

## About the Division

The Division of Pediatric Endocrinology, Diabetes, and Metabolism at UPMC Children's Hospital of Pittsburgh provides diagnostic and therapeutic services for children with diabetes mellitus, hypoglycemia, and disorders of physical growth, sexual maturation, thyroid function, pituitary function, and calcium and phosphorous metabolism, as well as other gender disorders. Patients are evaluated in collaboration with multidisciplinary teams to come to a unifying diagnosis and provide the best outcomes for patients and families.

For a referral or consultation, please contact us at 412-692-5170. Visit us online at [CHP.edu/diabetes](http://CHP.edu/diabetes).

## Obesity and Diabetes:

# The Intertwined Role of Inflammation, Insulin Resistance, and the FoxO1 Transcription Factor



**H. Henry Dong, PhD**, professor of pediatrics in the Department of Pediatrics at the University of Pittsburgh School of Medicine and the Division of Pediatric Endocrinology, Diabetes, and Metabolism at UPMC Children's Hospital of Pittsburgh, studies the molecular basis that links insulin resistance to diabetic dyslipidemia and nonalcoholic fatty liver disease in subjects with morbid obesity and type 2 diabetes.

Insulin resistance is the significantly diminished state of responsiveness of the body to normal plasma insulin concentrations. To overcome insulin resistance in peripheral tissues, pancreatic beta cells are recruited to produce more insulin via a compensatory mechanism. Over time, this compensatory pathway can lead to beta-cell failure and overt type 2 diabetes in human subjects who exhibit morbid obesity.

Dr. Dong's lab focuses on the characterization of genetic factors in glucose and lipid metabolism to understand how insulin resistance perturbs carbohydrate metabolism, contributing to the development of diabetic dyslipidemia and nonalcoholic fatty liver disease in obesity and type 2 diabetes. These studies have gathered insight into the molecular events that link insulin resistance to metabolic abnormalities, providing a knowledge base for the development of small molecule drugs for better clinical management of diabetic dyslipidemia and nonalcoholic fatty liver disease in obesity and type 2 diabetes.

"We know that individuals with obesity and type 2 diabetes have two things in common: insulin resistance and low-grade inflammation. The inflammation is categorized by consistent production of the pro-inflammatory cytokine IL-1 $\beta$ . The molecular mechanisms that couple insulin resistance with this low-grade inflammation seen in obesity and type 2 diabetes is not well understood," says Dr. Dong.

However, while these mechanisms that link the two states together have yet to be fully explained, Dr. Dong's team in prior research has identified a key downstream regulator of insulin signaling — the forkhead box O1 (FoxO1) transcription factor.

"This is a unique protein. It mediates the inhibitory action of insulin. Usually, insulin positively impacts the body by lowering blood glucose levels, promoting cell growth, and fostering cell differentiation. However, insulin

## Disorders of Sex Development: A Multidisciplinary Team Approach to Clinical Care and Research

Disorders of sex development (DSD) are characterized by divergence between chromosomal, gonadal, and phenotypic sex associated with atypical development of the internal and/or external reproductive systems. Individuals affected by a DSD can present during infancy, childhood, or adolescence. In some instances, individuals are ascertained by prenatal testing.

These disorders may encumber pubertal development and future fertility. At UPMC Children's Hospital of Pittsburgh, health care for these individuals involves a multidisciplinary integrated team approach. Team members include pediatric endocrinology, pediatric urology, genetics, gynecology, reproductive endocrinology, pathology, and behavioral health experts. The team's mission focuses on developing individualized plans of care specific for each patient and family.

**Selma Feldman Witchel, MD**, professor of pediatrics and director of the Pediatric Endocrinology Fellowship Program, leads the pediatric endocrine component of this team. The DSD Multidisciplinary Team meets monthly to discuss specific cases and

review novel scientific discoveries. She and her team members also are engaged in research activities.

"The patients affected by these complex disorders require a high level of expertise. A multidisciplinary approach is essential to promote healthy outcomes and high quality of life for our patients," says Dr. Witchel.

### Fertility Preservation for Pediatric Patients: Considerations, Options, and the Advancing Science

Fertility preservation options are rapidly advancing for pediatric patients on numerous fronts. At UPMC Children's, clinicians such as Dr. Witchel and her colleagues are on the forefront of advancing programs for fertility

preservation for patients with DSD and for transgender patients. In collaboration with colleagues such as **Kyle Orwig, PhD**, professor in the Department of Obstetrics, Gynecology, and Reproductive Sciences and Director of the Fertility Preservation Program in Pittsburgh ([FertilityPreservationPittsburgh.org](http://FertilityPreservationPittsburgh.org)), and clinicians such as **Marie N. Menke, MD, MPH**, director of the Division of Reproductive Endocrinology and Infertility in the Department of Obstetrics, Gynecology and Reproductive Sciences at UPMC Magee-Womens Hospital, Dr. Witchel has helped transgender patients navigate the confusing world of fertility.

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### Team Members



#### ENDOCRINOLOGY

##### Selma Feldman Witchel, MD

*Professor of Pediatrics, Department of Pediatrics, University of Pittsburgh School of Medicine  
Director, Pediatric Endocrinology Fellowship Program*



#### PEDIATRIC PATHOLOGY

##### Miguel Reyes-Múgica, MD

*Marjory K. Harmer Endowed Chair in Pediatric Pathology  
Division Chief, Pediatric Pathology, Department of Pathology, University of Pittsburgh School of Medicine  
Director of Laboratories, UPMC Children's Hospital of Pittsburgh*



#### GENETICS

##### Svetlana A. Yatsenko, MD, PhD

*Associate Professor, Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh School of Medicine  
Associate Professor, Department of Pathology, University of Pittsburgh School of Medicine  
Director, Pittsburgh Cytogenetics Laboratory*



#### REPRODUCTIVE ENDOCRINOLOGY

##### Marie Menke, MD, MPH

*Assistant Professor, Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh School of Medicine  
Division Director, Reproductive Endocrinology and Infertility*



#### PEDIATRIC UROLOGY

##### Francis X. Schneck, MD

*Clinical Director, Division of Pediatric Urology  
Associate Professor of Urology, Department of Urology, University of Pittsburgh School of Medicine  
Fellowship Director, Pediatric Urology*



#### PEDIATRIC GYNECOLOGY

##### Serena Chan, MD

*Assistant Professor, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Pittsburgh School of Medicine*

# Advanced Practice Provider Fellowship Training Program at UPMC Children's

A new training program for advanced practice providers (APP) within the Department of Pediatrics at the University of Pittsburgh School of Medicine and UPMC Children's Hospital of Pittsburgh is providing focused, specialty-specific, and general pediatrics training to APPs that will increase their level of expertise in their subspecialty and also provide additional general- and cross-training in other areas of pediatric medicine.

The goals of the program are to provide an advanced level of training to APPs, allowing them to function autonomously within their division, seeing patients and, thereby, expanding access to needed subspecialty care for patients and families.

The Pediatric APP Fellowship Program cultivates a mastery of pediatric fundamentals, including acute care, ambulatory care, procedure performance, and principles of pediatric subspecialty medicine. Pediatric APP Fellows are employed, paid learners, and the goal is to provide them with the manual skill, fundamental knowledge, and critical thinking skills they'll need to make sound clinical judgments on a daily basis. Pediatric APP Fellows are trained to provide autonomous comprehensive pediatric care within the scope of their license and in collaboration with their supervising physician.

The Pediatric APP Fellowship features a year-long curriculum of both didactics and clinical rotations. Fellowships currently exist in 15 different pediatric medical subspecialties, with expansion into surgical disciplines likely to occur in the future.



"Each medical specialty has developed its curriculum for APP fellows who will eventually be practicing in that specialty. This training works in tandem with the more general pediatrics training fellows receive as part of the program," says **Amanda Flint, MD**, assistant professor of pediatrics in the Division of Pediatric Endocrinology, Diabetes, and Metabolism, who serves as the APP Fellowship Program director for the Division's program.

Supporting Dr. Flint in the Division's program are two co-directors who are APPs in the Division of Endocrinology, Diabetes, and Metabolism — **Erica Cordell, CRNP**, and **Kathleen Sorkin, CRNP**.

"Erica was instrumental in helping to spearhead the development of the written endocrinology curriculum along with **Diana DeArment, PA-C**, from our Division. Kathleen's primary role as co-director has been to mentor the new APPs as they start the program and monitor their progress.

"The written curriculum we have developed is a comprehensive battery of lectures and readings and tests that span the full breadth of the Division's clinical work. This written curriculum is assigned during the first six months of the fellows' training. The written curriculum is complemented by clinical experience in all of the different clinics we have in our Division, so APPs receive a very well-rounded education," says Dr. Flint.

Fellows must keep a patient logbook to document their cases and ensure they are exposed to an adequate amount of case variety. Additionally, fellows are given the opportunity to work on a quality improvement project as part of their training, and they take part in a four-week boot camp early on in the program that covers much of the general training and rotations in other divisions.

"The boot camp covers all of the basics that any good pediatric APP ought to know and be proficient at regardless of their specialty," explains Dr. Flint.



The Division's first endocrinology APP fellow began training in the spring of 2019 and will soon complete the program. Three other endocrinology APP fellows are currently in training at various stages of progression.

To ensure that trainees are progressing and attaining the clinical competencies needed, a formal evaluation system is in place that captures and assesses a fellow's performance in a variety of domains, including medical knowledge, clinical skills, and interpersonal interactions.

"The Department of Pediatrics and UPMC Children's have invested heavily in this program because of its ability to transform the way we train our practitioners to become independent clinicians, which, in turn, can expand our ability to care for more people. Many subspecialties struggle with not having enough physicians to meet patient demand. This is one way we can help to solve that problem and open up access for more patients while continuing to provide excellent care," says Dr. Flint.

## UPMC Children's "That's Pediatrics" Podcast Series



UPMC Children's Hospital of Pittsburgh "That's Pediatrics" podcast series for physicians, scientists, and other health care professionals features compelling interviews with the hospital's leading researchers and clinicians discussing innovative basic, translational, and clinical research. New episodes are released every two weeks.

Subscribe to "That's Pediatrics" in iTunes or Google Play Music to have new episodes automatically download to your phone for free when they become available. To see the current list of archived podcasts, visit [CHP.edu/health-care-professionals/podcast](http://CHP.edu/health-care-professionals/podcast).

Current episodes of "That's Pediatrics" podcasts from pediatric endocrinology faculty include:



*Beyond Corn and Carrots: The Future of Pediatric Diabetes*, presented by **Radhika Muzumdar, MD**, chief of the Division of Pediatric Endocrinology, Diabetes, and Metabolism at UPMC Children's.

## Disorders of Sex Development *Continued from Page 2*

"We counsel all our DSD and gender dysphoria patients about future fertility options and fertility preservation. At present, minimal evidence-based data exists in the medical literature on this subject, but this area is rapidly evolving," says Dr. Witchel.

Drs. Witchel, Menke, and Orwig have collaborated on several studies in the recent past that have dealt with fertility preservation for transgender children and adolescents.

In February 2019, Dr. Witchel and UPMC Magee colleagues **Stephanie S. Rothenberg, MD**, and Dr. Menke published their experience with "Oocyte Cryopreservation in a Transgender Male Adolescent" in the *New England Journal of Medicine*. This publication described their work with a transgender male adolescent. The authors highlighted the challenges of the fertility preservation options currently available for patients who have not completed natal puberty.

"Through our multidisciplinary approach, we were able to successfully retrieve and preserve a small number of mature eggs that one day may allow this individual to have biological children," explains Dr. Witchel "It is too early to know the feasibility of achieving the goal of fertility preservation for all individuals.

Importantly, the science has rapidly advanced and experimental protocols are underway in the UPMC system."

Other patients with DSD may benefit from this approach. Patients with Klinefelter syndrome or other disorders of sex development may benefit from similar fertility preservation techniques and protocols.

"Right now, for some of these patients, we can preserve the potential to have children in the future," says Dr. Witchel. "Nevertheless, many questions remain unanswered regarding future fertility derived from frozen tissue samples."

Collaborative work between UPMC Children's and UPMC Magee regarding fertility preservation in adolescent and young adult feminizing transgender patients were published in the September 2019 issue of the journal *Pediatrics*. Importantly, this study of 11 transfemales showed that semen cryopreservation was a viable fertility preservation option for these individuals; semen preservation may also be possible for individuals who have already started gender affirming therapies. However, additional studies will be needed in the future to determine the specific protocols to preserve the most viable sperm.

### References and Further Reading

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## Obesity and Diabetes *Continued from Page 1*

also has an inhibitory action, and the FoxO1 protein is the transcription factor that mediates the inhibitory action of insulin,” says Dr. Dong.

### Past Research on FoxO1 Links It to Insulin Resistance, Inflammation, Macrophage Function, and VLDL Production

In 2008, Dr. Dong and colleagues published a paper in the *Journal of Clinical Investigation* related to the role of FoxO1 in hepatic insulin signaling. Their animal model research linked an increase in FoxO1 activity with increases in microsomal triglyceride transfer protein (MTP) expression, increased very-low-density lipoprotein (VLDL) production, and consequently higher levels of plasma triglycerides.

“We found that FoxO1 plays a key role in lipid metabolism in the liver and that FoxO1 is responsible for mediated insulin function on its MTP target,” says Dr. Dong.

In 2009, in the journal *Diabetes*, Dr. Dong and colleagues published findings that showed the FoxO1 protein is responsible for regulating the expression of IL-1 $\beta$  and that it plays an important role in the linking of insulin resistance and inflammation in type 2 diabetes and obesity.

“The immune or inflammatory response appears to be primarily carried out or propagated by FoxO1 dysregulated macrophages that produce enhanced levels of IL-1 $\beta$ ,” says Dr. Dong.

It is on the basis of these and other prior findings that Dr. Dong pursued and obtained a new grant to continue his FoxO1 studies.

### New Grant Will Further Probe the Role of FoxO1

In 2019, Dr. Dong was awarded a new National Institutes of Health (NIH) R01 grant to continue his studies elucidating the molecular mechanisms by which the FoxO1 transcription factor

mediates insulin resistance and inflammation and the regulation of abnormal macrophage activity. This research will build upon the considerable knowledge base he has worked to uncover previously on the FoxO1 transcription factor and its functions. If successful in proving their hypothesis, Dr. Dong’s research could lead to an understanding of FoxO1 as a target for drug therapies to mitigate insulin resistance and low-grade inflammation.

### Further Reading

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Su D, Coudriet GM, Kim DH, Yu Y, Perdomo G, Qu S, Slusher S, Tse HM, Piganelli J, Giannoukakis N, Zhang J, Dong HH. FoxO1 Links Insulin Resistance to Proinflammatory Cytokine IL-1 $\beta$  Production in Macrophages. *Diabetes*. 2009; 58: 2624-2633.

## UPMC Physician Resources

For the latest news, events, videos, and free CME courses presented by UPMC clinicians and researchers, visit [UPMCPPhysicianResources.com/Pediatrics](http://UPMCPPhysicianResources.com/Pediatrics).

Current CME courses in pediatric endocrinology include:



### Pediatric Endocrinology: Diagnose It

**Nursen Gurtunca, MD, and Pushpa Viswanathan, MD,** present three cases of challenging, complex, and rare disorders for discussion. Case presentations include:

- Primary ovarian failure
- Hypophosphatemic rickets
- Selenoprotein deficiency



### Management of Thyroid Nodules and Thyroid Cancer in Pediatric Patients

**Pushpa Viswanathan, MD,** discusses the prevalence and risk of malignancy among thyroid nodules in children, the difference in molecular genetics markers in pediatric differentiated thyroid cancer, and the increased risk of nodules and thyroid cancer in certain genetic syndromes.

## Video Rounds

*Video Rounds* is a series of short, informative, and educational videos created for physicians and covering a variety of medical and surgical disciplines. Current topics in pediatric endocrinology include:



### The Clinical Approach to Disorders of Sex Development

Presented by **Selma Witchel, MD**

Affiliated with the University of Pittsburgh School of Medicine and ranked among the nation's best children's hospitals by *U.S. News & World Report*.



## About UPMC Children's Hospital of Pittsburgh

Regionally, nationally, and globally, UPMC Children's Hospital of Pittsburgh is a leader in the treatment of childhood conditions and diseases, a pioneer in the development of new and improved therapies, and a top educator of the next generation of pediatricians and pediatric subspecialists. With generous community support, UPMC Children's Hospital has fulfilled this mission since its founding in 1890. UPMC Children's is recognized consistently for its clinical, research, educational, and advocacy-related accomplishments, including ranking 15th among children's hospitals and schools of medicine in funding for pediatric research provided by the National Institutes of Health (FY2018) and ranking on *U.S. News & World Report's* Honor Roll of America's Best Children's Hospitals (2019–20).