Endocrinology

Division Photo

First Row: P. Stenger, M. Rutter, N. Crimmins; Second Row: P. Backeljauw, L. Dolan, S. Handwerger, D. Klein

Division Data Summary

Research and Training Details

Number of Faculty	11
Number of Joint Appointment Faculty	1
Number of Support Personnel	26
Direct Annual Grant Support	$1,293,430
Direct Annual Industry Support	$211,750
Peer Reviewed Publications	25

Clinical Activities and Training

Number of Clinical Fellows	6
Number of Clinical Students	3
Inpatient Encounters	1,951
Outpatient Encounters	10,173

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 proteogycan 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 & hypoplasia; 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 comon 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.

Elder, D.A., et al. Glucose tolerance, insulin secretion, and insulin sensitivity in children and adolescents with cystic fibrosis and no prior history of diabetes

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; Gastroenerology

Collaborating Faculty: Christopher Bolling, MD; Holly Ippisch, MD; Stavra Xanthakos, MD, MS

Abnormal Weight Gain Clinic. Clinical and Research collaboration.

Collaboration with Center for Adherance 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 Kwalkorf, 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 offstring 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

1. Albers JJ, Marcovina SM, Imperatore G, Snively BM, Stafford J, Fujimoto WY, Mayer-Davis EJ, Petitti DB, Pihoker C, Dolan L, Dabelea DM. **Prevalence and determinants of elevated apolipoprotein B and dense low-density lipoprotein in youths with type 1 and type 2 diabetes**. *J Clin Endocrinol Metab.* 2008; 93: 735-42.
2. Backeljauw P. **Statement 5: the first line of treatment for children with idiopathic short stature (ISS) and low serum insulin-like growth factor-I (IGF-I) should be IGF-I**. *Pediatr Endocrinol Rev.* 2008; 5 Suppl 3: 853-6.
3. Backeljauw P. **Does growth hormone therapy before 4 years of age enhance the linear growth of girls with Turner's syndrome?**. *Nat Clin Pract Endocrinol Metab.* 2008; 4: 78-9.
4. Crimmins NA, Dolan LM, Martin LJ, Bean JA, Daniels SR, Lawson ML, Goodman E, Woo JG. **Stability of adolescent body mass index during three years of follow-up**. *J Pediatr.* 2007; 151: 383-7.
5. Crimmins NA, Martin LJ. **Polymorphisms in adiponectin receptor genes ADIPOR1 and ADIPOR2 and insulin resistance**. *Obes Rev.* 2007; 8: 419-23.
6. Crimmins NA, Woo JG, Kaushal RD, Deka R, Dolan LM, Martin LJ. **Adiponectin receptor 1 variants associated with lower insulin resistance in African Americans**. *Obesity (Silver Spring).* 2007; 15: 1903-7.
7. Dorn LD, Rose SR, Rotenstein D, Susman EJ, Huang B, Loucks TL, Berga SL. **Differences in endocrine parameters and psychopathology in girls with premature adrenarche versus on-time adrenarche**. *J Pediatr Endocrinol Metab.* 2008; 21: 439-48.
8. Elder DA, Wooldridge JL, Dolan LM, D'Alessio DA. **Glucose tolerance, insulin secretion, and insulin sensitivity in children and adolescents with cystic fibrosis and no prior history of diabetes**. *J Pediatr.* 2007; 151: 653-8.
9. Inge TH, Pfluger P, Zeller M, Rose SR, Burget L, Sundararajan S, Daniels SR, Tschop MH. **Gastric bypass surgery for treatment of hypothalamic obesity after craniopharyngioma therapy**. *Nat Clin Pract Endocrinol Metab.* 2007; 3: 606-9.
10. Leung W, Ahn H, Rose SR, Phipps S, Smith T, Gan K, O'Connor M, Hale GA, Kasow KA, Barfield RC, Madden RM, Pui CH. **A prospective cohort study of late sequelae of pediatric allogeneic hematopoietic stem cell transplantation**. *Medicine (Baltimore).* 2007; 86: 215-24.
11. Maahs DM, Snively BM, Bell RA, Dolan L, Hirsch I, Imperatore G, Linder B, Marcovina SM, Mayer-Davis EJ, Pettitt DJ, Rodriguez BL, Dabelea D. **Higher prevalence of elevated albumin excretion in youth with type 2 than type 1 diabetes: the SEARCH for Diabetes in Youth study**. *Diabetes Care.* 2007; 30: 2593-8.
12. May M, Rose SR. **Oral hydration during growth hormone stimulation with clonidine**. *J Pediatr Nurs.* 2007; 22: 383-7.
13. Patton SR, Dolan LM, Henry R, Powers SW. **Parental fear of hypoglycemia: young children treated with continuous subcutaneous insulin infusion**. *Pediatr Diabetes.* 2007; 8: 362-8.
14. Piazza-Waggoner C, Modi AC, Powers SW, Williams LB, Dolan LM, Patton SR. **Observational assessment of family functioning in families with children who have type 1 diabetes mellitus**. *J Dev Behav Pediatr.* 2008; 29: 101-5.
15. Pinzone JJ, Eng C, Paik J, Brindle KA, Ringel MD, Katz JD. **A novel PTEN mutation in Cowden syndrome is associated with a mixed degenerative-erosive arthritic process: potential molecular pathogenic mechanisms**. *Am J Med Genet A.* 2007; 143A: 1522-7.
16. Rewers A, Klingensmith G, Davis C, Petitti DB, Pihoker C, Rodriguez B, Schwartz ID, Imperatore G, Williams D, Dolan LM, Dabelea D. **Presence of diabetic ketoacidosis at diagnosis of diabetes mellitus in youth: the Search for Diabetes in Youth Study**. *Pediatrics.* 2008; 121: e1258-66.
17. Rose SR. **Obesity and growth disorders: festschrift dedicated to George A Burghen.** *The Endocrinologist.* 2007; 17: 267-72.
18. Rose SR. **Use of GnRH agonists in GH-deficient patients: arguments for and against. The case against GnRH agonists in GH-deficient patients**. *Pediatr Endocrinol Rev.* 2008; 5 Suppl 2: 744, 750-4.
19. Rose SR. **Mechanisms of hypothalamic-pituitary injury in oncologic disease.** *The Endocrinologist.* 2008; 18: 85-89.
20. Rutter MM, Rose SR. **Long-term endocrine sequelae of childhood cancer**. *Curr Opin Pediatr.* 2007; 19: 480-7.
21. Saxena V, Ondr JK, Magnusen AF, Munn DH, Katz JD. **The countervailing actions of myeloid and plasmacytoid**

dendritic cells control autoimmune diabetes in the nonobese diabetic mouse. *J Immunol.* 2007; 179: 5041-53.

22. Sherafat-Kazemzadeh R, Mehta SN, Care MM, Kim MO, Williams DA, Rose SR. Small pituitary size in children with Fanconi anemia. *Pediatr Blood Cancer.* 2007; 49: 166-70.
23. Walitt BT, Constantinescu F, Katz JD, Weinstein A, Wang H, Hernandez RK, Hsia J, Howard BV. Validation of self-report of rheumatoid arthritis and systemic lupus erythematosus: The Women's Health Initiative. *J Rheumatol.* 2008; 35: 811-8.
24. Wojciechowski S, Tripathi P, Bourdeau T, Acero L, Grimes HL, Katz JD, Finkelman FD, Hildeman DA. Bim/Bcl-2 balance is critical for maintaining naive and memory T cell homeostasis. *J Exp Med.* 2007; 204: 1665-75.
25. Woo JG, Dolan LM, Morrow AL, Geraghty SR, Goodman E. Breastfeeding helps explain racial and socioeconomic status disparities in adolescent adiposity. *Pediatrics.* 2008; 121: e458-65.

Grants, Contracts, and Industry Agreements

Grant and Contract Awards		Annual Direct / Project Period Direct
Dolan, L		
Study of Monogenic Forms of Diabetes Juvenile Diabetes Research Foundation (Wake Forest University)	03/01/08 - 02/28/09	$14,611 / $14,611
SEARCH For Diabetes in Youth 2: Ohio Site Centers for Disease Control and Prevention U01 DP 000248	09/30/05 - 09/29/10	$459,513 / $2,261,046
SEARCH Nutrition Ancillary Study National Institutes of Health (University of South Carolina) R01 DK 077131	01/15/07 - 12/31/10	$3,973 / $19,865
Understanding Social Status Impact on Adolescent Health National Institutes of Health (New England Medical Center Hospital, Inc) R01 HD 041527	02/01/08 - 01/31/12	$147,513 / $590,052
Nutrition and Metabolic Status in Youth with Type 1 DM: SEARCH Ancillary Study National Institutes of Health (University of North Carolina) R01 DK 077949	04/01/08 - 03/31/12	$27,051 / $93,372
Elder, D		
Beta Cell Function in Adolescents with Type II Diabetes National Institutes of Health K23 DK 070775	09/01/05 - 08/31/10	$116,500 / $582,500
Handwerger, S		
Training In Developmental and Perinatal Endocrinology National Institutes of Health T32 HD 007436	05/01/06 - 04/30/11	$217,480 / $905,850
Katz, J		
The Insulitis Reporter Mouse National Institutes of Health R21 DK 075769	07/01/06 - 06/30/08	$125,000 / $275,000
Pulling Back the Covers on Insulitis - the Insulitis Reporter Mouse Juvenile Diabetes Research Foundation 1-2006-744	09/01/06 - 08/31/09	$122,135 / $365,310
Ondr, J		
The Insulitis Reporter Mouse Juvenile Diabetes Research Foundation	08/01/06 - 07/31/08	$48,928 / $96,224
Schafer-Kalkhoff, T		
Understanding Social Status Impact on Adolescent Health National Institutes of Health (New England Medical Center Hospital, Inc)		

R01 HD 041527	10/01/07 - 12/31/07	$10,726 / $10,726

Current Year Direct	**$1,293,430**

Industry Contracts

Backeljauw, P	
Eli Lilly and Company	$ 17,806
Tercica, Inc.	$ 117,639
Novo Nordisk Pharmaceuticals	$ 9,798
Klein, D	
American Diabetes Association	$ 5,000
Repaske, D	
Pfizer Inc.	$ 2,233
Rose, S	
Pfizer Inc.	$ 52,556
Genentech, Inc.	$ 6,718

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