Endocrinology

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

Adults with type 2 diabetes (T2DM) have broad impairments in β-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 β-cell mass. In adolescents with T2DM there is some evidence that β-cell dysfunction may be less severe. Our objectives were to determine the β-cell sensitivity to rising glucose and determine the amount of functional β-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 ± 6.4 months, were treated with conventional therapies, and had good metabolic control (HbA1c 6.7 ± 1.2 %). We found that the insulin response to increasing plasma glucose concentrations was blunted in the diabetic compared with control subjects (34.8 ± 11.9 vs. 280.5 ± 57.8 pmol/mmol; $p < 0.0001$), and AIRMAX was also significantly reduced in the diabetic group (1868 ± 330 vs. 4445 ± 606, $p = 0.0005$). We concluded that even adolescents with well-controlled T2DM have severe impairments of insulin secretion. These data support β-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 call 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

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

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 Adherance 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 fybrosis

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

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 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 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

Jessica Woo, PhD, Assistant Professor
Epidemiology

Trainees

- **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

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

1. :

Grants, Contracts, and Industry Agreements

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

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
Dolan, L	
Benaroya Research Institute	$ 24,000

Current Year Direct Receipts	**$244,351**
Total	**$1,505,351**