

Division Photo



First Row: S. Rose, N. Crimmins, P. Stenger, D. Elder; Second Row: N. Yayah Jones, P. Backeljauw, L. Dolan, D. Klein, M. Rutter

Division Data Summary

Research and Training Details

Number of Faculty	11
Number of Joint Appointment Faculty	1
Number of Support Personnel	24
Direct Annual Grant Support	\$1,261,000
Direct Annual Industry Support	\$244,351
Peer Reviewed Publications	19

Clinical Activities and Training

Number of Clinical Fellows	9
Inpatient Encounters	1585
Outpatient Encounters	12,778

Significant Publications

Impaired  $\beta$ -cell sensitivity to glucose and maximal insulin secretory capacity in adolescents with type 2 diabetes. Deborah A. Elder M.D.<sup>1</sup>, Jessica G. Woo, Ph.D.<sup>1</sup>, David A. D'Alessio M.D. <sup>2</sup> <sup>1</sup>Cincinnati Children's Hospital Medical Center Department of Pediatrics, Division of Endocrinology, Cincinnati, Ohio, U.S.A. 45229 and <sup>2</sup>Department of Medicine, University of Cincinnati College of Medicine, Cincinnati, OH, U.S.A 45267.

Adults with type 2 diabetes (T2DM) have broad impairments in  $\beta$ -cell function, the cell responsible for insulin secretion. These defects include severe attenuation of the the earliest release of insulin in response to a glucose

bolus, and reduced  $\beta$ -cell mass. In adolescents with T2DM there is some evidence that  $\beta$ -cell dysfunction may be less severe. Our objectives were to determine the  $\beta$ -cell sensitivity to rising glucose and determine the amount of functional  $\beta$ -cell mass by calculating the acute insulin response when the beta-cell was maximally stimulated (AIRMAX) in teenagers with T2DM.

We studied 15 adolescents with T2DM and 10 nondiabetic control subjects matched for age race gender and degree of obesity. T2DM subjects had a mean duration of diabetes of  $48.8 \pm 6.4$  months, were treated with conventional therapies, and had good metabolic control (HbA1c  $6.7 \pm 1.2$  %). We found that the insulin response to increasing plasma glucose concentrations was blunted in the diabetic compared with control subjects ( $34.8 \pm 11.9$  vs.  $280.5 \pm 57.8$  pmol/mmol;  $p < 0.0001$ ), and AIRMAX was also significantly reduced in the diabetic group ( $1868 \pm 330$  vs.  $4445 \pm 606$ ,  $p = 0.0005$ ). We concluded that even adolescents with well-controlled T2DM have severe impairments of insulin secretion. These data support  $\beta$ -cell dysfunction as central in the pathogenesis of T2DM in young people, and indicate that these abnormalities can develop over a period of just several years.

### **Cutting Edge: Merocytic dendritic cells break T cell tolerance to beta cell antigens in NOD mouse diabetes[1]**

**Jonathan D Katz†,‡,\* , Jennifer K Ondr†,§,\* , Robert J Opoka†,‡, Zacharias Garcia\*, Edith M Janssen‡**  
†Diabetes Research Center, Division of Endocrinology, ‡Division of Molecular Immunology, and §Division of Immunobiology, Cincinnati Children's Research Foundation, Department of Pediatrics, University of Cincinnati College of Medicine, 3333 Burnet Avenue, Cincinnati, OH 45229 \*La Jolla Institute for Allergy and Immunology, 9420 Athena Circle, La Jolla, CA 92037 \* Author contributed equally to the work [1] This work is supported by JDRF grant (5-2008-944) to JDK and EMJ, NIH grant R01 DK08179 to JDK and NIH grant R21 AI079545 to EMJ.

In type 1 diabetes (T1D), also known as juvenile or autoimmune diabetes, white blood cells known as T lymphocytes destroy the insulin-producing, pancreatic beta cells. When a significant number of beta cells are lost, T1D results. Normally, most T cells that invade and attack the beta cells are kept in check by a process called peripheral tolerance. But in individuals with T1D, this natural regulatory process breaks down. We have recently identify a critical sub-population of white blood cells called dendritic cells that mediate the breaking of peripheral tolerance and allow for the activation of the T cells that kill beta cells. These dendritic cells are called merocytic dendritic cells (mcDC). We found that they are more numerous in nonobese diabetic (NOD) mouse, the mouse model for T1D in humans, and that these dendritic cells stimulate islet-reactive CD4+ and CD8+ T cells. When purified from the pancreatic lymph nodes of overtly diabetic NOD mice, the mcDC break peripheral T cell tolerance to beta cells, lead to T cell activation and induce rapid onset T1D in young NOD mouse. Thus, the mcDC subset appears to represent the long-sought accessory white blood cell responsible for breaking peripheral tolerance to beta cell antigen. The identification of these cells as critical players in the initiation of the disease process may provide us with a new target for anti-diabetes therapy.

## **Division Highlights**

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### **Peggy J. Stenger, D.O.**

Peggy J. Stenger, D.O., Assistant Professor of Pediatrics, has developed a special interest in treating children with metabolic bone disease. She obtained certification as a clinical bone densitometrist (interpretation of DXA scans) in 2007, and in late 2009, established a clinic dedicated to the diagnosis and treatment of children and adolescents with disorders which affect skeletal health. Referrals have been made for patients with a variety of abnormalities of phosphorus, calcium and vitamin D metabolism, including rickets of all kinds, as well as patients with osteoporosis, recurrent fractures, high or low bone density and bowlegs. The clinic meets monthly on the 3rd Tuesday and is coordinated by Pamela Burwinkel, RN.

Long-term goals include the provision of a comprehensive, multispecialty clinic, including endocrinology, genetics, orthopedics, renal, dietary and gastroenterology. Children's Hospital should strive for a prominent role as a regional/national referral center for patients with metabolic bone disease. Because our patient population is large, there is an excellent opportunity for clinical studies aimed at prevention and treatment of such common conditions as corticosteroid-induced osteoporosis. To achieve those goals will require the recruitment of physicians/scientists who are interested in both clinical and basic science research. With increasing use of DXA, now the gold-standard for diagnosis of bone density disorders, we expect that formal interpretation of those results would be standard procedure. In the future, we envision a focus group of individuals in different specialties sharing the common interest of exchanging information (personal research, journal articles) to further interest and learning in metabolic bone disorders. Finally, excellent and compassionate care of our patients remains the ultimate goal, both short and long-term.

## Division Collaboration

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### 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; Jeffrey Whitsett, MD

Research collaboration

### Collaboration with Biomedical Informatics

**Collaborating Faculty:** Bruce Aronow, PhD; Anil Jegga, MS, DVM

Research collaboration

### Collaboration with Pathology

**Collaborating Faculty:** Jerzy Stanek, MD, PhD

Research collaboration

### Collaboration with Molecular and Developmental Biology

**Collaborating Faculty:** James Wells, PhD

Research collaboration

### Collaboration with Healthworks; Preventive Cardiology; Gastroenterology

**Collaborating Faculty:** Holly Ippisch, MD; Stavra Xanthakos, MD, MS; Robert Siegel, MD

Center for Better Health and Nutrition clinical collaboration

### Collaboration with Center for Adherence in Psychiatry

**Collaborating Faculty:** Denny Drotar, PhD; Korey Hood, PhD

Research collaboration

Depression in diabetes

### Collaboration with Pulmonary

**Collaborating Faculty:** Mike Seid, PhD; James Acton, MD; Jamie Wooldridge, MD

Growth hormone therapy in patients with cystic fibrosis

Cystic fibrosis insulin study

### 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; Curtis Sheldon, MD

Clinical collaboration - Disorders of Sexual Differentiation 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; Robert Kowatch, 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 Adolescent Medicine

**Collaborating Faculty:** Heidi Kwalkorf, PhD; Lorah Dorn, RN, PhD

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; Jessica Woo, PhD**

Contribution of genetics to obesity in adolescents

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

Creation of clinical database for the Comprehensive Weight Management Center

**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

## **Faculty Members**

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**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 Clinical

**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 & hypoplasia; genital reproductive developmental disorders; thyroid disorders

**Susan Rose, MD**, Professor Clinical

**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

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**Jessica Woo, PhD**, Assistant Professor  
Epidemiology

## Trainees

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- **Sureka Bollepalli, MD**, PL-6, Albert Einstein Medical Center
- **Anne-Marie Kaulfers, MD**, PL-6, University of Kentucky
- **Iris Gutmark-Little, MD**, PL-5, Cincinnati Children's Hospital Medical Center
- **Amy Shah, MD**, PL-5, Loyola University Medical Center
- **Sarah Lawson, MD**, PL-4, University of Kentucky
- **Erica Reynolds, MD**, PL-4, Wake Forest University Baptist Medical Center
- **Stephanie Sisley, MD**, PL-4, Indiana University

## Significant Accomplishments

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### Obesity clinic launched

As the obesity epidemic continues, the prevalence of obesity in very young children ages 2-5 years is increasing. As a result of this, the Center for Better Health and Nutrition has received increasing numbers of referrals to see children within this age range.

In response, Nancy Crimmins, MD, started a monthly clinic dedicated to treating obese children ages 2-5. An exercise physiologist, nutritionist, and social worker also work at the clinic, where we encourage parents to model a healthy lifestyle and limit-setting.

Crimmins recently presented data at the Endocrine Society national meeting showing that young children referred to Cincinnati Children's during the past two years frequently have body mass indexes within the adult range for obesity. Many of these children already manifest obesity-related disease such as insulin resistance, dyslipidemia, and fatty liver disease. Crimmins is working to define the frequency and extent of these co-morbidities of obesity with the goal of developing effective interventions.

### Treating hereditary MEN 2B

Clinical fellow Roopa Shankar's abstract, "Infants with Hereditary MEN 2B Should Undergo Prenatal Surgical Referral and Prophylactic Thyroidectomy within the First Month of Life" won the Presidential Poster Competition at ENDO 2010. This competition is reserved for trainees who are both first and presenting author of the abstract. Trainee authors of the highest scoring abstracts from each poster category were invited to participate.

The poster was a case report on the youngest reported patient in the literature, an infant with inherited MEN 2B and microscopic medullary thyroid carcinoma in the thyroidectomy specimen at 9 weeks of age. The present guidelines give room up to 6-12 months of age for prophylactic thyroidectomy. We concluded from our case that prophylactic thyroidectomy may be performed by one month of age. In order to facilitate the early thyroidectomy, we suggested an algorithm of prenatal genetic and surgical referral with scheduling of anticipated date of surgery prior to birth and RET

testing thereafter. If RET mutation positive for MEN 2B, the baby would undergo prophylactic thyroidectomy by one month of age at a center with expertise in neonatal thyroid surgery.

## Division Publications

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1. :

## Grants, Contracts, and Industry Agreements

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### Grant and Contract Awards

### Annual Direct / Project Period Direct

#### Dolan, L

##### SEARCH For Diabetes in Youth 2: Ohio Site

Centers for Disease Control

U01 DP 000248

09/30/05 - 09/29/10

\$466,170 / \$2,261,046

##### Nutrition and Metabolic Status in Youth with Type 1 DM: Search Ancillary Study

University of North Carolina (National Institutes of Health)

R01 DK 077949

04/01/08 - 03/31/12

\$26,489 / \$93,605

##### SubClinical Cardiovascular disease in Youth (CVD)

University of Colorado (National Institutes of Health)

R01 DK 078542

09/22/09 - 08/31/11

\$208,682 / \$406,005

#### 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 / \$583,500

#### Handwerger, S

##### Training In Developmental And Perinatal Endocrinology

National Institutes of Health

T32 HD 007463

05/01/06 - 04/30/11

\$203,159 / \$1,007,965

#### Katz, J

##### Dissecting Dendritic Cell Function in Autoimmune Diabetes

National Institutes of Health

R01 DK 078179

08/01/09 - 07/31/14

\$240,000 / \$1,132,500

**Current Year Direct**

**\$1,261,000**

## Industry Contracts

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#### Backeljauw, P

Eli Lilly and Company

\$ 5,115

Tercica, Inc.

\$ 43,679

Novo Nordisk Pharmaceuticals

\$ 24,700

#### Handwerger, S

Pfizer Inc.

\$ 5,313

#### Klein, D

American Diabetes Association

\$ 3,850

Novo Nordisk Pharmaceuticals

\$ 35,571

#### Lawson, S

Novo Nordisk Pharmaceuticals

\$ 15,400

#### Rose, S

Pfizer Inc.

\$ 51,037

Genentech, Inc.

\$ 23,447

Altus

\$ 12,239

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**Dolan, L**

Benaroya Research Institute

\$ 24,000

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**Current Year Direct Receipts**

**\$244,351**

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**Total \$1,505,351**

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