



Research Horizons

A PUBLICATION OF THE CINCINNATI CHILDREN'S RESEARCH FOUNDATION

SUMMER 2013

Born Too Soon

Is prematurity
in your genes?

Our researchers probe
the mysteries of
preterm birth

Four steps
that could curb
prematurity

Jorge Bezerra, MD, **Gastroenterology, Hepatology and Nutrition**, received \$2.2 million for four years from the National Institute of Diabetes and Digestive and Kidney Diseases to study “Immunologic dysfunction in biliary atresia.”

Karen Edwards, MD, MPH, **Developmental Disabilities and Behavioral Pediatrics**, received a five-year, \$2.4 million grant from the Administration on Developmental Disabilities to work with the University of Cincinnati in creating the “University Center for Excellence in Developmental Disabilities.”

Jacqueline Grupp-Phelan, MD, **Emergency Medicine**, will use \$1.1 million in Centers for Disease Control and Prevention funds over three years to study “Suicidal teens accessing treatment in the ED (STAT-ED).”

Richard Lang, PhD, **Ophthalmology**, with the help of a three-year, \$1.7 million grant from the National Eye Institute, will study “Light-regulated vascular development of the eye.”

Jessica Kahn, MD, **Adolescent Medicine**, received a four-year, \$2.7 million grant from the National Institute of Allergy and Infectious Diseases to examine the “Epidemiologic impact of HPV vaccination.”

Darcy Krueger, MD, PhD, **Neurology**, will use a five-year, \$1.5 million grant from the National Institute of Neurological Disorders and Stroke, in conjunction with the Children’s Hospital of Boston, to examine “Early biomarkers of autism spectrum disorders in infants.”

Jeffrey Molkentin, PhD, **Molecular Cardiovascular Biology**, will study “Improving cardiac function after myocardial infarction” with the help of a \$3.2 million, five-year grant from the National Heart, Lung and Blood Institute.

Jill Huppert, MD, MPH, **Pediatric and Adolescent Gynecology**, will use a five-year, \$1.4 million award from the National Institute of Biomedical Imaging and Bioengineering to work with Johns Hopkins University on a “Center for point of care technologies research for sexually transmitted disease testing.”

Jennie Noll, PhD, **Behavioral Medicine and Clinical Psychology**, will use \$3.4 million over five years from the National Institute of Child Health and Human Development to study “Health and well-being of sexually abused females and their offspring.”

Aimen Shabaan, MD, **Fetal Cellular and Molecular Therapy**, will use a three-year, \$1.9 million grant from the National Heart, Lung and Blood Institute to examine “NK cell response to prenatal allotransplantation.”

Joshua Waxman, PhD, **Molecular Cardiovascular Biology**, will use a five-year, \$1.7 million award from the National Heart, Lung and Blood Institute to study “Coup-tf dependent mechanisms of ventricular and hemangioblast specification.”

Sing Sing Way, MD, PhD, **Infectious Diseases**, will study “The immune pathogenesis of prenatal *Listeria monocytogenes*” with a \$2.2 million, five-year grant from the National Institute of Allergy and Infectious Diseases.

Research Horizons

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About the Cover: As one of the nation’s top neonatology programs, Cincinnati Children’s cares for some 700 premature infants each year in our NICU.

Grant Accelerates Research

March Of Dimes Grant Amps Up Statewide Research on Prematurity

Too many babies in this country are born before their time. Too many die before their first birthday. In a country that prides itself on exceptional healthcare and the world’s finest hospitals, our rates of prematurity and infant mortality remain a quiet but persistent failure. The problems caused by preterm birth are so devastating to child health that The March of Dimes has identified prematurity as its “new polio campaign.” Determined to find solutions, the organization has pledged \$10 million over five years to fund the Prematurity Research Center Ohio Collaborative. The project brings together Ohio’s health research powerhouses – the University of Cincinnati College of Medicine/Cincinnati Children’s Hospital Medical Center; Ohio State University Wexner Medical Center/Nationwide Children’s Hospital; and Case Western Reserve University/University Hospitals MacDonal Women’s Hospital/Rainbow Babies & Children’s Hospital/MetroHealth System.

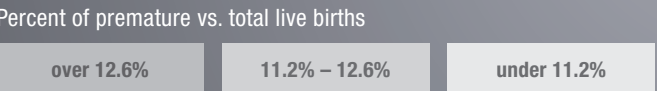
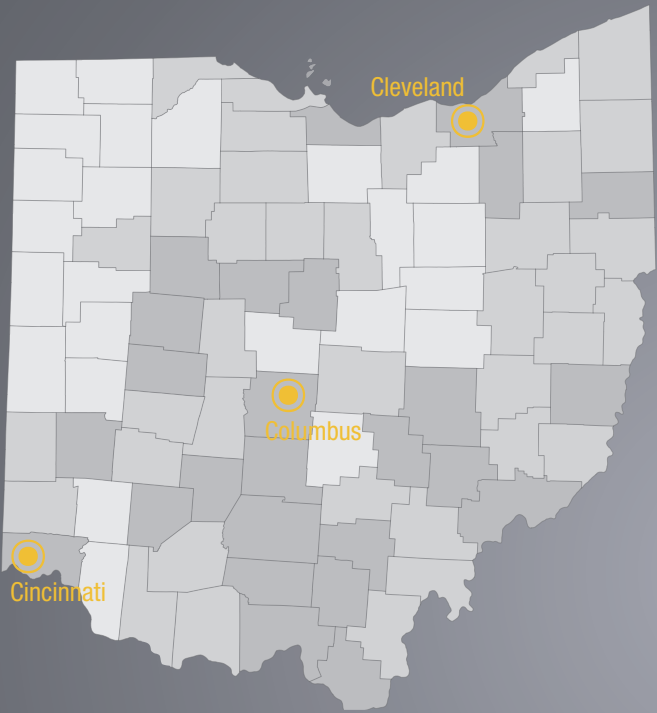
A TRANSFORMATIVE RESEARCH APPROACH

All three institutions already have strong research and clinical programs aimed at reducing prematurity, says Louis Muglia, MD, PhD, Director of the Center for Prevention of Preterm Birth at Cincinnati Children’s, and they have shared information informally. But the Collaborative will forge a truly innovative type of cooperation.

“Traditionally, investigators have applied research approaches that involve a single discipline at a time, with little crosstalk, and even competition, between investigators,” Muglia says. “The Collaborative will develop an integrated, transdisciplinary research team that transcends those usual boundaries.”

Muglia, who will serve as coordinating principal investigator of the Collaborative, adds that this arrangement will allow each institution to pursue its research strengths while minimizing overlap. Findings will be shared in a structured manner, and “each institution will contribute valuable population data from our respective regions.”

The Collaborative plans to tackle prematurity on a number of fronts, from the evolution of human pregnancy to genetic variants in prematurity and the role of progesterone signaling in maintaining pregnancy.



The Prematurity Research Center Ohio Collaborative will bring together research institutions in Cleveland, Columbus, and Cincinnati. Ohio’s rate of preterm births remains stubbornly high, at around 15 percent.

Source: National Center for Health Statistics, marchofdimes.com.

EXTENSIVE RESOURCE COMMITMENT

Beyond contributing talent and time, several participating institutions also have pledged significant funding to further the aims of the Collaborative.

Cincinnati Children’s will invest \$10 million over five years: \$5 million for projects and recruitment and a \$5 million endowment to ensure sustainability of the effort. The University of Cincinnati’s UC Health has committed \$1.25 million. Ohio State and Nationwide will provide 10 years of in-kind research support worth approximately \$20 million. Similarly, Case Western University Hospitals and MetroHealth are supporting research programs and faculty effort to partner in this endeavor.

Merck Grant Fuels Fragile X Research

A \$1 million grant from the John Merck Fund will expand translational research at Cincinnati Children’s to improve outcomes for children born with Fragile X Syndrome (FXS).

The syndrome is a genetic condition that causes intellectual disability, behavioral and learning challenges and some physical characteristics. Though FXS occurs in both genders, males are more frequently affected than females, and generally with greater severity.

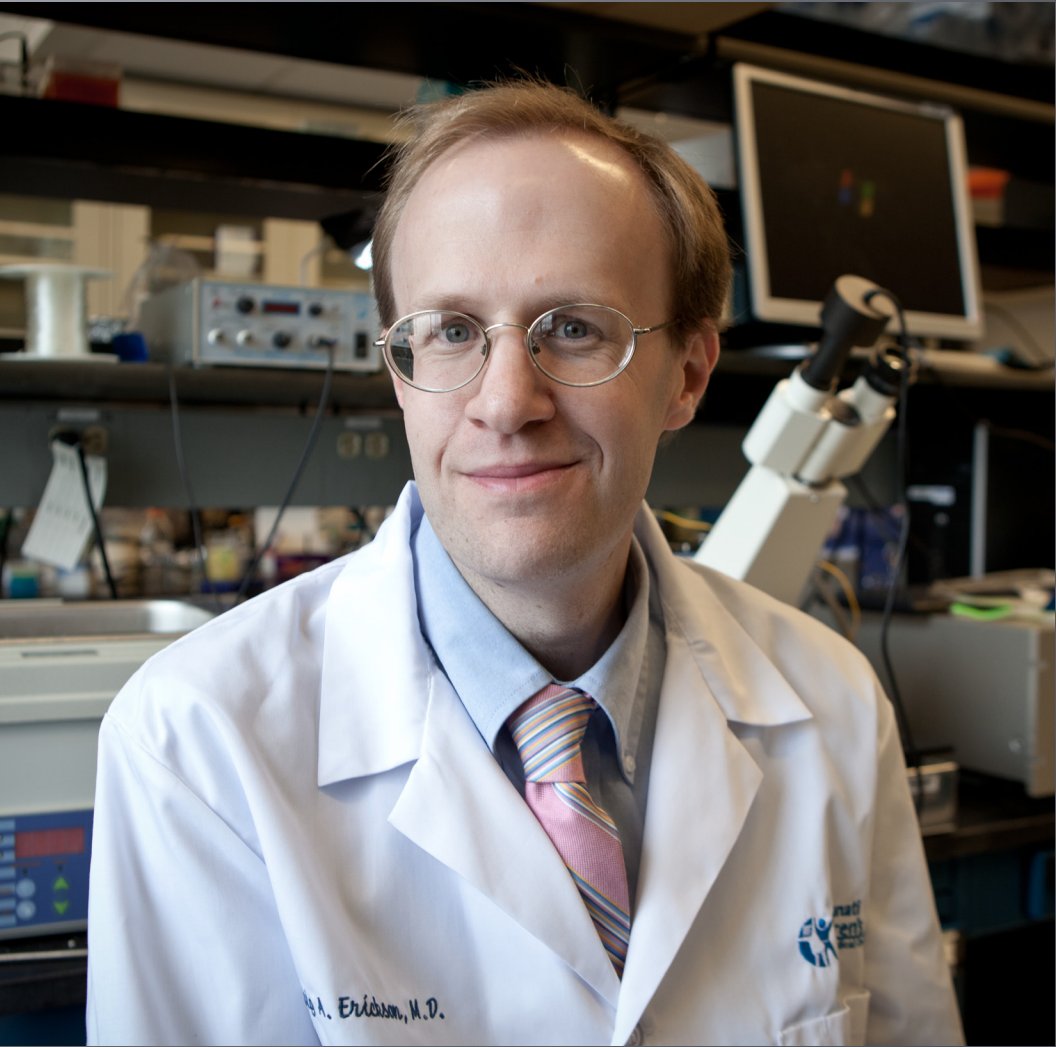
Craig Erickson, MD, Division of Child and Adolescent Psychiatry, plans to use the funds to launch a clinical trial to evaluate acamprosate – a drug currently used to treat alcohol dependence – as a potential treatment for youth with FXS.

In previous, early-stage studies at Indiana University, Erickson reported that acamprosate’s

effects on brain chemistry may help improve communication and social behavior skills for people with FXS. If the new trial proves successful, the drug also could be evaluated for use in other forms of developmental disability.

The grant is one of three recently announced by the John Merck Fund’s new Developmental Disabilities Translational Research Program, established in 2011. The three recent grant awards were selected from more than 100 proposals.

“What’s especially exciting about this program,” says Marsha Mailick, PhD, Chair of the Fund’s Scientific Advisory Board, “is that it supports research with potential game-changing impact that is within the realm of probability – not just possibility – and could be achieved within 10 years.”



More Manageable Weight Loss Program Proves Just as Effective

Obesity management programs need not be intense to improve outcomes for children with non-alcoholic fatty liver disease (NAFLD), according to a recent study led by our researchers.

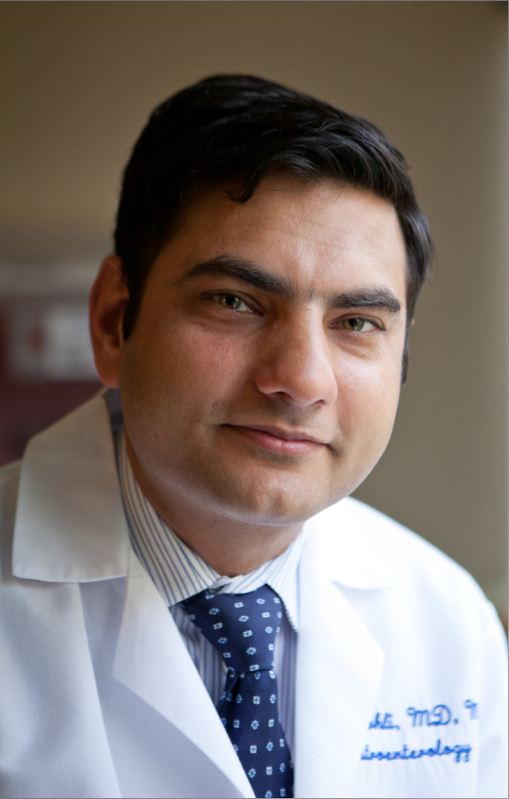
Published online March 19 in the *Journal of Pediatric Gastroenterology & Nutrition*, the study tracked children who completed one year in a “clinically feasible” weight loss program that involved 30-minute patient visits every three months to set and monitor nutrition and exercise goals.

The study was led by Rohit Kohli, MBBS, MS (right), a member of Cincinnati Children’s Steatohepatitis Center, and Stephanie DeVore, a Clinical Research Coordinator at the Center. Stavra Xanthakos, MD, MS, Co-Director of the Center, was senior author.

The researchers found that children who stayed with a weight loss program experienced statistically significant improvements in body mass index (BMI), total cholesterol levels and two key NAFLD biomarkers: alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

Fatty liver disease affects 10 percent of US children. Its more severe form – non-alcoholic steatohepatitis (NASH) – occurs in about two percent of US children. Experts know that weight loss helps manage the disease, but have struggled to develop diet and exercise programs that work for patients and in a busy clinic setting.

Patients in the study met with a gastroenterologist and dietician every three months for 30 minutes to set goals and monitor progress. Doc-



tors recommended exercise and set dietary goals focused on reducing sugar and saturated fat.

Kohli and DeVore noted that the children’s improvement was “comparable to that seen in more intensive pediatric weight management programs.”

Alternative to Bariatric Surgery?

In related work, Kohli and colleagues at the University of Cincinnati College of Medicine successfully tested a procedure in obese laboratory rats that could lead to less invasive alternatives to bariatric weight-loss surgery.

As reported online in *Endocrinology*, scientists used a catheter to re-direct bile from the bile duct into the small intestine, resulting in the same metabolic and weight-loss benefits as bariatric surgery.

“This may help us identify novel ways to treat obesity-related conditions,” says Kohli, who was lead investigator on the study. “Our results provide compelling evidence that manipulation of

bile acids is sufficient to recreate the key effects of bariatric procedures, including gastric bypass, and may be especially beneficial to people with obesity-related liver dysfunction.”

Emphasizing that extensive additional research is still required, Kohli adds that eventually, researchers hope to develop therapeutic agents that can produce the same benefits as bariatric surgery without the surgical procedures that alter intestinal anatomy.

Funding for the study came from the National Institute of Diabetes and Digestive and Kidney Diseases and Ethicon Endo-Surgery.

International Partnerships Expand

Cincinnati Children’s has established a formal collaboration with the Children’s Hospital of Chongqing Medical University, one of the largest pediatric hospitals and research centers in China.

The three-year agreement, which will focus on cancer and blood diseases, came about as a result of multiple visits between Cincinnati Children’s and Chongqing Children’s faculty and leadership over the years.

Chongqing Children’s faculty will make extended visits here to gain clinical experience in hematology/oncology. Chongqing will host several of our faculty each year for education and to consult on complex cases.

The hospitals also will hold virtual case conferences addressing complex patient scenarios several times a month and will consult on research program development and research protocol design.

“We are fortunate to have the opportunity to work with such a strong institution to advance our research programs,” says Tingyu Li, MD, President of Chongqing Children’s. “Our hope is that through our patients we can make our contribution to translational research at Cincinnati Children’s.”

Dr. Tingyu Li, President of Chongqing Children’s Hospital, and Dr. Arnold Strauss, Director of the Cincinnati Children’s Research Foundation, sign a three-year teaching and clinical agreement.



Anesthesia Toxic to Adult Brains, Too



Pediatric specialists are well aware of potential harmful effects of anesthesia on children's developing brains. But new research suggests adults may also be at risk.

Researchers from Cincinnati Children's report in the June 5 *Annals of Neurology* that testing in laboratory mice shows anesthesia's neurotoxic effects depend on the age of brain neurons, not the age of the animal, as once thought.

"Anesthesia-induced cell death in neurons is not limited to the immature brain," says Andreas Loepke, MD, PhD, a clinician and researcher in the Department of Anesthesiology. "Vulnerability seems to be dependent on the age of the neuron and targets brain cells of a specific age and maturational stage."

The younger the neuron, the more susceptible it seems.

New neurons are generated abundantly in most regions of a very young brain, explaining why research had focused on that developmental stage. In a mature brain, neuron formation slows considerably except in the dentate gyrus, which controls learning and memory and keeps forming

new neurons late into life. Researchers focused on this area in their study.

They exposed newborn, juvenile and young adult mice to the widely used anesthetic isoflurane in doses approximating those used in surgery.

Newborn mice had widespread neuronal loss in forebrain structures, confirming previous research, with no significant impact on the dentate gyrus. However, in juvenile and young adult mice, the results were reversed. The team discovered that age and maturational stage of the neurons were the defining characteristics for vulnerability to anesthesia-induced neuronal cell death.

More research is needed to confirm the study's relevance to humans. But Loepke says the goal is to learn enough about anesthesia's impact on brain chemistry to develop new protective strategies during surgery. He is collaborating with researchers from the Pediatric Neuroimaging Research Consortium at Cincinnati Children's to examine anesthesia's impact on children's brains using non-invasive magnetic resonance imaging technology.



Acute lymphoid leukemia (ALL) cells become much more vulnerable to conventional chemo and radiation therapies by inhibiting expression of the Gfi1 protein, according to early-stage studies using humanized mouse models.

A research team led by Cincinnati Children's and the Institut de Recherches Cliniques de Montreal (ICRM) reported the findings February 11 in the journal *Cancer Cell*.

Researchers at Cincinnati Children's have identified 14 more genes linked to juvenile idiopathic arthritis (JIA), the most common rheumatic disease of childhood.

The discovery, reported in the April 21 *Nature Genetics*, increased the number of genes with a recognized link to JIA from 3 to 17. The analysis re-confirmed JIA's connection to the original three genes, identified a link to 14 new genes and suggested that at least another 11 genetic regions may be implicated.



"Chemo and radiation therapies are very non-specific and can be toxic to patients. Our findings suggest that combining the inhibition of Gfi1 with these treatments may allow the use of lower cytotoxic doses to directly benefit patients," says H. Leighton Grimes, PhD, co-senior investigator and researcher in the Divisions of Cellular and Molecular Immunology and Experimental Hematology at Cincinnati Children's.

ALL is the most common type of leukemia affecting children. Improved treatments are needed because many patients relapse after achieving remission from initial treatment.

Researchers found that the protein Gfi1 is overexpressed in leukemic cells, which helps the cells escape destruction by p53, a well-known tumor-suppressing protein. Inhibiting Gfi1 allowed the tumor suppressor function to return to normal and did not cause harmful side effects in mice.

Research continues to determine if the approach used in the mouse models can be applied to human patients.

Collaborators in the study included co-senior investigator, Tarik Mörröy, PhD, President and Scientific Director of the ICRM; and James Phelan, PhD, and Cyrus Khandanpour, MD.

"These findings will help us understand how long-suspected genetic contributions to JIA are driving the disease process, with the ultimate goal being earlier and improved diagnosis and treatment," says Susan Thompson, PhD, Division of Rheumatology, who led the study.

An international research team analyzed nearly 3,000 patients recruited from more than 40 pediatric rheumatology clinics across the US, Germany and the United Kingdom. It was the largest population of patients with JIA ever studied.

The cause of JIA remains unknown. It can be treated with medications and physical therapy, but for many patients persists into adulthood.

The scientists stressed that they will continue their work to identify additional genetic links and to begin conducting functional studies to pinpoint disease processes.

Researchers from Wake Forest School of Medicine, the University of Manchester in the United Kingdom, and Emory University School of Medicine collaborated on the study. Funding came, in part, from the National Institutes of Health.

A Boost For Conventional Leukemia Treatment

New Genes Linked to Juvenile Arthritis

Nursing Expands Research

More nurse-scientists will soon be joining our ranks as part of a new initiative to expand research by nurses at Cincinnati Children's.

Rita Pickler, PhD, RN, has taken on the new role of Scientific Director of Nursing Research. She will lead efforts to increase the number of nurse-scientists on staff as well as the number of projects they oversee.

"Nationwide, the numbers of PhD-level nurses who are focused on children's health are relatively limited," Pickler says. "But with Cincinnati Children's so well established in pediatric research, we have great potential to develop a large, patient-oriented research program in nursing."

In addition to leading her own NIH-funded research, Pickler will work to enhance nursing research collaborations between Cincinnati Children's, the University of Cincinnati, and other academic institutions. She also will serve as a mentor for junior research faculty, says Scott Holland, PhD, Director of Research in Patient

Services at Cincinnati Children's.

Pickler joined Cincinnati Children's in May 2011 following a 21-year career at Virginia Commonwealth University, where she held an endowed professorship and was acting Associate Dean for Research. Her research has focused on preterm infant care and feeding, maternal well-being and pregnancy outcomes, and the impact of transitions between intensive care and home.

She received her bachelor's and master's degrees in nursing from the University of North Carolina at Greensboro and her PhD from the University of Virginia. She is a Fellow in the American Academy of Nursing and Co-Chair of the Child, Adolescent, and Family Expert Panel. Pickler also belongs to the National Association of Neonatal Nurses; the Association of Women's Health, Obstetric, and Neonatal Nursing; the Midwest Nursing Research Society; the Council for the Advancement of Nursing Science; and the National Association of Pediatric Nurse Practitioners.



The Division of Hematology will have a new Director beginning July 1. Russell Ware, MD, PhD,



will assume the post, as well as that of Executive Co-Director of the Cancer and Blood Diseases Institute. He will also serve as Associate Director of the Center for Child Global Health.

Ware's research interests focus on sickle cell disease, especially the use of hydroxyurea to ameliorate symptoms, including preventing stroke and managing iron overload, while improving quality of life. His efforts extend to treating sickle cell disease in Africa, leading to his focus in global child health. He is well funded by the NIH and several foundations for this work.

Ware received his medical degree from Duke University and completed his pediatric residency at Baylor College of Medicine and Texas Children's Hospital. He completed a fellowship in pediatric hematology and oncology and a PhD in Immunology at Duke University. Ware began his academic career at Duke before moving to St. Jude Children's Hospital, then Baylor, where he served as Chief of Hematology.

Sickle Cell a Focus for New Hematology Director

Developmental Biology Director Named

Raphael Kopan, PhD, will join Cincinnati Children's as Director of the Division of Developmental Biology this fall.

Kopan's primary research interest is the Notch1 protein, instrumental in guiding the development of embryonic cells into a variety of cell types, organs and tissues.

Studying the effects of Notch1 disruption has proved challenging because of the protein's essential role in embryonic development. Kopan's team solved the problem by engineering a mouse in which the Notch1 gene remains present throughout embryogenesis but becomes conditionally knocked out in adults.

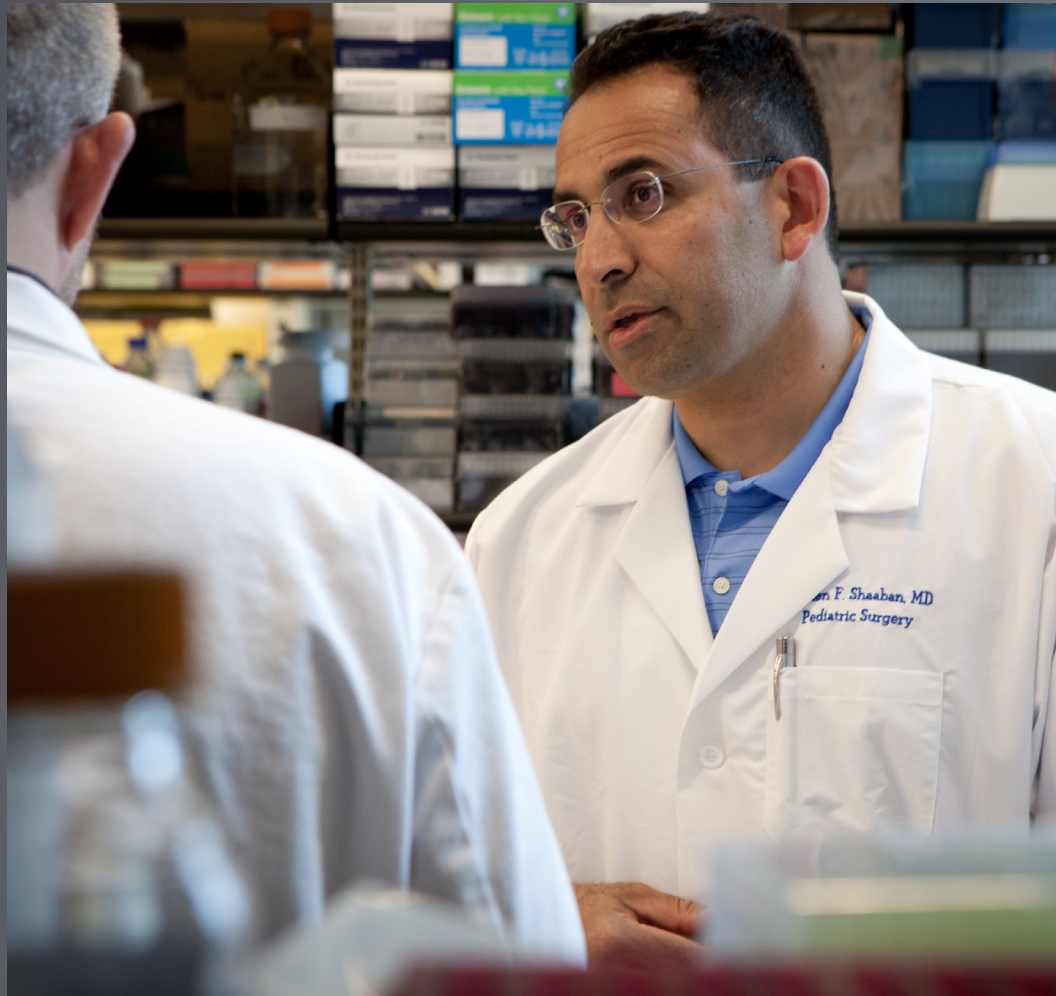
One of their recent findings, reported in the *The Journal of Clinical Investigation*, suggests that inactivating Notch1 in mice may cause abnormal proliferation of endothelial tissue, leading to vascular tumors, particularly in the liver.

Kopan has been the Wolff Distinguished Professor of Molecular Biology and of Medicine at Washington University School of Medicine in St. Louis, where he has worked since 1994. He earned a bachelor's degree in biology in 1981 and a master's degree in zoology in 1984, both from

Tel Aviv University. Following a stint in the Israeli Defense Force, Kopan received his doctorate in molecular genetics and cell biology at the University of Chicago and completed post-doctoral training at the Fred Hutchinson Cancer Research Center in Seattle.



Fetal Therapy Study Aims to Cure Disease Before Birth



Prenatal stem cell transplant is emerging as an alternative to bone marrow transplant for hereditary conditions such as sickle cell disease and thalassemia. But first, experts must find a way to beat a developing infant's natural killer (NK) cells.

That's the mission for Aimen Shaaban, MD, a fetal surgeon who joined Cincinnati Children's last year to become Director of the Center for Fetal Cellular and Molecular Therapy. He is using a five-year, \$1.9 million grant from the National Heart, Lung & Blood Institute to learn more about when NK cells become active during fetal development.

The potential advantage of fetal stem cell therapy comes from providing treatment before the immune system develops.

"We have the technology to detect specific genetic diseases as early as six or seven weeks' gestation, which gives us an opportunity to provide therapy while the fetus still has no immune system. This could cure certain diseases before symptoms ever begin," Shaaban says.

While some successes in human fetal therapy have been reported, clinicians also have reported unexpected, repeated failures. Shaaban and colleagues may have found a way to improve the odds.

Preliminary studies in mice reveal that knocking down the function of NK cells – an early-developing part of the immune system – gives transplanted stem cells the time they need to establish themselves. After a few weeks, when NK-suppressing drugs are stopped, the transplanted cells continue to function as intended.

Shaaban's team is expanding on these findings by determining more precisely how and when NK cells become active during fetal development. Their findings could help set new protocols for fetal therapy ranging from the timing and volume of donor cell doses to determining the need for booster transplants.

Prior to joining Cincinnati Children's, Shaaban directed fetal cellular therapy laboratories at the University of Iowa and the University of Wisconsin.

Improving Outcomes for Kids on Dialysis

Children with end stage kidney disease (ESKD) face enormous health hurdles, and a significantly shorter life expectancy. But a recent report shows that the outcome of dialysis treatment they require is improving.

In a study published in the May 8 issue of the *Journal of the American Medical Association*, Mark Mitsnefes, MD, MS, of the Division of Nephrology at Cincinnati Children's, and co-investigators from McGill University and Children's Hospital of Philadelphia found that death rates among children and adolescents undergoing dialysis for ESKD in the United States have declined significantly over the past two decades.

For children whose kidney disease has progressed to end stage, kidney transplant remains the treatment of choice. But while they await transplant, dialysis is a life-saving therapy.

The researchers conducted a study to determine if all-cause, cardiovascular and infection-related death rates changed between 1990 and

2010 among patients younger than 21 with ESKD initially treated with dialysis.

They identified a total of 23,401 children and adolescents in the United States who began ESKD treatment with dialysis during those two decades, and noted a significant decrease in mortality rates among the patients over that time period.

Children under age 5 who started dialysis in 1990-1994 had a mortality rate of 112.2 per 1,000 person-years. For those who began dialysis in 2005-2010, the rate fell to 83.4 per 1,000 person-years. Among those 5 and older, the mortality rates declined from 44.6 per 1,000 person-years to 25.9 over the same time period. Significant decline occurred in both cardiovascular and infection-related mortality.

Although further research is needed to determine the factors responsible for the decrease, the investigators reported that "improved pre-dialysis care, advances in dialysis technology and greater experience of clinicians may have played a role."



Pollution Linked to Hyperactivity

In a study published May 21 in *Environmental Health Perspectives*, a team led by Nicholas Newman, DO, MS, Director of the Pediatric Environmental Health and Lead Clinic at Cincinnati Children's, reported that children exposed to high levels of traffic-related air pollution (TRAP) during their first year of life were more likely to have "at risk" scores for hyperactivity by age 7.

The study followed children enrolled in the Cincinnati Childhood Allergy and Air Pollution Study. They were born in the Cincinnati metropolitan area between 2001 and 2003 and were selected based on family history of allergy and proximity to a major highway or bus route. They were followed from infancy to age 7, at which time parents completed a behavioral questionnaire and reported on symptoms including hyperactivity, attention problems, aggression, conduct problems and atypical behavior.

Of 762 children initially enrolled in the study, 576 completed the tasks necessary for inclusion

in the final analysis. Results showed that children exposed to the highest amount of TRAP during the first year of life were more likely to have hyperactivity scores in the "at risk" range. "At risk" means that children should be monitored for the development of clinically important symptoms.

Newman says "several biological mechanisms" could explain the connection between TRAP and hyperactive behaviors, including direct toxicity to the brain. Investigators at Cincinnati Children's are currently working to better understand these mechanisms.

He notes that studies have shown that approximately 11 percent of the US population lives within 100 meters (328 ft.) of a four-lane highway and that 40 percent of children attend school within 400 meters of a major highway.

"Traffic-related air pollution is one of many factors associated with changes in neurodevelopment," Newman says, "but it is one that is potentially preventable."



Dr. Nicholas Newman found that children exposed to traffic-related air pollution in their first year of life were at higher risk of ADHD by age 7. His research was carried out in collaboration with the University of Cincinnati College of Medicine's Department of Environmental Health.



Studies performed by pediatric rheumatologists in the US, Europe and South America have led to US Food and Drug Administration (FDA) approval of canakinumab (Ilaris) to treat active systemic juvenile idiopathic arthritis (SJIA) in patients aged 2 and older.

Canakinumab, an interleukin-1 beta (IL-1 beta) inhibitor, works by blocking an immune system protein that plays a key role in some inflammatory disorders. The drug is given as a monthly subcutaneous injection.

Approval came as a result of two international, multicenter phase III trials in children with SJIA between the ages of 2 to 19; the majority of children treated showed significant improvement. Hermine Brunner, MD, MSc, and Daniel Lovell, MD, MPH, in the Division of Rheumatology at Cincinnati Children's, led the studies.

Only one other drug is currently approved to treat SJIA - tocilizumab, an IL-6 inhibitor. Children with SJIA suffer from a variety of debilitating systemic symptoms and having another treatment option that controls these symptoms is, says Lovell, "a huge breakthrough."

He adds that having two approved treatments also improves the odds of more children living healthier lives with this serious disease.

"We have more options to discuss with families and a much greater chance of having at least one therapy work. I'm very excited about what the future holds for these kids."

New Treatment for Severe Arthritis Gets Thumbs Up

Logan to Lead Sports Medicine

Kelsey Logan, MD, MPH, will begin as Director of the Division of Sports Medicine July 1.

Logan's primary interest is in mild traumatic brain injury. Her publications address evaluating cognitive function after concussions for safe return to sports activities. Most recently, she led the sports concussion program at Ohio State University.

Logan received her medical degree from the University of Alabama and completed a combined medicine and pediatrics residency at the University of Mississippi Medical Center. She completed a fellowship in pediatric and adolescent sports medicine at the University of Wisconsin.

She is active in the American Academy of Pediatrics Section on Young Physicians, Council on Sports Medicine and Fitness, and Section on Combined Internal Medicine and Pediatrics. Logan also serves on the Research and Publications committees for the American Medical Society for Sports Medicine and has been appointed to the

National Collegiate Athletic Association Committee on Competitive Safeguards and Medical Aspects of Sports.



How early is too early?

The giant toll of saving the tiniest babies



The current model of saving the tiniest, most fragile premature infants “is not economically sustainable or biologically plausible,” says Dr. James Greenberg.

Three decades ago, most infants born at 28 weeks gestation – 12 weeks premature – did not survive their first year. Today, more than 90 percent do. Medical science has pushed the envelope of survival thanks to improvements that include better ventilators, wider use of prenatal steroids, artificial surfactant (developed in part based on research at Cincinnati Children’s) and other advances in neonatal care.

Survival odds for infants born at a once-unimaginable 25 weeks have soared beyond 50 percent. There are isolated reports of survival for infants born as early as 21 weeks and as small as 260 grams (9.17 oz.).

“With these kinds of improvements, people start asking, how low can we go? Why not 24 weeks, 23 weeks, or even lower?” says James Greenberg, MD, Co-Director of our Perinatal Institute.

SHIFTING FOCUS TO QUALITY OF LIFE

However, Greenberg adds, our ability to rescue ever younger and smaller preterm infants is approaching a point where the risks and required resources outweigh the potential benefits.

“It’s true that survival has continued to improve for extremely low gestational age babies. But it’s also clear that the incremental cost is exponential,” Greenberg says. “Many of these babies have long-term problems. The current model with its singular focus on caring for progressively smaller, more immature babies is not economically sustainable or biologically plausible.”

Physician-scientists at Cincinnati Children’s are focusing more on developing ways to keep babies in the womb longer. “If we can change a 28-week delivery to a 32-week delivery, outcomes will be better. Even a few days longer in the womb are beneficial,” Greenberg says.

One sign of progress: A four-year effort led by the Ohio Perinatal

Quality Collaborative (supported by Cincinnati Children’s) is improving health outcomes and saving costs by reducing elective C-sections in the last few weeks of pregnancy. “At first, obstetricians fought it, but the protocols were well enforced and we have significantly fewer late-preterm births now,” Greenberg says.

IVF COURSE CORRECTION

Meanwhile, IVF technology has improved to help correct a problem of its own making.

As more women delayed childbearing into their 30s and 40s, demand grew for ever more complex *in vitro* fertilization (IVF) treatments. In the early days of IVF, fertility specialists needed to transfer multiple embryos in hopes of generating just one live birth. But over time, multiple embryo transfers became more of a problem than a solution.

They caused a spike in IVF-related multiple births, many of which were preterm and required intensive care, says Maurizio Macaluso, MD, DPH, Director of Biostatistics and Epidemiology.

“Now as success with IVF has improved, the emphasis has started to shift toward single-embryo transfer,” Macaluso says.

Most treatment cycles still involve two transferred embryos. But the number of cycles involving four or more embryos has dropped from 32 percent in 2001 to 10 percent in 2010, according to the CDC. Meanwhile, single-embryo transfers have climbed from 6 percent in 2001 to 15 percent in 2010.

As a result, the numbers of multiple births stemming from infertility treatments have begun to fall.

In 2001, 64 percent of births after IVF treatment were singletons, 32 percent were twins and 4 percent were triplets or more, the CDC reports. By 2010, 70 percent of births were singletons, 29 percent were twins and just one percent were triplets or more. ■



vaginal birth \$10,166
vaginal birth with complications \$13,170
cesarean section \$17,052
cesarean section with complications \$23,111
preterm births \$52,400

Graph above shows the average cost of each type of birth. Preterm births cost a total of \$26.2 billion per year in the United States.

Building A Healthy Baby

Our Researchers and Clinicians Work to Prevent Disruptions Throughout Pregnancy



Can something as common as a yeast infection trigger early labor? Margaret Hostetter, MD, is using a Gates Foundation grant to learn more about whether infections can disrupt the delicate balance of a mother's immune system.
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SK Dey, PhD, studies the molecular dialogue flowing between mother and embryo during implantation. When this cross-talk goes awry, it can lead to miscarriage and preterm birth.
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Studies led by Sing Sing Way, MD, PhD, into how a mother's immune system changes to accept a developing fetus could lead to a pregnancy-protecting vaccine.
Page 23

Maternal stress alone may not trigger preterm birth, but it may have a multiplying effect when infections occur during pregnancy, according to research led by Claire Chougnnet, PharmD, PhD.
Page 27



ZYGOTE – BLASTOCYST



EMBRYO



FETUS

Cincinnati Children's has a relationship with regional maternity units that helps detect high-risk pregnancies, provides advanced support to minimize preterm labor and routes mothers to the most appropriate hospital for delivery and neonatal care.

Cincinnati Children's ranks among the nation's top neonatology programs, in large part due to the work of Dr. Jeff Whitsett. Artificial surfactant, which has saved a generation of preterm infants, was developed based on research led by Whitsett.

Since 2004, the Fetal Care Center of Cincinnati has performed more than 900 fetal surgeries. The center is one of three nationwide providing the full range of fetal therapies.

Poverty, race and other social disparities can have a "weathering effect" on women that can influence their risk of preterm delivery, says sociologist Jennifer Malat, PhD. Our community health outreach programs are working to combat this effect.
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LABOR & DELIVERY



NEONATAL CARE



WELCOME HOME
NEW BABY

The Genetic Connection

Keys to prematurity may hide in 'experiments of nature'



Genes could be one of the many possible causes of preterm birth, says Dr. Louis Muglia. A new genetics study will add to a growing body of research on women with family histories of preterm birth.

After decades of research and continued puzzlement over the causes of preterm birth, the answers are likely closer than we think – although well hidden inside us.

Uncovering those answers is the impetus behind a new comprehensive study into the human genetics of prematurity – a collaborative, multi-institutional effort led by Louis Muglia, MD, PhD, Director of the Center for Prevention of Preterm Birth and Co-Director of the Perinatal Institute at Cincinnati Children's.

"I don't want to give the impression that we think genetic variations drive the majority of preterm births, but we think genetics will allow us to get a handle on the molecular pathways and processes of prematurity," Muglia explains.

This is not the first time researchers have analyzed how genes might affect birth timing and particularly, the timing of premature birth. Plenty of effort has gone into trying to understand this health challenge, but with fairly modest results. Mainly because of changes in obstetric practices, the US preterm birth rate has declined slightly in the past few years. Still, preterm birth rates remain nearly 30 percent higher than 20 years ago, Muglia says.

GOING BIG AND BOLD

In hopes of turning the tide, the new genetics study will gather a large and well-characterized group of research participants. These new participants will be added to a list of about 2,000 families Muglia has recruited since 2004 in research collaborations involving the University of Iowa, Washington University, Vanderbilt University and the University of Helsinki in Finland.

Attracting a larger complement of participants – especially members of families prone to preterm birth – will help strengthen the study's statistical and informational power, according to Emily DeFranco, DO, a maternal-fetal medicine specialist at the University of Cincinnati and Cincinnati Children's who is collaborating on the project.

"Because the study is an avenue to give us a better perspective of the genetic influences of prematurity, we will invite the participation

of families who have multiple members affected by prematurity," DeFranco says.

What makes the new study different from past efforts is the sheer magnitude of the scientific and human resources that researchers will assemble – locally, statewide and beyond.

CLINIC TO FOCUS ON FAMILY HISTORY

On the local level, a new Familial Preterm Birth Clinic will open at Cincinnati Children's this fall. The clinic will enlist women with family histories of preterm birth to participate in the study, whether they are planning a pregnancy, are currently pregnant, or have had an earlier preterm birth.

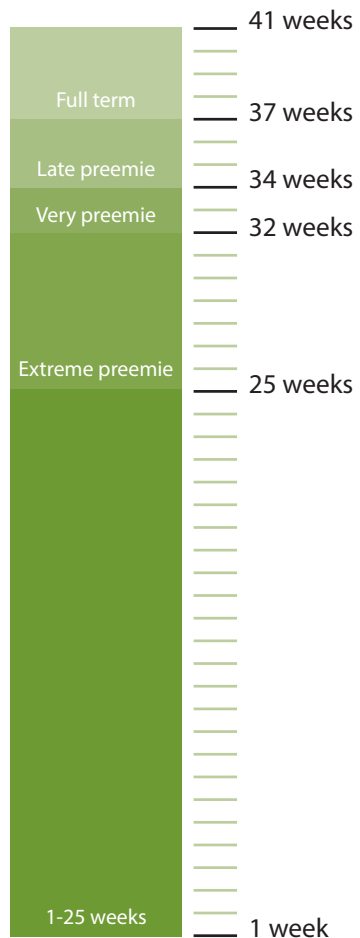
They will receive a comprehensive medical evaluation, be made aware of preventive interventions, and have the opportunity to participate in the genetic research studies. Using the latest genetic sequencing and analysis technology, Muglia will attempt to identify genes associated with preterm birth and look for variations between normal populations and those prone to prematurity. The goal is to find strong genetic associations for preterm birth, then use this information to feed studies linking genetic indicators to environmental factors such as lifestyle, health influences and socioeconomic traits.

STARTING WITH THE BASICS

Muglia says it makes sense to start by looking first at the genetics of families prone to preterm birth for no apparent reason, who have no obvious contributing lifestyle or other strong risk factors. Focusing on women who have risk factors highly associated with preterm birth could create too many potential variables.

Researchers believe families who lack obvious risks might serve as proverbial "canaries in the coal mine" – their genetic indications might rise to the surface more clearly.

Scientists then plan to see if genes identified in these families might also apply to Cincinnati's and Ohio's populations at high risk



for preterm birth – especially those in Ohio’s inner cities.

Although earlier studies by Muglia and others have identified a few candidate genes for preterm birth, researchers enter the new study with a more or less blank slate.

“The thing about modern genomic approaches is we don’t have to restrict ourselves or hedge our bets to what we think may most likely be involved,” Muglia says. “We’ll let the information we find tell us. What we are doing is focusing on experiments of nature – identifying and studying families that have multiple instances of children born prematurely for no reason we can identify.”

WORKING WITH COMMUNITY OBSTETRICIANS

Multi-institutional collaboration will be critical to the study’s success. Cincinnati Children’s will collaborate with obstetrical providers throughout Cincinnati. Muglia says the Familial Preterm Birth Clinic will not replace a woman’s current pregnancy care provider. “We just want to understand why some families are at such high risk,” he says.

The clinic will obtain DNA samples for research, get the family medical history related to preterm birth, and offer perinatal health counseling that might be beneficial to the women, according to DeFranco.

“The majority of women who come to the clinic will probably be those who have had spontaneous preterm births, where they just go into labor early for no apparent reason,” she says. “Those are the preterm births that tend to cluster in families,”

DeFranco says she expects research participation rates to be high among this group of women, who tend to be proactive about their reproductive health. She also believes it will yield useful information.

“We hope the study will help increase awareness and we will gain a lot of knowledge that will help us find potential interventions to reduce prematurity.”

Prematurity: Is It All in the Family?



The Familial Preterm Birth Clinic hopes to explore the genetic links in families like Linda Cyr’s that have a high incidence of prematurity. Linda and her four children were all born prematurely. From top left: Linda as a toddler on her mother’s lap; Linda today; and Linda’s four children.

Linda Cyr’s four children were all born prematurely. So was she. She still has questions about why the births happened the way they did. Now that her kids range in age from 13 to 21, Linda considers her family fortunate, but continues to look for answers.

“I have no idea why this happened,” she says. “If there is any thinking that it could be a genetic issue, I wish I’d known. I could have been a lot more prepared.”

Now almost 50, Linda was born a month before she was due.

“They never really did tell my mother why,” she says. “My father tells me my mother would go to the grocery store and pick up chickens and cry because I weighed less than the chickens.”

When Linda and her husband, Billy, decided to have their own family, both were

type-A Princeton graduates who planned everything meticulously. They even researched how to have a healthy pregnancy.

Most of the first pregnancy went smoothly, until contractions started coming early. Their son Britt was born a month ahead of schedule.

With her second child, doctors put Linda on bed rest for two weeks to delay delivery. But daughter Peppar arrived 13 weeks premature. Linda credits steroid shots for helping Peppar’s lungs develop quickly. After three months in the hospital, Peppar came home with no major health complications.

With her third and fourth babies, Linda had her cervix sewn shut to try to prevent more early deliveries. But Tigar’s traumatic birth came at 35 weeks, and a car accident prompted Tindar, her fourth child, to arrive early as well.

Each early birth carried its own set of worries, including an emergency blood transfusion, jaundice, breathing and heart-beat scares, pneumonia, concerns about eyesight, hearing and balance, signs of autism – and with one child, even mild cerebral palsy.

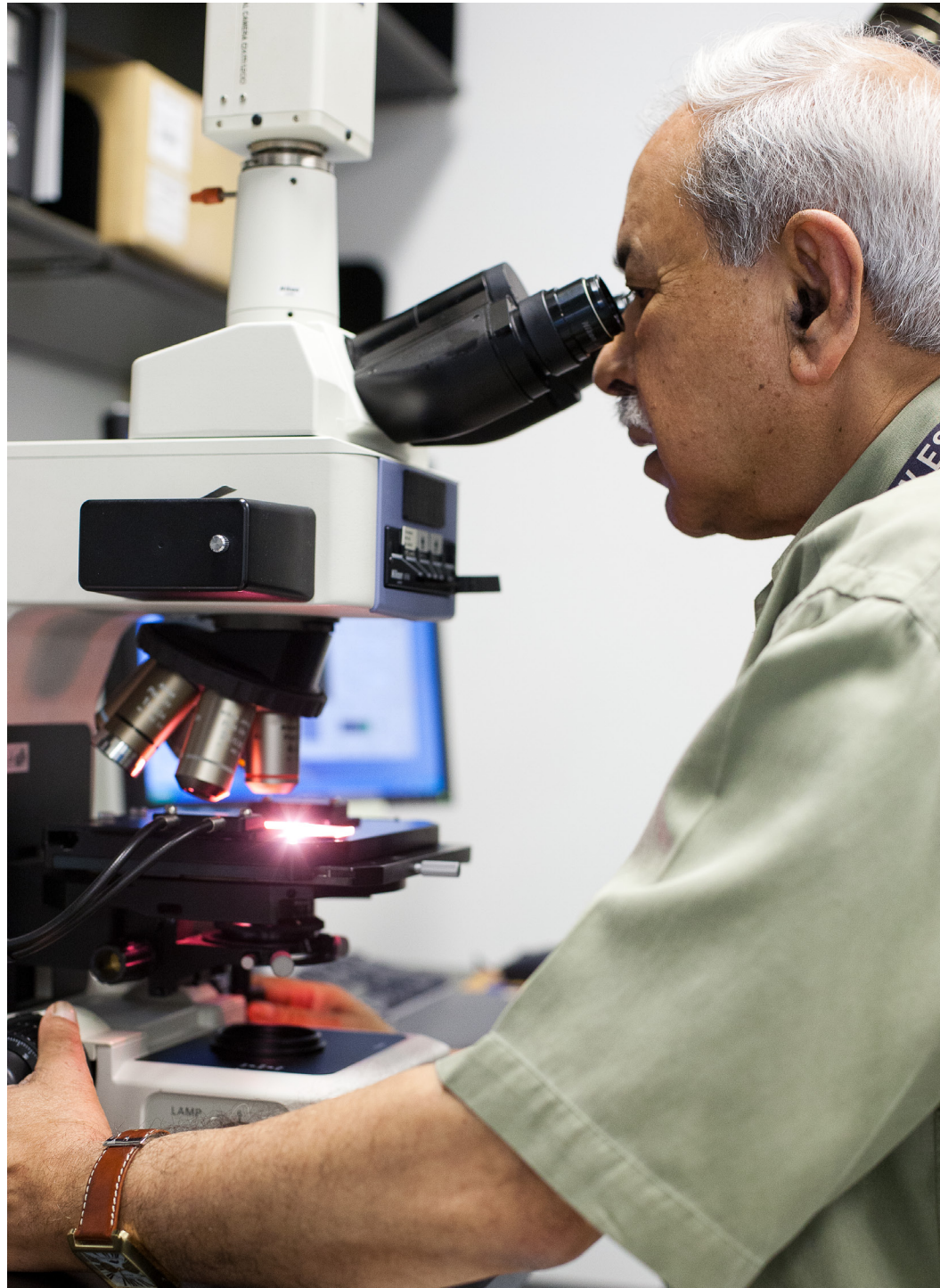
The experience left Linda feeling that more needs to be done to advance research. Daughter Peppar, now 19, hopes to study medicine and work on finding those answers.

“Even though my family has come out of this with positive outcomes, we see it as an important thing to have research going,” Peppar says. “Just because you have positive outcomes doesn’t mean you should be banking on that.”

Learn more about the Cyr family’s experience at www.cincinnatichildrens.org/prematurity.

No Easy Answers

Varied research mirrors the complexity of preterm birth



What happens at the very beginning of a pregnancy - when the embryo implants - can determine the health of a pregnancy and a baby, says Dr. S.K. Dey. His research focuses on the molecular cross-talk that takes place between mother and embryo during implantation.

Even when a zygote starts out with a healthy mix of genes, the 40-week journey for a human infant to reach full-term can be thrown off balance in many ways.

Some disruptions occur within days of conception, others happen months into the process. Any can trigger miscarriage and premature birth. Research efforts at Cincinnati Children's are exploring ways to prevent disruptions and help more pregnancies end in success.

"We are talking about addressing fundamental, unanswered biological questions. What controls the duration of human gestation? Why are human pregnancies supposed to last 270 days, and who controls the timing - the mother? The fetus? Both?" says James Greenberg, MD, Co-Director of the Perinatal Institute at Cincinnati Children's. "We need to understand the problem of preterm birth in a more granular sense than we do now."

GETTING A GOOD START

S.K. Dey, PhD, Director, Division of Reproductive Sciences at Cincinnati Children's, has devoted years of research to that understanding. Dey focuses on pinning down the molecular mechanisms of embryo implantation. Failed implantation ends a pregnancy within two weeks of fertilization. Not-quite-perfect implantation can lead to a variety of poor outcomes.

In a review article published in December 2012 in *Nature Medicine*, Dey and colleagues describe a "molecular dialogue" that flows between mother and embryo during implantation. When this cross-talk goes awry, it can lead to problems including preeclampsia, miscarriage and preterm birth.

Their work also shows how defects in specific genes - and the proteins they produce - can prevent successful implantation. It explains previ-

ously unknown details of the early stages of development and suggests a potential therapy to rescue some at-risk pregnancies.

In studies of mice, a single low dose of rapamycin (an immune suppressant used in organ transplantation) prevented preterm birth in mice genetically engineered to produce preterm pups. Published online in the October 2011 *Proceedings of the National Academy of Sciences (PNAS)*, the study reports that the mTORC1 signaling pathway plays a critical role in fetal development and that it can be manipulated.

"Implantation is where the process starts. But our knowledge about this stage is lacking. What are the molecular players? How do the transitions work?" Dey asks. "Understanding these molecular signaling networks may lead to approaches to improve the outcome of natural pregnancy and pregnancy conceived through *in vitro* fertilization techniques."

Several years of preparatory research must be completed first, Dey says, but the next major step will be to test these mouse model findings in human clinical trials.

MAINTAINING A DELICATE BALANCE

Other researchers at Cincinnati Children's are exploring the ways in which the mother's body tricks its own immune system into accepting the developing fetus rather than attacking it as a foreign invader.

Sing Sing Way, MD, PhD, a pediatrician and researcher in the Division of Infectious Diseases, has published three important recent findings that describe the roles played during pregnancy by an immune suppressive CD4 T-cell subset called regulatory T-cells (T-regs).

First, Way and colleagues reported that pregnancy triggers an accumulation in T-reg levels, which dampens the mother's immune system to

"We need to understand the problem of preterm birth in a more granular sense than we do now."

The United States ranks 34th in infant mortality

01	Singapore	1.92
02	Iceland	2.07
03	Japan	2.62
04	Sweden	2.56
05	Finland	2.81
06	Norway	3.00
07	Luxembourg	2.32
08	Czech Republic	3.19
09	France	3.54
10	Slovenia	3.51
11	Switzerland	3.75
12	Germany	3.71
13	Spain	3.76
14	Austria	3.97
15	Belgium	3.81
16	Italy	3.51
17	Denmark	4.03
18	Netherlands	4.42
19	Australia	4.66
20	Israel	3.85
21	Ireland	4.04
22	South Korea	3.76
23	Portugal	4.45
24	Canada	5.22
25	United Kingdom	4.91
26	New Caledonia	4.78
27	Greece	4.65
28	Brunei	4.78
29	New Zealand	5.07
30	Macau	4.43
31	Cyprus	4.60
32	Croatia	6.05
33	Cuba	5.13
34	United States	6.81

The number to the left is the rank of infant mortality (death by age 1) by country based on averages from 1950-2010. The number shown on the right represents the deaths per 1,000 births between 2005-2010.

Source: 2010 revision of World Population Prospects, United Nations Department of Economic and Social Affairs.

allow the “invasion” of a developing fetus. However, this process also makes the mother more vulnerable to infections. These findings were published in July 2011 in *Cell Host Microbe*.

Then in a study published August 2012 in *Public Library of Science (PLOS) Pathogens*, Way and colleagues described how the prenatal pathogen *Listeria monocytogenes* can override the T-reg levels that maintain the mother’s immune system. This causes her body to attack the fetus and trigger a miscarriage. A similar process occurring later in pregnancy may be the cause of some premature births, Way says.

T-REGS WITH A MEMORY

These findings led to a breakthrough study published in October 2012 in *Nature* reporting that pregnancy does not simply trigger a surge in T-reg cells. Instead, the mother experiences a dramatic increase in T-regs that can “remember” past pregnancies. These T-reg cells recognize paternal antigens so that when the same father impregnates the mother again, the fetus is better protected.

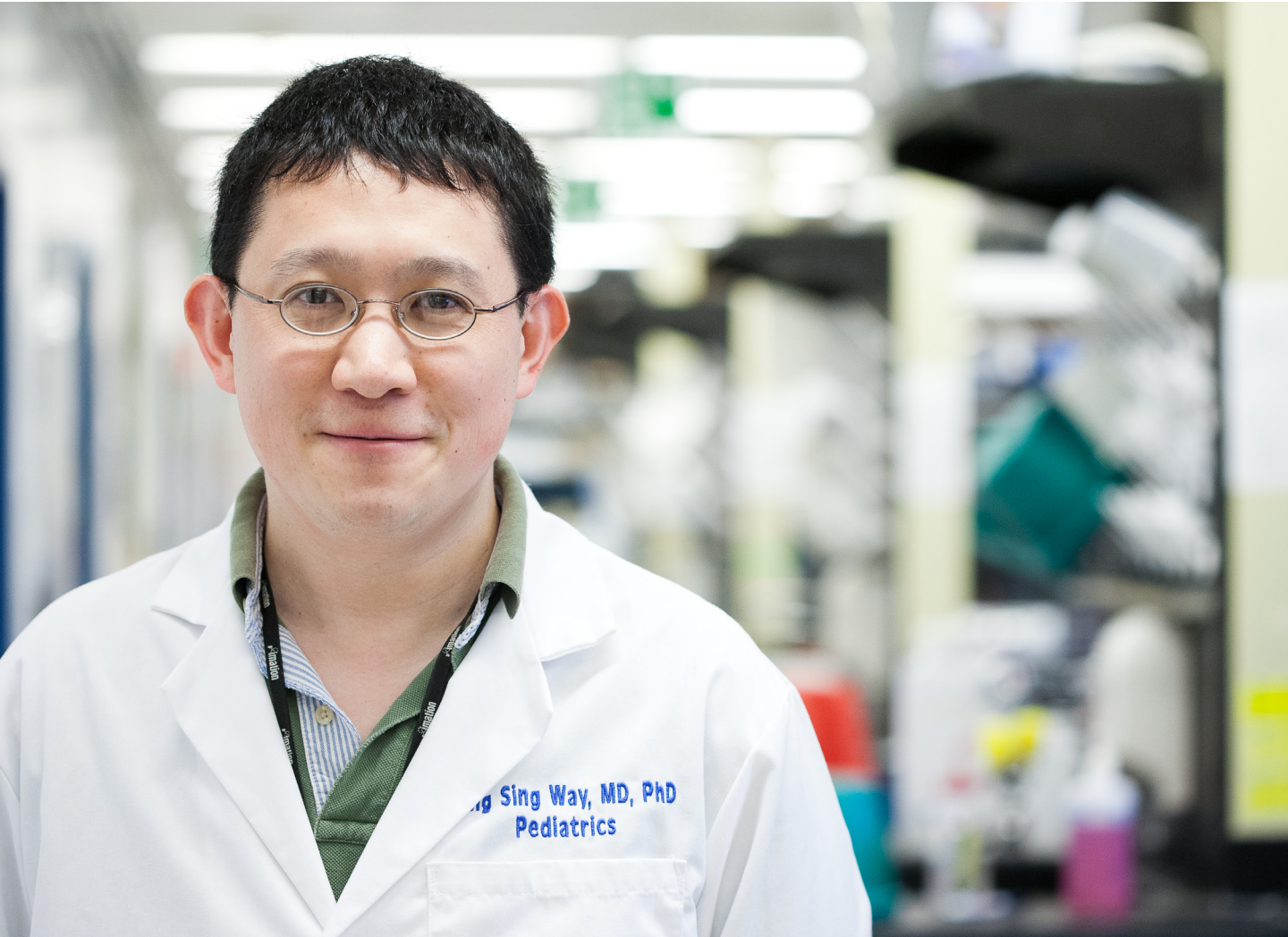
This protective feature increases with multiple pregnancies involving the same father, making future miscarriages less likely. But the effect does not apply to pregnancies involving a new father. If the mother changes partners, Way’s team found that she reacts to a new fetus as if she had never been pregnant before.

VACCINATING AGAINST MISCARRIAGE

This finding supports the possibility of developing a vaccine to protect pregnancy, Way says.

Unlike typical vaccines, which boost immune response to an invading pathogen, a pregnancy vaccine would help suppress an expectant mother’s immune system. More importantly, vaccines could be tailored to match the father, which would preserve the T-regs with “memory” while suppressing T-regs that could attack a fetus.

If this process translates from mice to humans, the result could be vaccines to boost the chances of full-term birth for couples going through IVF treatments, first-time mothers, or women with a history of miscarriages.



A mother’s body should reject a fetus like any other foreign body, yet it does not. Dr. Sing Sing Way has shown that a surge in regulatory T-cells suppresses the mother’s immune system and allows the “invasion” of a fetus.



INFECTION AND PREGNANCY

Vaginal yeast infections have plagued women worldwide for generations, but only in recent years has science begun to connect vaginal *Candida* colonization during pregnancy with an increased risk of premature birth.

Margaret Hostetter, MD, Director of the Division of Infectious Diseases, is using a \$1 million grant from the Gates Foundation to study why such a common infection can cause such an uncommon outcome.

Candida vaginal infections occur in 22 to 38 percent of pregnant women in the US and in as many as 60 percent of pregnancies in low-resource nations. In many cases, symptoms are so mild that women may not even realize they have been infected.

For some women – experts cannot yet predict which women are most at risk – untreated yeast infections appear to disrupt the delicate balance of T-reg cells that protects the developing fetus from attack by the mother's immune system.

A LINK TO PRETERM BIRTH?

Hostetter is leading a three-year project to understand the mechanisms at work during a *Candida* vaginal infection. She hopes to determine why some infections are associated with premature births, while others are not. Her study was one of only five to be funded from more than 320 applications to the Global Alliance to Prevent Prematurity and Stillbirth, an initiative led by Seattle Children's Hospital and funded by the Gates Foundation.

"The idea of a link between *Candida* colonization and premature birth is still debated," Hostetter says. "But I think we may find that this pathogen is more directly involved than we thought."

Hostetter's team hypothesizes that yeast infections trigger a spike in inflammatory Th17 cells, which help attack the infection, but at the expense of T-reg cells needed to protect the fetus. This disruption in the immune system's balance can lead to fetal wastage and premature birth.

Left: Dr. Margaret Hostetter (top, center) with John Paluszynski and Kris Orsborn; the researchers are exploring whether overgrowth of the common *Candida Albicans* yeast (in plate) can increase a woman's risk of premature birth.

"Preterm birth is the leading cause of death for newborns, affecting rich and poor countries alike," says Gary Darmstadt, Director of Family Health at the Gates Foundation. "We urgently need to develop new resolutions to give every baby a healthy start to life."

The good news is that inexpensive antifungal treatments are widely available, even in low-resource nations. Results from this study could help identify the best times to screen for *Candida* and begin treatment.

The longer term goal is to understand how the immune system responds to *Candida*. It may reveal a pathway that also could be used to prevent pregnancy complications associated with other pathogens, such as *E. coli*, *Trichomonas* and *Gardnerella* bacteria.

THE IMPACT OF STRESS

Scientists at Cincinnati Children's also are working to gather hard data on a long-debated question – how much impact does

maternal stress play in triggering preterm births?

Some studies suggest that psychological stress by itself plays no significant role in causing premature birth. However, other research clearly shows that stress can synergize with inflammation to cause preterm birth.

Louis Muglia, MD, PhD, Director of the Center for Prevention of Preterm Birth, and Claire Chougnnet, PharmD, PhD, a researcher in the Division of Cellular and Molecular Immunology recently received notice that their application was well received by the NIH, and hope to co-lead a multidisciplinary effort to learn more about the connections between stress, infections and the immune response.

"We know that some people cope with stress much better than others. We also know that not every infection during pregnancy leads to preterm birth. So we theorize that there may be a complementary effect," Chougnnet says.

The challenge is how to glean precise

data from such hard-to-measure factors. "Proving this theory is very difficult with observational studies in humans. There are too many uncontrollable variables," Chougnnet says.

Their project involves studying rhesus macaques under a variety of carefully controlled laboratory conditions, and will be done in collaboration with the California National Primate Research Center, one of the largest primate centers in the US. The research team involves experts in the physiology of pregnancy, immunology/inflammation, primate behavior and psychology, biostatistics and other fields.

The project will take several years to complete. But if successful, she says, the findings could suggest more effective ways to help anxious, would-be mothers minimize their risk of going into labor too early. ■

Dr. Claire Chougnnet and a team of researchers are studying how stress contributes to inflammation and premature birth.





For many disadvantaged women, prenatal care falls to the end of a long list of basic needs that must be taken care of first, says Dr. Elizabeth Kelly. A new program will attempt to remove barriers so that women can stay healthier during pregnancy and deliver healthy, full-term babies.

Blending Heart and Science

An innovative community program puts the science of evidence-based care behind the art of preventing preterm births among women at risk



Fueled by a decades-long, higher-than-average rate of preterm birth and infant mortality in this region, Cincinnati Children’s physicians and researchers have a vested interest in determining why babies are born too early. Experts here are tackling the problem on multiple fronts, but answers remain elusive. Until we know more, we continue to expand community-based efforts to curb the incidence of premature births among the most vulnerable women.

INNOVATION WHERE IT MATTERS

One such effort has brought Cincinnati Children’s, the University of Cincinnati (UC) and the Cincinnati Health Department together in a novel approach to reducing the incidence of preterm births. The program targets poor, uninsured minority women, the group most at risk of giving birth to very early, small and fragile babies.

The program grew out of an innovative program started by Elizabeth Kelly, MD, an obstetrician-gynecologist with UC’s Department of Obstetrics and Gynecology and Director of the Division of Community Women’s Health. Kelly has worked with disadvantaged women for more than two decades. She is well acquainted with the inequities and obstacles they face in receiving prenatal care. Giving birth to the earliest and most frail preterm babies is one of the most devastating results of those inequities.

Kelly knows that a major obstacle facing the women she serves is making and keeping prenatal appointments. Lack of transportation, no child care, job demands, struggles with food and housing all contribute to a perfect storm of reasons why disadvantaged women do not receive needed prenatal care. So a few years ago, she began offering same-day access to prenatal care at one of the Cincinnati Health Department’s health centers.

Dr. Rob Kahn and team will measure whether interventions aimed at improving women’s health will result in fewer preterm births.

REMOVING BARRIERS

“A woman could walk into a health center, get a pregnancy test, and we offered her care that day,” Kelly says. The clinic made allowances in staffing and schedules to accommodate the enthusiastic response. It was a positive first step.

Before long, quality improvement (QI) specialists in the Anderson Center for Health Systems Excellence at Cincinnati Children’s learned about Kelly’s same-day program and asked if they could work with her.

Together, they identified four evidence-based interventions that are crucial to ensuring a healthy pregnancy and reducing infant mortality:

- Providing same-day access to care
- Addressing “social determinants,” the social and economic issues that affect a woman’s health
- Help to stop using tobacco and other harmful substances
- Ensuring a safe sleeping place for newborns

The program now operates in the Cincinnati Health Department’s Elm Street and Price Hill Health Centers and receives strong support from community organizations. Women who receive prenatal care at those centers have access to most of the interventions; the tobacco cessation portion is still in development. The QI specialists ensure that interventions are offered systematically and track outcomes – which they hope will be healthy, full-term babies.

Robert Kahn, MD, MPH, Associate Director of General and Community Pediatrics at Cincinnati Children’s, worked with the QI

team and Kelly to put the interventions in place.

“It’s been fantastic to have an obstetrician as a partner because child well-being is so dependent on a healthy pregnancy,” Kahn says. “Dr. Kelly and her team at the Cincinnati Health Department clinics are incredibly committed to the women they serve and to achieving improved birth outcomes.”

PAVING THE WAY
FOR A HEALTHIER PREGNANCY

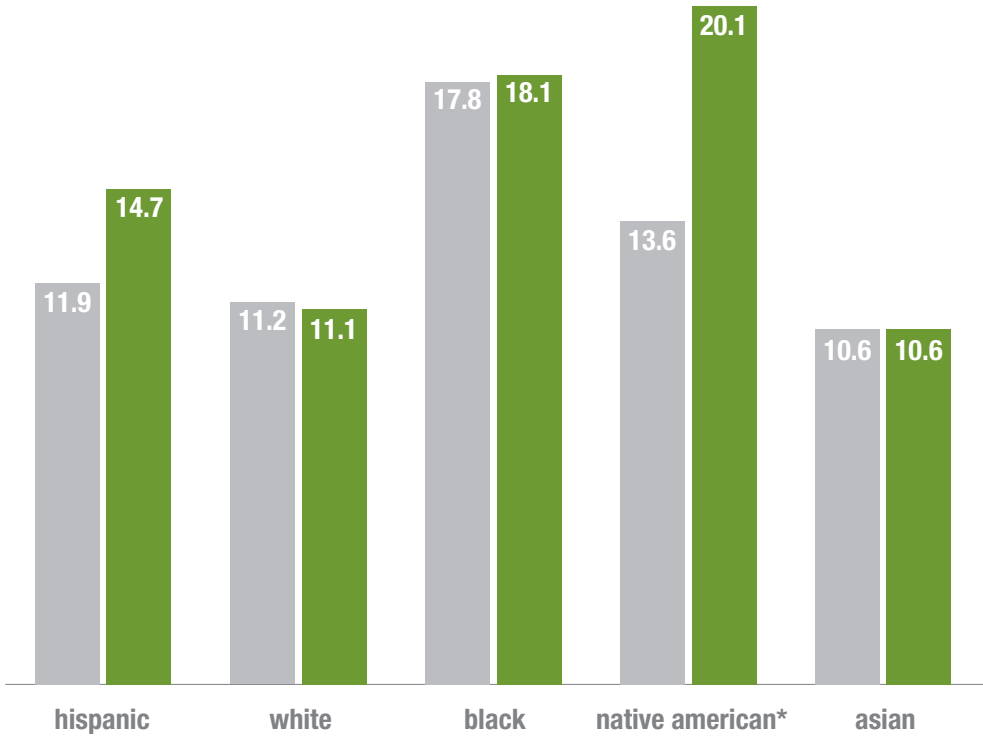
Kelly welcomes “putting science behind” what her years of experience have taught to be major obstacles to receiving good prenatal care.

“Until a woman is free of things like being a victim of domestic violence, and has heat in her home, and food, and a ride to her appointments, it’s pretty hard for her to adhere to her health care,” she says. “The QI team is providing their expertise in improvement science to implement and measure the impact of removing some of these barriers.”

Although it remains too early to report the program’s impact, Kelly has already seen some positive results.

“Our patients love it,” she says. “They are genuinely concerned about their health and the health of their babies. This program allows more of their basic needs to be met so they can focus on staying healthier.”

Preterm births remain high among minorities



Graph shows disparity in preterm birth rate by race and ethnicity. Averages are from data accumulated over 10 years (2000-2010) and represent national vs. Hamilton County, Ohio (Cincinnati) rates.

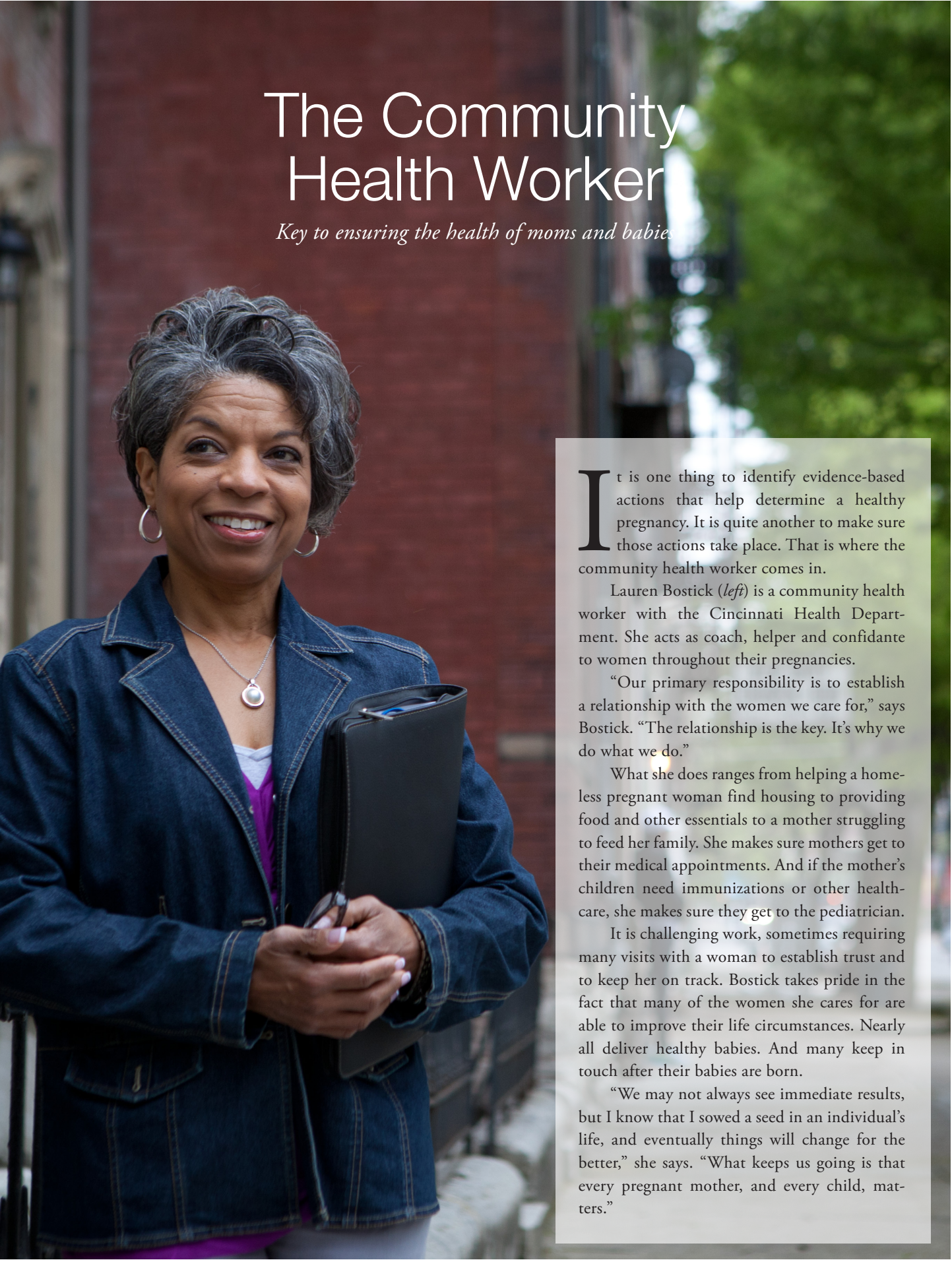
*Native American data in Hamilton County ended in 2009.

Source: National Center for Health Statistics, final natality data. Retrieved May 3, 2013, from www.marchofdimes.com/peristats.

Preterm by race/ethnicity	
	National Average
	Hamilton County Average

The Community Health Worker

Key to ensuring the health of moms and babies



It is one thing to identify evidence-based actions that help determine a healthy pregnancy. It is quite another to make sure those actions take place. That is where the community health worker comes in.

Lauren Bostick (*left*) is a community health worker with the Cincinnati Health Department. She acts as coach, helper and confidante to women throughout their pregnancies.

“Our primary responsibility is to establish a relationship with the women we care for,” says Bostick. “The relationship is the key. It’s why we do what we do.”

What she does ranges from helping a homeless pregnant woman find housing to providing food and other essentials to a mother struggling to feed her family. She makes sure mothers get to their medical appointments. And if the mother’s children need immunizations or other health-care, she makes sure they get to the pediatrician.

It is challenging work, sometimes requiring many visits with a woman to establish trust and to keep her on track. Bostick takes pride in the fact that many of the women she cares for are able to improve their life circumstances. Nearly all deliver healthy babies. And many keep in touch after their babies are born.

“We may not always see immediate results, but I know that I sowed a seed in an individual’s life, and eventually things will change for the better,” she says. “What keeps us going is that every pregnant mother, and every child, matters.”



The problems that contribute to a twofold-higher incidence of preterm birth among African Americans begin long before pregnancy, says sociologist Dr. Jennifer Malat, and the solutions are far beyond medicine's scope.

Looking Beyond Medicine

Health problems faced by people who are disadvantaged cannot be solved with medicine alone

The Center for Preterm Birth at Cincinnati Children's has teamed with experts in the University of Cincinnati (UC) Department of Sociology to gain insight into how social factors – particularly social disparities – affect the incidence of prematurity.

UC sociologist Jennifer Malat, PhD (left), studies racial and economic inequality in health. She says factors that lead to a poor pregnancy outcome can occur long before a baby is conceived.

“From the sociological perspective, women's health – all people's health – is shaped by a lifetime of experiences – a lifetime of exposure to stress, to toxins, whether people have access to healthy food,” Malat says. “Healthcare usually focuses on behaviors and the choices people make. Sociologists look at the opportunities or obstacles people face that affect those behaviors and choices.”

In the United States, long-standing economic and social advantages give whites a distinct health edge over African Americans.

“In understanding preterm birth or any health disparities, it is important that we think about advantage as well as disadvantage,” says Malat. “There are vast social and economic differences that allow white people to better protect their health. Instead of saying, ‘People don't have access to healthy food,’ we should ask, ‘How is it that some people do, while others don't?’ There are much bigger questions we should be looking at.”

BEHIND THE HIGHER MORTALITY RATES

Malat offers a concept called the “weathering hypothesis,” developed by sociologist Arline Geronimus, to help explain why infant mortality in this country is more than twice as high among African American women.

“The idea is that in our society, the health of African American women begins to deteriorate earlier in adulthood as a consequence of a lifetime of economic and social disadvantage. And this can affect birth outcomes. Birth outcomes are af-

fected not only by disadvantage during the nine months a woman is pregnant, but by experiences before pregnancy, too.”

BIGGER CHANGES ARE NEEDED

Malat is quick to point out that she is a researcher and teacher, not a clinician. “My role is to provide organizations like Cincinnati Children's with information about bigger patterns and trends that I hope will help inform their work.”

And although she acknowledges that clinicians' work is vitally important to making a difference, Malat says reducing prematurity and infant mortality will require changes in social policy and economics at a national level.

“The doctors' job is to pull drowning people out of the river, and it is admirable work. But we need to ask, ‘Why do all these people need to be rescued downstream? What is happening upstream?’ It's the upstream questions that make us uncomfortable. What are the big picture things we can do to make a difference?” ■

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much remains unknown

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A community response,
one baby at a time

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