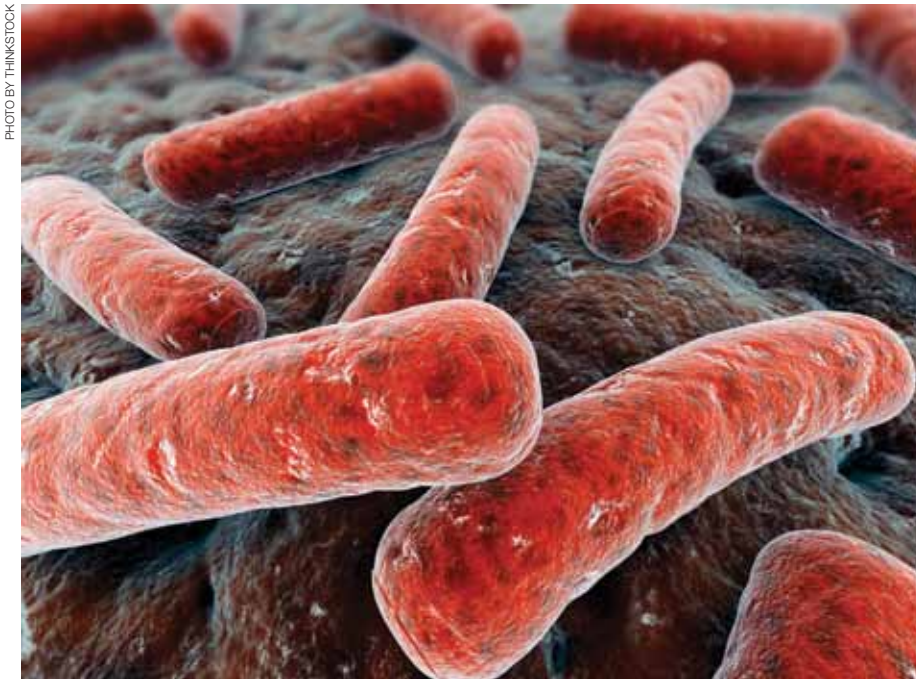


INNOVATIONS

in Pediatrics



New Strategies To Thwart Antibiotic Resistance

pg 4

Study of T cells may unlock new gastrointestinal treatments pg 3

TWiTCH trial explores safety of daily oral pill for sickle cell disease pg 6

Progesterone-based therapies hold promise for reducing preterm births pg 7



UH Rainbow Babies & Children's Hospital and Case Western Reserve University School of Medicine are consistently recognized as premier institutions in the nation, according to U.S. News & World Report's annual rankings.

Chairman's Message

UH Rainbow Again Recognized as Elite Children's Hospital



We are proud to once again be recognized as one of the nation's best children's hospitals in nine pediatric specialties. University Hospitals Rainbow Babies & Children's Hospital ranks No. 2 in the nation in neonatology for its care of newborns in the Quentin & Elisabeth Alexander Level IV Neonatal Intensive Care Unit and No. 7 in pulmonology, according to U.S. News & World Report's annual rankings of pediatric hospitals. The hospital has ranked as a top children's hospital on this elite list for 23 years. The complete rankings are available at RainbowBabies.org/USNews.

This prestigious recognition demonstrates our commitment to caring for children, including the most complex cases, through our vast network of medical and surgical specialists. Some examples of that work can be found in the pages of this publication.

Sharon B. Meropol, MD, PhD, is studying the impact of unnecessary antibiotic use on antibiotic-resistant bacterial infections. She is examining the relationship between the types of bacteria living in our bodies and whether they are antibiotic resistant, as well as antibiotic use by children and families. She also is planning to use behavioral economics to elucidate how to best improve decision-making regarding antibiotic prescribing.

Zili Zhang, MD, PhD, is looking at T cell costimulatory molecules and the role they play in the pathogenesis of eosinophilic esophagitis. By uncovering

the mechanism by which T cells function in the disease process, Dr. Zhang hopes to develop new treatment strategies for gastrointestinal diseases.

Sam Mesiano, PhD, is addressing the problem of preterm birth by exploiting something Mother Nature already provides – the hormone progesterone. His work is part of an Ohio research collaborative funded through March of Dimes to prevent premature birth.

Connie Piccone, MD, is comparing standard erythrocyte transfusion therapy with alternative hydroxyurea therapy for pediatric patients with sickle cell disease who have abnormal transcranial Doppler velocities and elevated risk for disease complications, such as stroke.

We welcome your comments, questions and suggestions at Peds.Innovations@UHHospitals.org.

Michael W. Konstan, MD

The Gertrude Lee Chandler Tucker Professor and Chairman
Department of Pediatrics
Case Western Reserve University School of Medicine
The Austin Ricci Chair in Pediatric Pulmonary Care and Research
UH Rainbow Babies & Children's Hospital



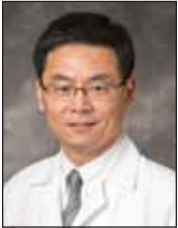
The commitment to exceptional patient care begins with revolutionary discovery. University Hospitals Case Medical Center is the primary affiliate of Case Western Reserve University School of Medicine, a national leader in medical research and education and consistently ranked among the top research medical schools in the country by U.S. News & World Report. Through their faculty appointments at Case Western Reserve University School of Medicine, physicians at UH Case Medical Center are advancing medical care through innovative research and discovery that bring the latest treatment options to patients.

Situated on the campus of University Hospitals Case Medical Center in Cleveland, Ohio, University Hospitals Rainbow Babies & Children's Hospital is a 244-bed, full-service pediatric hospital and academic medical center, with a dedicated team that uses the most advanced treatments and latest innovations to deliver the complete range of pediatric specialty services. A trusted leader in children's health care for more than 125 years, UH Rainbow Babies & Children's Hospital consistently ranks among the top children's hospitals in the nation by U.S. News & World Report. Learn more at RainbowBabies.org.



Unraveling the Mysteries of T Cells to Treat Gastrointestinal Diseases

Narrowing in on the potential role of molecules in initiating eosinophilic esophagitis



Zili Zhang, MD, PhD, Director of Pediatric Gastrointestinal Research at UH Rainbow Babies & Children's Hospital and Associate Professor of Pediatrics at Case Western Reserve University School of Medicine

By uncovering the mechanism by which T cells are activated, regulated and malfunction in the disease process, scientists at UH Rainbow Babies & Children's Hospital hope to develop new treatment strategies for gastrointestinal diseases.

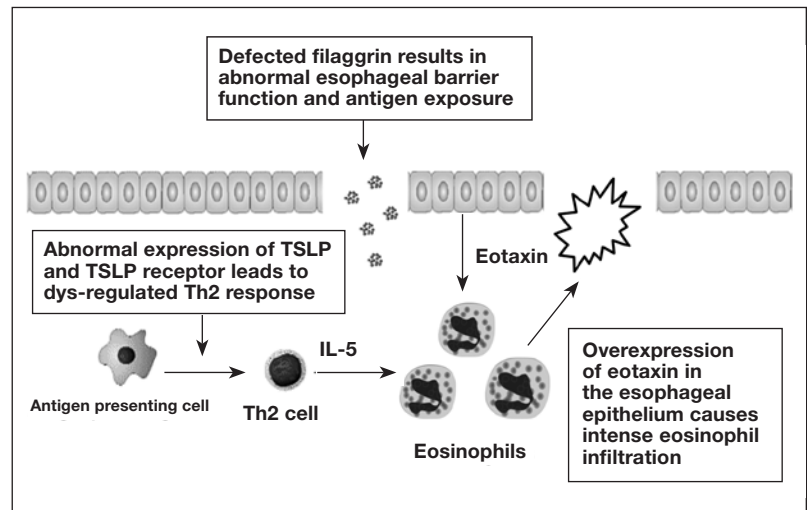
Zili Zhang, MD, PhD, Director of Pediatric Gastrointestinal Research at UH Rainbow Babies & Children's Hospital and Associate Professor of Pediatrics at Case Western Reserve University School of Medicine, is studying T cell co-stimulatory molecules and their role in the pathogenesis of eosinophilic esophagitis (EoE), a special group of white blood cells that build up in the esophagus in reaction to foods, allergens or acid reflux. This buildup can lead to inflamed or injured esophageal tissue.

EoE is a special type of inflammation in the esophagus that can cause swallowing problems, vomiting and abdominal pain. It also is closely associated with allergies. Dr. Zhang says in addition to the eosinophil cells, T cells appear to initiate the disease process. He is studying those costimulatory molecules that may trigger EoE.

"This has become an increasingly common disease. We're still in the relatively early stages of understanding this disease," Dr. Zhang says. "This study will help us understand the disease from an immunologic point of view. If we understand the disease better, we can devise better or novel treatment strategies."

Specifically, Dr. Zhang's lab is zeroing in on OX40, LIGHT and HVEM (herpesvirus entry mediator) to determine how the expression of these molecules might trigger EoE by turning up the T cell response. Findings could impact the treatment of EoE and other gastrointestinal diseases, including inflammatory bowel disease, Crohn's disease and ulcerative colitis.

Twenty years ago, EoE was a rare diagnosis. Since that time, the incidence has increased tenfold and, today, it is the most common disease seen by gastroenterologists in daily practice. Dr. Zhang says some gastrointestinal diseases occur due to a dysfunction of the immune system; others, like EoE, are mediated by T cells.



"We are very interested in understanding how T cells are activated and regulated, and how they malfunction in the disease process," Dr. Zhang says. "By understanding this process, it could allow us to develop a new treatment strategy."

Dr. Zhang says he hopes to apply this basic research to the clinical setting. The study, "T Cell Co-Stimulatory Molecules: A Co-conspirator in the Pathogenesis of Eosinophilic Esophagitis?," was published in the March 2, 2013, issue of *Digestive Diseases and Sciences* and funded by Takeda Pharmaceuticals U.S.A. Inc.

Contact Dr. Zhang at Peds.Innovations@UHhospitals.org.

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Join us via live webcast for weekly Pediatric Grand Rounds, held Thursdays from 8 to 9 a.m. Learn more at RainbowBabies.org/GrandRounds.

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Going Overboard

Changing decision-making to reduce antibiotic-resistant infections



Sharon B. Meropol, MD, PhD, a specialist in the Division of General Pediatrics & Adolescent Medicine at UH Rainbow Babies & Children's Hospital and Assistant Professor of Pediatrics and Epidemiology & Biostatistics at Case Western Reserve University School of Medicine

Unnecessary antibiotic use contributes to rising risks of antibiotic-resistant bacterial infections, pushing medicine further behind in the ability to treat infections.

Sharon B. Meropol, MD, PhD, a specialist in the Division of General Pediatrics & Adolescent Medicine at UH Rainbow Babies & Children's Hospital and Assistant Professor of Pediatrics and Epidemiology & Biostatistics at Case Western Reserve University School of Medicine, is the lead author of "Risks and Benefits Associated With Antibiotic Use for Acute Respiratory Infections: A Cohort Study."

Dr. Meropol completed an observational study of more than 1.5 million adult patient visits using U.K. electronic medical records and found that 65 percent of patients were prescribed antibiotics for acute nonspecific respiratory infections, which are usually of viral etiology and unlikely to respond to antibiotic treatment. While there was a small benefit – decreased risk for hospitalization for pneumonia in one out of 12,255 treated patients – and only a small risk of side effects, this overprescribing of antibiotics for likely viral illness is contributing to increased antibiotic-resistant infections.

The study was published in the March/April 2013 issue of the *Annals of Family Medicine*.

"The discovery of antibiotics revolutionized health care. But almost as soon as we started to use them, we found that germs were becoming resistant to them," Dr. Meropol says. "The pipeline for new antibiotics is going dry; we don't have many new options being developed."

On average, each individual in the United States and Europe, depending on his or her age, is prescribed oral antibiotics once every six months to three years. While antibiotics taken for a viral illness have no effect on the virus, they do change the nature of the other bacteria living in the body. Dr. Meropol says antibiotics kill some bacteria and may promote the development and growth of others resistant to antibiotics.

"When someone feels sick today, they may not be considering future antibiotic resistance for society, the country, themselves or their family," she says.

Another contributing factor is the frequent misconception among parents and child care providers about the need for antibiotics for fevers associated with common viral infections, due to often exaggerated concern about the risk of possible underlying occult serious bacterial infection. Although the introduction of highly effective pediatric immunizations against serious



bacterial infections has dramatically decreased that risk, antibiotics may still be prescribed "just in case," often unnecessarily in an immunized child.

Behavioral Economics

To curb the prescribing of unnecessary antibiotics, Dr. Meropol is looking at behavioral economics, or the way certain aspects of decisions – based on beliefs and emotions – bend the rules of how we would otherwise consider costs and benefits.

"People may consider small chances of very severe outcomes differently than they look at large risks of minor outcomes, even though in classic decision theory, they should balance out," she says. "This may result in illogical decision making."

The U.S. Centers for Disease Control and Prevention's "Get Smart" campaign is working to educate the public and health professionals about the overuse of antibiotics. Dr. Meropol says that while the initial campaign did contribute to a decrease in antibiotic use, scientists are looking for additional strategies.

"I'm interested in win-win solutions," Dr. Meropol says. "Parents, doctors and the public are most likely to accept solutions that simultaneously meet or prevent

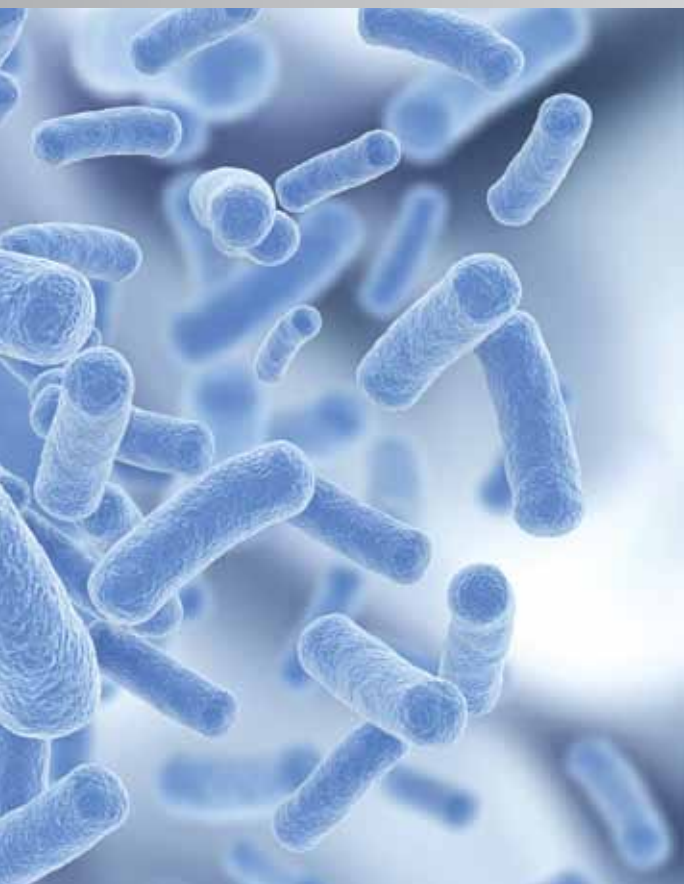


PHOTO BY THINKSTOCK

The overprescribing of antibiotics for illnesses that are likely viral can change the nature of bacteria, illustrated above.

current health challenges and at the same time decrease future antibiotic resistance.”

Flu shots, she says, are a win-win solution because they help children avoid not only viral influenza but also secondary infections, such as bacterial pneumonia or ear infections. Another win-win solution is rapid office-based testing to distinguish viral sore throats from bacterial streptococcal throat infections. Although antibiotics help speed the resolution of strep throat and make it less contagious, they do not treat viral sore throats, which gradually resolve on their own.

Antibiotics in Agriculture

A separate issue affecting the emergence of antibiotic-resistant germs in our environment is the use of antibiotics in agriculture. Dr. Meropol estimates up to 80 percent of the antibiotics used in the United States are for agricultural purposes.

“Most of these antibiotics are not being used to treat infections in animals; they are being used to promote growth and prevent disease,” she says, adding that regulations are needed to restrict the types of antibiotics

added to animal feed to those least like antibiotics used for humans, and eventually to limit agricultural antibiotic use to treat animals’ bacterial illnesses.

Dr. Meropol’s research examines the types of bacteria living in, or “colonizing,” the body and whether they are antibiotic-resistant.

Our bodies are sterile at birth, but as soon as a baby passes through the birth canal and enters the world, he or she begins picking up organisms in the nose, respiratory system, throat and gastrointestinal system, eventually harboring more than 100 trillion organisms – mostly bacteria.

Dr. Meropol is culturing healthy babies at birth at University Hospitals MacDonald Women’s Hospital and periodically during the first year of life to examine the relationship between colonization with resistant bacteria and antibiotic use by children and their household members.

“The precise balance of different types of bacteria living in our bodies helps us in a lot of ways we are just beginning to understand,” Dr. Meropol says. “Some feel when that delicate balance is upset by antibiotic treatment, this change in the balance of germs within the body could be associated with illnesses later in life, such as asthma, allergies, autoimmune diseases and inflammatory bowel disease.”

She also is looking at other factors thought to influence how our bodies are exposed to certain bacteria and how those germs are transmitted through communities, such as day care attendance, breast milk or formula consumption, medication use, and household tobacco smoke exposure.

“If you give a child an antibiotic today, what is the increased risk that child will be colonized with an antibiotic-resistant bacteria in the future, and what other factors influence that risk?” Dr. Meropol asks.

Information from the first cohort of babies should be out within two years. Data will be used to develop a model of possible strategies for antibiotic use decision making, and then to study which strategies are most effective in treating illness while minimizing future resistance.

Dr. Meropol’s work is supported by grants through Case Western Reserve University School of Medicine from the National Institute of Allergy and Infectious Diseases and the Medical School’s Clinical and Translational Science Award program from the National Institutes of Health.

Contact Dr. Meropol at **Peds.Innovations@UHhospitals.org**.

Transfusion Trade-Off?

TWITCH trial studies safety of hydroxyurea in high-risk children with sickle cell disease



Connie Piccone, MD, Medical Director of the Sickle Cell Anemia Center at UH Rainbow Babies & Children's Hospital and Assistant Professor of Pediatrics at Case Western Reserve University School of Medicine

Hematologists at the Sickle Cell Anemia Center at UH Rainbow Babies & Children's Hospital are major contributors to a national study comparing standard transfusion therapy with a daily pill for pediatric sickle cell anemia patients at high risk for stroke.

The "TCD With Transfusions Changing to Hydroxyurea (TWITCH)" study is a Phase III multicenter trial that will assess nearly 150 children between the ages of 4 and 15 at 27 clinical sites in the United States and Canada. Children with sickle cell disease who have a history of abnormal transcranial Doppler (TCD) velocities and are currently on standard therapy for stroke prevention (chronic blood transfusions) will be randomized to continuing standard therapy versus transitioning to a daily oral medication called hydroxyurea.

Sickle cell disease is an inherited blood disorder that affects about 100,000 Americans, causing chronic anemia and complications that include pain, stroke, lung damage and kidney failure. Neurologic complications, including stroke or transient ischemic attack (TIA), are among the most morbid complications of sickle cell disease. About 11 percent of children with sickle cell disease will experience a clinical stroke before age 20.

TCD measures how fast blood flows through blood vessels in the brain. Children with sickle cell disease and increased (abnormal) velocities have a stroke risk that is more than 3,000 times greater than that of a healthy child without sickle cell disease. Transfusions lower the velocities and risk of stroke but carry serious side effects, including iron overload, the development of antibodies, and possible infection.

"TCD is really an amazing tool," says

Connie Piccone, MD, Medical Director of the Sickle Cell Anemia Center at UH Rainbow Babies & Children's Hospital and Assistant Professor of Pediatrics at Case Western Reserve University School of Medicine. "A clinical nurse can do the ultrasound test during a regular office visit," Dr. Piccone says. "It is a noninvasive way of assessing for stroke risk in kids. Because of the research done previously – in part by UH Rainbow Babies & Children's Hospital – we are now at the point where we can do the TWITCH study. Our Sickle Cell Anemia Center has played an important role

in moving research forward to help determine the best treatment for kids."

Hydroxyurea is a daily oral medication that can decrease the number of painful events, acute chest (pneumonia) episodes, blood transfusions and hospital admissions. Previous studies show the drug can lower TCD velocities, but it is unknown whether it works as well as blood transfusions to prevent stroke. Side effects of hydroxyurea include a decrease in blood cells in the body, including the type that fights infections. This requires monthly blood count checks.

Hydroxyurea Treatment for Children

While hydroxyurea has been around for decades and has been used in adults with sickle cell disease, it was not until the BABY HUG pediatric hydroxyurea Phase III clinical trial that the medication was formally evaluated in children as young as 9 months. That study showed hydroxyurea not only works to decrease the side effects of sickle cell disease, but it also proved to be a safe and easy treatment for young children.

"With that kind of evidence behind it, hydroxyurea is being prescribed much more often for children," says Dr. Piccone. "It is a pill you have to take every day, but it could potentially mean children do not have to come to clinic for an IV and blood transfusions every month. That would significantly improve the quality of life for those kids who have to live with this chronic illness."

The TWITCH study will follow both groups of children for two years. The study is still enrolling patients – UH Rainbow Babies & Children's Hospital has screened and enrolled nine patients in the study – and Dr. Piccone expects findings will be ready for publication within the next few years.

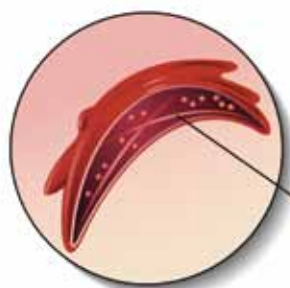
"At this point, we do not know how hydroxyurea is going to compare to standard blood transfusions,"

Dr. Piccone says. "We really will be waiting to see the final results from the TWITCH study before moving forward with future trials."

The TWITCH trial is funded by the National Heart, Lung, and Blood Institute under the National Institutes of Health through a grant to Case Western Reserve University School of Medicine.

Contact Dr. Piccone at **Peds.Innovations@UHHospitals.org**.

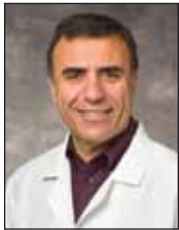
Abnormal sickle red blood cell section



Abnormal hemoglobin form strands that cause sickle shape

Exploiting Mother Nature to Prevent Preterm Births

Progesterone-based therapies may help facilitate full-term pregnancies



Sam Mesiano, PhD, Co-Director of the Research Division at UH MacDonald Women's Hospital and Associate Professor of Reproductive Biology at Case Western Reserve University

More than one in 10 babies is born prematurely every year and more than 1 million children die each year from complications of preterm birth.

And preterm birth rates are increasing.

Sam Mesiano, PhD, Co-Director of the Research Division at UH MacDonald Women's Hospital and Associate Professor of Reproductive Biology at Case Western Reserve University, is Site Director for the Northeast Ohio component of a \$10 million March of Dimes Ohio research collaborative to understand and prevent premature births.

Dr. Mesiano says his team is addressing the challenge by exploiting something Mother Nature already provides – the hormone progesterone.

During pregnancy, progesterone is produced in large amounts by the placenta and, as its name implies, is progestational; it functions to promote pregnancy mainly by keeping the uterine muscle relaxed and quiescent. He further explains that the end of pregnancy is triggered by the withdrawal of the “progesterone block to labor.” Dr. Mesiano says his goal is to understand how progesterone promotes uterine quiescence and how its actions are withdrawn to initiate labor. “We hope to then exploit that process therapeutically to augment its progestational actions as a strategy to prevent or delay preterm birth,” he says.

Currently, progesterone-based therapies are used to prevent preterm birth but are effective in only a small subset of pregnancies, and the therapy is limited to women at risk for preterm birth.

“The main thrust of what we do in the lab is to understand the molecular biology of how progesterone promotes pregnancy and causes the muscle cells of the uterus to stay relaxed,” he says. “If we understand that mechanism, then we can identify targets for therapies to make it work even better.”

Dr. Mesiano's team developed cell line models for muscle cells of the uterus and is using those cells to activate signaling pathways and genes involved in mediating the effects of progesterone to keep the cells relaxed.

“Our cell models provide excellent screening platforms to test different drugs that could modulate the progesterone-signaling pathways in favor of sustaining pregnancy,” he says. “This can open the pipeline to the development of drugs that specifically target the uterine muscle.”

The March of Dimes Prematurity Research Center – Ohio Collaborative is a transdisciplinary program involving investigators at UH Rainbow Babies & Children's Hospital, UH MacDonald Women's Hospital, Case Western Reserve University and MetroHealth Medical Center in Cleveland; The Ohio State University and Nationwide Children's Hospital in Columbus; and Cincinnati Children's Hospital and the University of Cincinnati. Investigators at Vanderbilt University, Dartmouth College, University of Iowa and Washington University in St. Louis are also involved.

Contact Dr. Mesiano at Peds.Innovations@UHHospitals.org.

New Staff

Ankita Patel Desai, MD, Division of Infectious Diseases, Assistant Professor of Pediatrics

Amy Edwards, MD, Division of Infectious Diseases, Clinical Instructor of Pediatrics

Amy DiMarino, DO, Division of Pulmonology, Assistant Professor of Pediatrics

James Hill, MD, Division of Cardiology, Assistant Professor of Pediatrics

Ali Khalili, MD, Division of Gastroenterology, Assistant Professor of Pediatrics

Lyndsay McMorro, DO, Division of General Pediatrics & Adolescent Medicine, Clinical Instructor of Pediatrics

Jun Tae Park, MD, Division of Epilepsy, Assistant Professor of Pediatrics

Keith Ponitz, MD, Division of General Pediatrics & Adolescent Medicine, Assistant Professor of Pediatrics

Thomas Raffay, MD, Division of Neonatology, Instructor of Pediatrics

Kenneth Rodriguez, MD, Department of Otolaryngology, Assistant Professor of Otolaryngology

Sarah Romero, MD, Division of Emergency Medicine, Assistant Professor of Pediatrics

Steven Shein, MD, Division of Critical Care, Assistant Professor of Pediatrics

Jill Shivapour, MD, Division of Cardiology, Assistant Professor of Pediatrics

Kimberly Spoonhower, MD, Division of Pulmonology, Assistant Professor of Pediatrics

Tamar Springel, MD, Division of Nephrology, Assistant Professor of Pediatrics



Physician News



Todd D. Otteson, MD, MPH, was named Chief of Pediatric Otolaryngology at UH Rainbow Babies & Children's Hospital and Visiting Associate Professor of Otolaryngology at Case Western Reserve University School of Medicine. He came from the University of Pittsburgh School of Medicine, where he served as Associate Professor of Otolaryngology and was a member of the clinical staff at Children's Hospital of Pittsburgh of University of Pittsburgh Medical Center. Dr. Otteson earned his medical degree and completed an otolaryngology residency at Georgetown University School of Medicine. He completed a pediatric otolaryngology fellowship at Children's Hospital of Pittsburgh of UPMC.



Robert Cunningham III, MD, was named Chief of Pediatric Nephrology and Vice Chair for Faculty Affairs at UH Rainbow Babies & Children's Hospital and Clinical Professor of Pediatrics at Case Western Reserve University School of Medicine. Dr. Cunningham came to UH from Ochsner Clinic Foundation in New Orleans, where he served as Vice Chairman of Pediatrics and Head of the Section of Pediatric Nephrology and Hypertension. He trained in pediatrics at Duke University and completed his pediatric nephrology fellowship at the University of Texas Medical Branch at Galveston.



Alexandre Rotta, MD, was named Chief of the Division of Pediatric Critical Care at UH Rainbow Babies & Children's Hospital; and Professor of Pediatrics at Case Western Reserve University School of Medicine. Dr. Rotta previously served as Director of Pediatric Cardiac Critical Care at Riley Hospital for Children at Indiana University. He received his medical degree from Universidade Federal do Rio Grande do Sul in Brazil, and completed a pediatric residency at Children's Hospital of Michigan and a pediatric critical care fellowship at Women & Children's Hospital of Buffalo. He is a fellow of the American Academy of Pediatrics, and he received the 2011 Presidential Citation from the Society of Critical Care Medicine.



Gerald Ferretti, DDS, MS, MPH, Chief of Pediatric Dentistry and Director of the Pediatric Dentistry Residency Program at UH Rainbow Babies & Children's Hospital, and Professor and Chair of Pediatric Dentistry at Case Western Reserve University School of Dental Medicine, was named the inaugural Anne Hunter Jenkins Endowed Master Clinician in Pediatric Dentistry and Orthodontics.



Carol Rosen, MD, Medical Director of the Pediatric Sleep Center at UH Rainbow Babies & Children's Hospital and Professor of Pediatrics at Case Western Reserve University School of Medicine, was named the inaugural J.S. Rube Endowed Chair in Pediatric Sleep Medicine.

Join Us! AAP 2013 NCE in Orlando

UH Rainbow Babies & Children's Hospital and Case Western Reserve University School of Medicine will host an Alumni & Friends Reception during the American Academy of Pediatrics 2013 National Conference & Exhibition in Orlando, Florida.

Date: Sunday, October 27, 2013

Time: 6:30 – 8 p.m.

Location: The Peabody Orlando – Silver Spring Room

RSVP to: Kellie.Crowe@UHhospitals.org

Please also visit Booth #531 in the AAP Exhibitor Hall.

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