and Healthy Children

In our continued efforts to battle child abuse and neglect, our staff evaluated 1,124 children for allegations of mistreatment this year and saw 85 children hospitalized at Cincinnati Children's for possible child abuse.

We trained more than 600 community mental health therapists in evidence-based treatments for traumatized children and families. We trained and supervised staff of the Division of Psychiatry to work with the hospital's trauma clinic. We are adapting a group trauma treatment model for adolescents in Ohio juvenile justice centers. Research shows that more than 90 percent of the children in these settings have experienced multiple severe traumas through exposure to family and community violence.

We expanded our telemedicine-based child abuse education programs to include pediatric sexual assault nurse

examiners; child forensic interviewers; and physicians and fellows working with child abuse.

Our research includes work with the Sarah Jane Brain Centers of Excellence initiative as the Ohio site for studying pediatric brain injury. We collaborate with the Division of Psychology on a study of the relationship of child sexual abuse to teen pregnancy.

We also coordinate mental health referrals for mothers in Ohio's Help-Me-Grow (HMG) program in 17 Ohio counties. The program has successfully connected hundreds of mothers with mental health providers for evaluation and treatment of depression. The governor has mandated expanding the program to 88 counties over the next few years. It was identified as a promising practice by the Institute of Medicine in its 2009 report on parental depression.

## Molecular Cardiovascular Biology

The research team of Jeffrey Robbins, PhD, identified the gene responsible for development of congenital heart abnormalities and accompanying craniofacial defects.

Too little of the gene SHP2 interferes with early embryonic development of neural crest cells, resulting in a failure of cell differentiation and anatomical and functional deficits so severe they preclude the fetus' viability. Findings from this study can be used to develop better medications to treat and prevent heart and craniofacial malformations. The team will now focus on exploring the alterations in neural crest cell migration, expansion and differentiation that contribute to defects in other organ systems.

The team led by Jeffery Molkentin, PhD, one of the year's new Howard Hughes Medical Institute investigators, has uncovered a novel gene, *Cdc42*, that controls how the heart

enlarges in response to disease. Collaborating with the Division of Experimental Biology, the investigators showed that mice lacking this gene had greater cardiac enlargement and more rapid progression to heart failure when challenged with disease-inducing insults. The results of the study, published in the *Journal of Clinical Investigation*, suggest that drugs used to modulate *Cdc42* might help treat heart abnormalities.

Stephanie Ware, MD, PhD, received a five-year, \$750,000 Burroughs Wellcome Fund Clinical Scientist Award in Translational Medicine to explore the genetic causes of heterotaxy and its connection to congenital heart defects. Through a combination of human genetics and developmental biology, new genetic changes in patients with heterotaxy will be identified, validated, and tested in animal models.

## Molecular Immunology

In what the American Asthma Foundation called "a breakthrough discovery," a research team led by Christopher Karp, MD, learned why dust mites are a major source of airborne allergens for patients with allergic asthma. Their study, published on *Nature.com*, revealed that dust mites trick the immune system into believing it is facing a bacterial infection. The immune system mounts a strong allergic response to the mites, triggering the asthma attack.

In another exploration, the Karp team examined the genes that modify cystic fibrosis, identifying genetic variation in the transcriptional co-regulator *IFRD1* as a factor in lung disease severity. Analysis showed that *IFRD1* modulates the pathogenesis of airway disease in CF by regulating neutrophil effector function. These data suggest that *IFRD1* could be a target for new therapies.

Edith Janssen, PhD, studies pathways activating antigen-specific adaptive immune responses involving a novel class of dendritic cells (DC). Seminal studies by Janssen have shown that the phagocytosis of apoptotic cells by such DCs can activate T cells. These insights can be used to develop therapeutic and preventive cancer vaccines.

Kasper Hoebe, PhD, identified a tie between NK cells and the adaptive immune system. Of key importance is that NK cells recognize and kill antigen-expressing target cells. This NK cell-induced cell death is recognized by DCs, leading to powerful immune responses. Hoebe's laboratory aims to exploit this learning to generate novel vaccines for chronic infectious diseases such as HIV/AIDS as well as for cancer.

Claire Chougnet, PhD, studies T-cell dysfunction associated with HIV/AIDS and aging. Her lab found dramatic accumulation of regulatory T (Treg) cells in lymphoid organs of both groups. The cells likely play an important role in immune responses to HIV infection as well as in the immune suppression seen in aging hosts, something that Chougnet has validated in mouse models. She is working with the Division of Immunobiology to better understand this. In related studies, Hoebe's work provides genetic evidence that there are two distinct mechanisms controlling Treg cell lineage commitment, in the thymus and the periphery.

The Neonatology, Perinatal and Pulmonary Biology Division offers one of the largest programs of care for newborns in the United States, including coverage and medical leadership for all three neonatal intensive care units in Cincinnati and seven Level II special care nurseries.

## Neonatology, Perinatal and Pulmonary Biology

This year, scientists in the Neonatology, Perinatal and Pulmonary Biology section made a major breakthrough in their work to advance the care of newborns – identifying a single gene required for producing mucus in the airways of both mice and men.

Called SPDEF (SAM pointed domain-containing ETS transcription factor), the gene regulates a larger group of genes that synthesize, package and secrete mucus. SPDEF is present in the lungs of children and adults and is induced in cystic fibrosis, asthma, chronic obstructive pulmonary disease and other respiratory disorders. Understanding genes like SPDEF and the processes influencing mucus secretion will ideally lead to improved diagnosis and treatment of childhood lung diseases.

A second discovery was made as physicians identified a new gene, FOXM1, that plays a critical role in lung maturation, lung function and survival, and the development of lung

tumors. One mice study illustrated that deletion of FOXM1 in the lung caused lung failure at birth. When the FOXM1 gene was deleted after birth, mice failed to develop lung tumors in response to carcinogens and cancer-causing agents. These studies not only identified a new pathway that is critical for perinatal lung maturation, they also found potential therapeutic targets for combating lung tumors.

Additional research identified a novel cause for the severe lung disease Pulmonary Alveolar Proteinosis (PAP) in children. Children with mutations in their Granulocyte Macrophage Colony-Stimulating Factor Receptor (GM-CSF Receptor) develop PAP when the receptor fails to signal macrophages to clear surfactant from the airways, thus causing respiratory distress and growth failure. Recent studies have identified a new cause of PAP, information that will ultimately lead to improved diagnosis and therapy for this life-threatening disorder.

A simple lab test can now  
predict acute kidney failure in

30 minutes  
or less — a process that used  
to take up to three days.

## Nephrology and Hypertension

A simple lab test can now predict acute kidney failure in 30 minutes or less.

Developed by a research team led by Prasad Devarajan, MD, the test measures the biomarker neutrophil gelatinase-associated lipocalin (NGAL), which appears in patients' blood or urine. The test can show kidney failure up to three days earlier than previous testing methods. Devarajan's team validated the biomarker in a wide variety of pediatric and adult patient populations. He has worked with industry experts to design standardized kits that can measure NGAL in a drop of urine or blood and provide results in 30 minutes or less. The tests are already in use worldwide and will become available in the U.S. within the next year.

Jens Goebel, MD, medical director of kidney transplantation, is leading a multi-center project investigating how to reduce the gastrointestinal and hematological toxicity

associated with mycophenolate mofetil (MMF), a commonly used anti-rejection medication. Goebel and David Hooper, MD, of the Division of Nephrology, published their findings online in *Clinical Pharmacology and Therapeutics*. Their work should allow prediction of individual patient responses to MMF and personalized dosing to avoid toxicity.

A research team led by Mark Mitsnefes, MD, showed that early markers of cardiovascular disease such as left ventricular hypertrophy and increased carotid artery thickness are already apparent in the early stages of kidney insufficiency in children. Mitsnefes is leading a multi-center effort to better understand how cardiovascular abnormalities develop in children with chronic kidney disease. Researchers expect that identifying risk factors associated with cardiac and vascular problems will allow them to treat and prevent these conditions in children with chronic kidney disease.

## Neurology

Our continued work with the Childhood Absence Epilepsy Study, the largest NIH-funded pediatric epilepsy trial ever conducted, yielded results in identifying the ideal anticonvulsant medication for children with untreated childhood absence epilepsy. We analyzed the effects of the three commonly used anticonvulsant medications and found differences in cognition, behavior and quality of life. Our findings have already begun to change clinical approaches in treating this common pediatric epilepsy syndrome; we hope to publish our results soon.

We joined researchers at Indiana University in a study of 350 children with first recognized seizure (FRS), identifying factors that predict behavioral adjustment and academic achievement. After following the children for 36 months, we found that they experienced a range of developmental

problems, including continued persistent seizures; impeded neuropsychological and cognitive function; sleep problems; depression; and attention problems. Our hope is that this study will allow us to better manage these co-morbidities.

Our Headache Center is using genomic expression to understand the underlying factors behind acute migraine attacks. We have identified preliminary biomarkers for patients at risk of developing medication overuse headaches and are identifying other sub-groups, including patients with cutaneous allodynia. Tests of adolescents during acute migraine attacks have shown altered cortical functioning, providing a foundation for further understanding the neurophysiological basis of migraine. With the help of an NIH-sponsored study, we are evaluating the benefit of teaching coping skills to children who have chronic migraine.

## Neurosurgery

Our Surgical Epilepsy program is one of the few national centers offering a surgical option for children with treatment-resistant epilepsy. Our surgeons use advanced methods to identify and resect the precise location of seizure origin in the brain. The goal of the surgery is to eliminate or significantly reduce the number of seizures patients experience. For scores of young patients, the treatment has taken them from frequent daily seizures to being seizure-free or to managing fewer episodes with minimal medication.

In another area of research, our investigation into hydrocephalus earned the American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS)

Pediatric Section Hydrocephalus Association Award. Using Diffusion Tensor Imaging (DTI), our study of hydrocephalus measures changes in periventricular white matter before and after surgery. The method may help predict a patient's long-term outcome based on pre-treatment diffusion within the white matter.

We continue our work with the structural defect in the cerebellum known as Chiari malformation, sharing knowledge about the problem's management and treatment. Neurosurgeons at Cincinnati Children's have performed more than 250 surgeries to correct Chiari malformation.





## Ophthalmology

The Abrahamson Pediatric Eye Institute and the Division of Pediatric Ophthalmology successfully recruited Robert Sisk, MD, a vitreoretinal specialist, this year. Dr. Sisk has special interest in pediatric retinal and surgical diseases, hereditary diseases of the retina and retinal electrophysiology.

Our Visual Systems Group welcomed two new faculty members, Zubair Ahmed, PhD, and Saima Riazuddin, PhD. Both are geneticists studying the mechanisms of ocular development and disease. They will conduct basic science research into the development and disease processes of the visual system.

## Orthopaedics

Cincinnati Children's Division of Orthopaedics ranked sixth in the nation among pediatric orthopedic specialties, according to the *U.S. News and World Report* 2009 edition of American's Best Children's Hospitals.

This year marked the launch of our multi-disciplinary Hand and Upper Extremity Center, directed by orthopaedic specialists Roger Cornwall, MD, and Mohab Foad, MD, and plastic and reconstructive surgeon Kevin Yakuboff, MD. The multi-specialty center offers surgical and non-surgical treatment of conditions involving the hand and upper arm, including fractures as well as tendon, nerve and vascular injuries.

Our division and Sports Medicine have established the world's first Juvenile Osteochondritis Dissecans (JOCD) Center. This condition can destroy the joint surface in high-performing young athletes who subject their bodies to repetitive stress. Patients who require surgical intervention are treated with minimally invasive arthroscopic bone grafting and fixation techniques pioneered at Cincinnati Children's.

Specialists here have  
performed more than

2,200

airway reconstructions  
to date, averaging about  
150 per year.

## Otolaryngology

The Cincinnati Children's Hearing Aid Trust (CCHAT) was created to give the gift of hearing to as many Ohio children as possible. CCHAT provides children from birth to age 3 with their first set of hearing aids at no cost. We partnered with organizations and individual sponsors to make this goal a reality for hundreds of children.

Saima Riazzudin, MD, has joined us to direct our laboratory of molecular genetics. Riazzudin's research focuses on identifying genetic mutations that cause hereditary hearing loss. Her research will continue to identify novel genes related to deafness as well as to examine the function of these genes at a cellular and organ level.

The Communication Sciences Research Center (CSRC) is a collaborative research program established this year that includes pediatric otolaryngology, audiology and speech-language pathology. The CSRC will conduct interdisciplinary research into the causes and treatment of communicative disorders in children, and it will coordinate the research activities of faculty members in the participating divisions. We will recruit two additional faculty members in hearing science and speech/voice science to help in this effort.

## Pathology and Laboratory Medicine

Our division partners closely with the Division of Gastroenterology, Hepatology and Nutrition, providing laboratory support for a variety of research and clinical programs that have made Cincinnati Children's a center of expertise in pediatric liver disease.

Since combining services with clinical mass spectrometry last year, we have expanded our ability to provide highly specialized diagnostic services, including analysis of the genetic defects linked to the rare forms of cholestatic liver disease.

Also this year, the National Institutes of Health renewed funding for five years for a consolidated research effort into biliary atresia and cholestatic liver disease. The programs have been consolidated into a central resource for collecting specimens for research studies. Our division houses the pathology core and the histopathology core lab for this consolidated study; a division pathologist chairs the pathology core for both groups.

We provide all the laboratory support for a large portion of the adult oncology services in our area, with more than 250,000 patient encounters a year. It is a joint venture among our division, Hematology/Oncology, and Human Genetics.

During the past year, our clinical lab has installed a new Cerner Millennium system. The system allows detailed reporting on genetic tests, cytogenetics, and flow cytometry testing as well as real-time monitoring of workflow, QA, and turnaround times. Other lab improvements include bar-coded processing of samples and the addition of a second Ortho Vitros Fusion chemistry analyzer to back up the highest volume analyzer in the lab.

In a first-ever achievement,  
a research team at Cincinnati Children's has  
**found a way to grow bone,**  
using stem cells from a patient's own fat.

## Plastic Surgery

The plastic surgery division at Cincinnati Children's was engaged in a number of innovative research initiatives and collaboration efforts in 2009.

Several surgeons explored how to better replicate the body's tissues, including improving bone allograft revitalization and maximizing bone repair through the use of an acellular, scaffold-like periosteum substitute. These cutting-edge approaches capitalize on using living bone created from an individual's own stem cells, thus avoiding the risk of rejection or reabsorption. SBones developed from the acellular material replicate the form and function of real bone, as well as its capacity to heal. The preliminary results of this work are promising.

The craniofacial anomalies team, comprising physicians from Plastic Surgery, Dentistry and Orthodontics, Speech Pathology, Genetics, Psychology and Nursing, is focused on improving the lives of patients with craniofacial abnormalities, including cleft lips and palates. The division is collaborating with researchers in Developmental Biology to create a world-class research program focusing on craniofacial anomalies.

Finally, the division works as part of a multidisciplinary team focused on treating patients with plagiocephaly (malformation of the head). In addition to promptly treating patients with this condition, our physicians serve as a regional resource to educate physicians and families about plagiocephaly and ways to improve the outcome for children.

## Psychiatry

The division expanded its services, geographical reach and research endeavors with several major accomplishments.

Through the generous support of the Health Foundation of Greater Cincinnati's Youth Behavioral Health Initiative, we opened a first-of-its-kind clinic – the Post-Traumatic Healing Center – to serve the special needs of children dealing with traumatic life events. The center uses trauma-focused cognitive behavioral therapy to help children cope with sexual or physical abuse, loss of a loved one, violence, exposure to disasters, and other emotional or physical trauma.

The division also expanded its emergency psychiatric services to the hospital's Liberty Campus. The expansion includes a branch of the Psychiatric Intake Response Center,

the largest mental health assessment center for children and adolescents in the region. Social workers in the new response center have completed 491 psychiatric evaluations and provided assessment, triage and treatment for children suffering from physical trauma or abuse in Butler County and beyond.

Our psychiatrists focused on research for children with anxiety disorders, including selective mutism and Tourette's disorder. To date, five new research protocols were developed to explore the neurobiology and treatment of these and other anxiety disorders. In addition, a transcranial magnetic stimulation (TMS) study is under way to develop a new therapy for patients with treatment-resistant obsessive-compulsive disorder.

## Pulmonary Medicine

Investigators in our Cystic Fibrosis (CF) Center participate in many multi-center trials of new therapies. They also investigate CF-related protocols involving mechanisms of immune dysfunction, inherent metabolic abnormalities and potential corrective interventions, and the effects of variations in care practices on clinical outcomes. The center was selected to participate in the Cystic Fibrosis Foundation (CFF) Research Development Program and as a translational center within the CFF Therapeutics Development Network. CF research conducted by Christopher Karp, MD, recently published in *Nature*, identified IFRD1 as a modifier gene for cystic fibrosis lung disease.

The division's outcomes research program works to improve pulmonary healthcare delivery and outcomes by researching factors that contribute to clinical and patient-reported outcomes; developing and testing interventions that enhance patient health care experiences, self-management, or quality of life; and speeding the translation of basic and clinical research to the bedside.

Gary McPhail, MD, led a study published in the *Journal of Pediatrics* that examines better nutrition, fewer chronic pseudomonas infections and dornase alfa use in lung function outcomes. Jamie Wooldridge, MD, co-authored a study published in the *Journal of Pediatric Psychology* on improving inpatient airway clearance. Michael Seid, PhD, and Rhonda Van Dyke, PhD, study ways to use CFF registry data to examine the links between care processes and outcomes.

Seid also leads a National Institutes of Health study to pilot a cell phone-based adherence intervention for adolescents with asthma as well as research using video recordings of clinical encounters to understand the link between clinical interactions and adherence in CF.

The division also has developed a research clinical testing and diagnostic core with state-of-the-art equipment to test for lung diseases.

Carolyn Kercsmar, MD, is an investigator in the NIH-funded Inner City Asthma Consortium.

## Radiology

The Division of Radiology faculty and fellows presented 15 scientific papers and offered 43 workshops and poster sessions at the 2009 Society for Pediatric Radiology meeting, the most presented by any institution. Also at the meeting, division staff won a Caffey Award for Outstanding Clinical Research Paper, "Improving Patient Safety – Effects of a Safety Program on Performance and Culture in a Department of Radiology at a Children's Hospital." Contributors included Lane Donnelly, Julie Dickerson, Martha Goodfriend and Stephen Muething. Marilyn Goske, Rebecca Phillips, Keith Mandel, Richard Gardner, Daniel McLinden and Laurie Perry received a special commendation for their work, "CT Radiation Safety in Children: A National Web-Based Practice Quality Improvement Program." Division director Lane Donnelly, MD, received the Singleton-Taybi Award for Lifetime Achievements in Education at the meeting.

Neil Johnson, MD, was named president of the Society for Pediatric Radiology for 2009-2010.

Susan Sharp, MD, and Michael Gelfand, MD, received the 2009 Pediatric Imaging Council Young Investigator Award from the Society of Nuclear Medicine for their work, "Utility of SPECT/CT Imaging in Neuroblastoma."

William Ball, MD, was awarded the 2009 Gold Medal from the American Society for Pediatric Neuroradiology (ASPNR).

The Division of Radiology this year named Charles Dumoulin, PhD, scientific director of the Imaging Research Center (IRC). Dumoulin's research interests are in neonatal MRI and new approaches in accelerating MR scanning.

With the help of an NIH S10 shared instrument grant, the IRC purchased a new 3 Tesla MRI scanner, which is being used to lead translational imaging research in child development and disease. Key areas of research within the IRC include the study of language development, environmental neurotoxicity, hearing loss, juvenile arthritis, cardiac abnormalities and brain disorders.

The Reproductive Sciences Division's  
research is establishing a connection between

early fetal development and the onset  
of heart disease, obesity, diabetes and  
osteoporosis in adult life.

## Reproductive Sciences

In early 2008, Cincinnati Children's welcomed this latest research division, which focuses on understanding the complex biology of the human reproductive system. Founded with a full-time faculty of three physicians/researchers, the division has already grown to include a number of research fellows, joint appointment faculty members and support staff – and the recent addition of a fourth full-time faculty member from Harvard University.

During the past year, several of the division's faculty received funding for their research. The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) is funding research into "Molecular Signaling in Decidualization," a project aimed at defining the potential roles key cell cycle regulators play in uterine biology

during both implantation and decidualization. The Concern Foundation, a leading supporter of cancer research, renewed a grant for research into establishing a link between the loss of uterine-specific PTEN genes and p53 tumor suppressors in mice and endometrial cancer. Meanwhile, Ohio Cancer Research Associates is funding a project to determine the role of COX-2, an enzyme responsible for inflammation and pain, in a mouse model for endometrial cancer.

The division went global this year, establishing an international training program for recruiting reproductive science specialists worldwide. In its inaugural year, the program recruited three young scientists – one of whom is the youngest recipient of the Japan Society of Obstetrics and Gynecology Research Award.





## Rheumatology

The Division of Rheumatology has continued to thrive in clinical and translational research. In the last year, major advances have been made in understanding the molecular basis of and finding promising treatments for Juvenile Idiopathic Arthritis (JIA), the most common chronic arthritis in children and one of the more common chronic childhood illnesses.

The division completed three international, multi-center Phase III interventional trials, the results of which were published in the *New England Journal of Medicine*, *Lancet* and *Arthritis & Rheumatism*. The studies led to FDA and European approval of two powerful treatments for children with JIA. Additional studies are seeking new therapies for children living with systemic JIA, another chronic arthritis for which there is only limited treatment.

Our laboratory investigations focused on understanding the molecular basis of JIA. Using gene expression profiling,

researchers sought to define the basis for genetic risk and identify distinct molecular profiles related to the disease's various subtypes. In the past year, they completed an unprecedented set of genomic JIA datasets and profiles. The JIA datasets revealed a set of risk factors in common with other autoimmune diseases, like lupus and Crohn's disease, as well as risk factors unique to JIA.

Another important finding suggests that patients who develop JIA as young children share a biological basis for the disease that differs from patients who develop it later in life. This gene-focused research approach illustrates a fundamental shift in medicine towards developing molecular definitions for disease that enable doctors to glean greater insights into a disease's origins and pathogenesis.

## Skin Sciences Institute

Our institute produced three key studies this year that expand understanding of how skin serves as a crucial barrier to pathogens, be it involving vulnerable premature infants or health care workers exposed to hospital-acquired infections.

At full term, infants rely on a complex mix of anti-infective lipids, anti-microbial defense proteins and the physical barrier provided by their skin to thrive in the microbe-rich setting after birth. However, the premature infant is poorly equipped for environmental stressors. By comparing premature infants, full-term infants and adults, we quantified several biomarkers of innate immunity, including Keratin 1, 10, 11, Keratin 6, involucrin, albumin, fibronectin, cortisol, IL-1, TNF $\alpha$ , IL-6, IL-8, MCP1 and IP10. This method offers promise for measuring the maturity of a premature infant's skin and its ability to fight off infection.

Our institute also conducted the first study to examine skin disinfection using 2 percent chlorhexidine gluconate (CHG) and the effect of repeated dressing changes on infants with central lines in the NICU. We found that the disinfection process, including tapes and dressings, can contribute to the infants' skin compromise. Our findings suggest that alternative dressings should be developed that do not occlude the skin surface or strip its outer layers.

Hand hygiene is important among health care workers for preventing hospital-acquired infections. However, compliance nationally is only 30-57 percent, primarily due to irritant contact dermatitis (ICD). We tested an aggressive cream treatment among workers who had substantial, chronic skin damage from hand washing. The results suggest that creams designed to mitigate inflammation may help achieve the goal of "clean hands without compromise."

## Sports Medicine

The Division of Sports Medicine welcomed a new full-time physician and research fellow and had a number of key accomplishments, research opportunities and awards.

A team of scientists on the Sports Physical Therapy team participated in studies investigating the short- and long-term rehabilitation outcomes of patients following anterior cruciate ligament (ACL) reconstruction. Additional research examined the efficacy of various end-stage rehabilitation interventions in athletic populations. These findings were presented at numerous national and regional meetings during the year.

Tim Hewett, PhD, FACSM, director of the Sports Medicine Biodynamics Center, was awarded three grants in 2009 for sports medicine research. Hewett received a four-year, \$2.5 million award from the NIH titled, "Neuromuscular Intervention Targeted to Mechanisms of ACL Load in Female Athletes." The proposal aims to provide evidence-based intervention to decrease ACL injury risk.

Hewett was awarded a second NIH grant, "A Multi-faceted Approach Modeling ACL Injury Mechanisms." This four-year, \$2 million award will develop, validate and optimize a computational knee model to study ACL injury mechanisms.

Finally, the division received an award from the National Football League Charities for the third consecutive year. The grant, "Anterior Cruciate Ligament Reconstruction (ACLR): Clinical and Biomechanical Predictors of a Poor Outcome," will determine the incidence of subsequent ACL injury following ACLR and identify factors predictive of a second ACL injury.

Hewett was also named to the NIH's Federal Advisory Committee on the Musculoskeletal Rehabilitation Sciences Study Section until 2015.

The new \$1.75 million

# da Vinci<sup>®</sup> Surgical System

was used in 18 successful minimally invasive  
pediatric urology cases in 2009.

## Urology

A new robotic surgery system will lead to shorter lengths of stay for more urology patients thanks to a gift from the division to Cincinnati Children's.

Under the leadership of Curtis Sheldon, MD, division director, the division purchased and donated a \$1.75 million da Vinci<sup>®</sup> Surgical System. Our surgical team subsequently performed 18 successful surgeries this year using the system. Reported results include decreased pain, blood loss and length of stay.

The division is collaborating with Endocrinology, Human Genetics, Gynecology, Psychology and Social Services on a new initiative entitled the Center for Disorders of Sexual Development. This team of experts manages the care of patients and families facing a diagnosis of ambiguous genitalia or intersex issues.

As part of an affiliation between Cincinnati Children's and Arkansas Children's Hospital, our doctors have traveled monthly to Little Rock to perform complex genitourinary procedures and other procedures for children with spina bifida.

Eugene Minevich, MD, FACS, FAAP, was named president-elect of the American Association of Pediatric Urologists, a national non-profit organization promoting pediatric urology practice; and Pramod Reddy, MD, was named secretary-treasurer-elect for the association. William Robert DeFoor, MD, director of Urology Clinical Research, principal investigator for a number of clinical trials, provided a plenary presentation at the 2009 annual meeting for the Society for Fetal Urology in Chicago.



This report focuses on our talented faculty and staff, who generate the ideas and discoveries that are changing the world.

The discoveries produced by these physicians and scientists, working in concert with outstanding graduate students, post-doctoral fellows, research and core support staff, have brought about advances at the Cincinnati Children's Research Foundation in 2009 that are improving the lives of children every day.

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