Endocrinology

Division Photo


Division Data Summary

Research and Training Details

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Clinical Activities and Training

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Faculty Members

**Stuart Handwerger, MD,** Professor; *Division Director, Robert and Mary Shoemaker Professor of Pediatrics; Professor of Cancer and Cell Biology*

*Research Interests:* Growth and thyroid disorders; perinatal endocrinology

**Philippe Backeljauw, MD,** Professor Clinical; *Director, Cincinnati Turner Syndrome Center*

*Research Interests:* Growth disorders; disorders of bone and calcium metabolism; Turner Syndrome

**Nancy Crimmins, MD,** Assistant Professor Clinical

*Research Interests:* Diabetes; obesity

**Lawrence M Dolan, MD,** Professor Clinical

*Research Interests:* Diabetes mellitus; non-insulin dependent diabetes; sexual development disorders; growth disorders; disorders of the thyroid; goiters; hypoglycemia

**Deborah Elder, MD,** Assistant Professor Clinical

*Research Interests:* Diabetes; growth disorders; precocious puberty; calcium disorders

**Jonathan Katz, PhD,** Associate Professor; *Director, Diabetes Research Center*
David J Klein, MD, PhD, Associate Professor
Research Interests: Diabetes mellitus; intensive diabetes management programs; early detection of renal disease; effects of diabetes mellitus on renal proteoglycan synthesis

David Repaske, PhD, MD, Associate Professor Clinical; Medical Director, Diabetes Center
Research Interests: Neuroendocrinology, including diabetes insipidus & pituitary disease; adrenal disorders, including congenital hyperplasia & hyperplasia; genital reproductive developmental disorders; thyroid disorders

Susan Rose, MD, Professor
Research Interests: Hypothalamic pituitary function; thyroid disorders; disorders of growth or puberty; endocrine function in cancer survivors; endocrine function after head injury

Meilan Rutter, MD, Assistant Professor Clinical
Research Interests: Calcium disorders; endocrine function in childhood cancer survivors; endocrine function in muscular dystrophy

Stenger Peggy, DO, Assistant Professor Clinical
Research Interests: Growth disorders; disorders of sexual development; pubertal disorders; disorders of the thyroid; goiter

Joint Appointment Faculty Members
Jessica Woo, PhD, Assistant Professor
Epidemiology

Trainees
- Adetokunbo Dawodu, MD, PL-6, Nassau University Medical Center
- Shilpa Gupta, MD, PL-6, Bronx Lebanon Hospital
- Sureka Bollepalli, MD, PL-5, Albert Einstein Medical Center
- Anne-Marie Kaulfers, MD, PL-5, University of Kentucky
- Iris Gutmark-Little, MD, PL-4, Cincinnati Children's Hospital Medical Center
- Amy Shah, MD, PL-4, Loyola University Medical Center

Significant Accomplishments in FY08
Juvenile Diabetes Research Foundation (JDRF) grant 1-2006-744 (jointly funded by the NIH R21 DK75769)
Type 1 diabetes mellitus (T1D) – the most common pediatric autoimmune disease – results from the total loss of the insulin-producing pancreatic beta cells. The underlying pathology of T1D is well modeled in the non-obese diabetic (NOD) mouse. The most vexing aspect of T1D in both the human clinical setting and the NOD research model, is the lack of clear indication of pre-clinical disease. As the initial phase of the disease is clinically silent. To reveal both the timing and severity of the pre-clinical disease and to develop better therapeutic interventions, this study is designed to produce an NOD mouse that self-reports the initiation and severity of the pre-clinical phase by using a surrogate molecular marker. Ultimately, the plan is to use these mice to assess the changes in circulating white blood cells in pre-diabetic mice to develop new bio-markers for T1D in mice, and then to extend these findings to humans.

JDRF 5-2008-944
Type 1 diabetes (T1D), the most common childhood autoimmune disease, is caused by the T lymphocyte-mediated destruction of insulin-producing pancreatic beta cells. The salient immunological features of T1D are well-modeled in the non-obese diabetic (NOD) mouse, which like human T1D patients exhibit spontaneous autoimmune diabetes mediated by both T cells. These so-called diabetogenic, or disease-causing, T cells are rare. Normally, it is thought that such cells are controlled by the host immune system. But in T1D patients and NOD mice they are not. This study is designed to determine why these cells are activated and not negatively controlled as they are in non-autoimmune individuals. It is believed that the activation of these T cells is by a distinct sub-population of dendritic cells (DC) that capture proteins from dying beta cells and present them to the T cells to initiate the immune response to these proteins. This study is designed to test this idea that NOD mice (and T1D patients) have alterations in this critical DC subset that allows them to break the regulation of diabetogenic T cells.

Significant Publications in FY08
Crimmins, N.A., et al. Adiponectin receptor 1 variants associated with lower insulin resistance in African
**Americans**

This paper demonstrated that variants in the adiponectin receptor 1 gene (ADIPOR1) were associated with decreased insulin resistance in non-lean African Americans. Our findings showed not only that ADIPOR1 variants might influence insulin resistance in the presence of adiposity, but also that certain variants might be protective in African Americans.


Abnormal glucose tolerance, insulin secretion and insulin sensitivity were found in a large percentage of children and adolescents with cystic fibrosis who had no prior history of diabetes. Thirty-eight percent of 73 patients had abnormal glucose metabolism, 43% had impaired glucose tolerance, 29% had impaired fasting glucose levels, 14% had both impaired glucose tolerance and fasting glucose levels and 14 had overt diabetes. All patients had significantly decreased insulin secretion and abnormalities in insulin sensitivity. These findings demonstrate that abnormalities in glucose metabolism are present in most children and adolescents with cystic fibrosis, even in the absence of a prior history of diabetes.

**Division Highlights**

David Klein, MD, PhD

Atypical anti-psychotics (AAP) are being used with increased frequency to treat psychiatric illness in children and adolescents. Although AAP treatment has resulted in symptomatic improvement, therapeutic success is often accompanied by significant weight gain, with the result in increased risk of developing insulin resistance syndromes (including diabetes), cardiovascular disease, and other complications of obesity. Weight gain is also a major reason for medication non-compliance and discontinuation, often necessitating changes in pharmacotherapy that may eliminate therapeutic gains and contribute to disease recurrence. Dr. Klein has undertaken a project to prevent AAP-induced obesity by using the insulin sensitizing agent Metformin.

Metformin has been shown to act directly on the hypothalamic appetite centers. In earlier studies, Dr. Klein and other investigators noted that Metformin prevents further weight gain in AAP treated subjects who had previously gained weight on these agents and also improved insulin sensitivity. He is now undertaking a project to determine whether Metformin given at the initiation of anti-psychotic treatment can prevent weight accretion, which occurs commonly in children on these agents. Dr. Klein will be working with colleagues in the Department of Psychiatry. He will establish a database that will follow patients started on AAPs at CCHMC, and look for risk factors that predict weight gain on these agents. The pathophysiology of weight gain will be studied by performing mixed meal challenge tests and analyzing gut hormone feedback in patients who do and do not gain weight on AAP. Preventing AAP-induced weight gain will not only help to better understand obesity but will also improve patient outcomes on AAPs by avoiding serious side effects.

Deborah Elder, MD

**Beta-cell Function in Adolescents with Type 2 Diabetes**

Studies were performed to characterize the metabolic phenotype of adolescents with type 2 diabetes mellitus. While many of the aspects of glucose metabolism in the adolescent subjects were similar to those observed in adults with type 2 diabetes, there were some striking differences between the adolescent and adult patients. Unlike adults with type 2 diabetes, the adolescents had a normal insulin response to gastrointestinal hormones. Although additional studies are necessary, these findings suggest that type 2 diabetes in adolescents may have a different pathogenesis than observed in adults. Understanding the ideology and natural history of beta cell function in adolescents with diabetes is essential for developing specific interventions to prevent, limit or reverse the disease process.

Stuart Handwerger, MD

Dr. Stuart Handwerger and his colleagues continue to investigate the factors that regulate placental and uterine development. In their placental studies, they have identified and characterized many of the transcription factors that regulate the expression of syncytin, a transmembrane glycoprotein that is critical in the early stages of villous trophoblast differentiation. In addition, they have shown that the transcription factor TFAP2A is critical for the terminal differentiation of villous trophoblast cells; and they have identified many of the transcription factors and signaling factors that modulate the expression of TFAP2A. In their uterine studies, they have identified several transcription factors that are critical for the induction of human uterine decidualization, the process by which endometrial stromal cells differentiate to become the predominant cell type lining the uterus during pregnancy. In addition, several proteins that are synthesized and secreted by these uterine cells have been shown to feedback on the cells during the
differentiation process and limit the extent of decidualization. These placental and uterine studies are of clinical importance since abnormalities in placental and uterine development are detected in many disorders of pregnancy, including preeclampsia and intrauterine growth retardation.

Division Collaboration

Collaboration with Reproductive Sciences
**Collaborating Faculty: S.K. Dey, MD; Sanjoy Das, PhD**
Research collaboration

Collaboration with Neonatology & Pulmonary Biology
**Collaborating Faculty: Cindy Bachurski, PhD**
Research collaboration

Collaboration with Biomedical Informatics
**Collaborating Faculty: Bruce Aronow, PhD; Anil Jegga, MS, DVM**
Research collaboration

Collaboration with HealthWorks; Preventive Cardiology; Gastroenterology
**Collaborating Faculty: Christopher Bolling, MD; Holly Ippisch, MD; Stavra Xanthakos, MD, MS**
Abnormal Weight Gain Clinic. Clinical and Research collaboration.

Collaboration with Center for Adherence in Psychiatry
**Collaborating Faculty: Denny Drotar, PhD; Korey Hood, PhD**
Research collaboration

Collaboration with Pulmonary
**Collaborating Faculty: Mike Seid, PhD; James Acton, MD; Jamie Wooldridge, MD**
Research collaboration

- Growth hormone therapy in patients with cystic fibrosis
- Catebolism in subjects with cystic fibrosis

Collaboration with General Pediatrics
**Collaborating Faculty: Maria Britto, MD, MPH**
Research collaboration

Collaboration with ICU
**Collaborating Faculty: Derek Wheeler, MD**
Research collaboration

Collaboration with Pharmacy
**Collaborating Faculty: Anne Lesko, PharmD**
Research collaboration

Collaboration with Adolescent Gyn; Urology
**Collaborating Faculty: Lesley Breech, MD; Curt Sheldon, MD**
Clinical - Disorders of Sexual Differentation Clinic

Collaboration with Gastroenterology
**Collaborating Faculty: Lee Denson, MD**
Study of the effects of Growth Hormone on patients with Crohn's Disease

Collaboration with Emergency Medicine
**Collaborating Faculty: Mike Gittelman, MD; Wendy Pomerantz, MD**
Injury prevention project (RWJ sponsored) in an obesity prevention project in an area experiencing health disparities

Collaboration with Psychiatry
**Collaborating Faculty: Mike Sorter, MD; Mary Matias-Akhtar, MD**
Project to see if Metformin given at the initiation of anti-psychotic treatment can prevent weight accretion, which
occurs commonly in children on these agents

Collaboration with Administration
Collaborating Faculty: Bill Kent
Project to change food offerings to parents and kids at CCHMC

Collaboration with Adolescent Medicine
Collaborating Faculty: Heidi Kwakorf, PhD; Lorah Dorn, RN, PhD
Gender identity treatment

NIH multicenter study of bone mineral in healthy children and adolescents

Grant application regarding smoking and pubertal development

Collaboration with Rheumatology
Collaborating Faculty: Hermine Brunner, MD
NIH funded grant of Triptorelin therapy in lupus patients

Collaboration with Hematology Oncology
Collaborating Faculty: Franklin Smith, MD
Funded study of oxandrolone therapy in children with Fanconi anemia

Collaboration with Mayerson Center
Collaborating Faculty: Kathi Makoroff, MD
Pfizer funded study shaken infants

Collaboration with Physical Medicine and Rehabilitation
Collaborating Faculty: Linda Michaud, MD
Pfizer-funded study of endocrine function after traumatic brain injury

Collaboration with Neurology
Collaborating Faculty: Brenda Wong, MD
Development of research regarding Duchenne Muscular Dystrophy

Collaboration with Hematology Oncology
Collaborating Faculty: Richard Harris, MD; Stella Davies, MD; Parinda Mehta, MD
Research, database, and multicenter care of patients with Fanconi Anemia and other bone marrow failure syndromes

Collaboration with Cardiology
Collaborating Faculty: William Gottliebson, MD; Elaine Urbina, MD; Thomas Kimball, MD; John Morrison, PhD
Clinical management protocol for cardiac disease in Turner syndrome

The epidemiology of peripheral cardiovascular disease in youth with a specific emphasis on the role of obesity, insulin resistance and diabetes

The epidemiology of central (heart) cardiovascular disease in youth with a specific emphasis on the role of obesity, insulin resistance and diabetes

The ability of pre-teen variables to predict the development of obesity, insulin resistance, diabetes and cardiovascular disease

Collaboration with Epidemiology and Biostatistics
Collaborating Faculty: Lisa Martin, PhD; Jane Khoury, PhD
Contribution of genetics to obesity in adolescents

The effect of maternal type 1 diabetes on adolescent and young adult offspring with a focus on obesity and carbohydrate metabolism

Collaboration with Psychology and Behavioral Medicine
Collaborating Faculty: Scott Powers, PhD
Eating behaviors in individuals 16 years of age with type 1 diabetes

Collaboration with Surgery
Collaborating Faculty: Thomas Inge, MD, PhD
Bariatric surgery in youth: safety, efficacy, and effect on carbohydrate and cardiovascular outcomes

Division Publications


5. Crimmins NA, Martin LJ. Polymorphisms in adiponectin receptor genes ADIPOR1 and ADIPOR2 and insulin resistance. Obes Rev. 2007; 8: 419-23.


21. Saxena V, Ondr JK, Magnusen AF, Munn DH, Katz JD. The countervailing actions of myeloid and plasmacytid


### Grants, Contracts, and Industry Agreements

#### Grant and Contract Awards

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Schafer-Kalkhoff, T

Understanding Social Status Impact on Adolescent Health

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| Current Year Direct Receipts       | $211,750            |
| Total                              | $1,505,180          |