Endocrinology

Division Photo

Front Row: S. Rose, S. Handwerger; Second Row: N. Yayah Jones, D. Klein, M. Rutter, N. Crimmins, P. Backeljauw, D. Elder

Division Data Summary

Research and Training Details

Number of Faculty	11
Number of Joint Appointment Faculty	1
Number of Support Personnel	23
Direct Annual Grant Support	$1,324,266
Direct Annual Industry Support	$254,404
Peer Reviewed Publications	20

Clinical Activities and Training

Number of Clinical Fellows	7
Inpatient Encounters	2,472
Outpatient Encounters	10,341

Significant Publications

Kessler, C.A., C.J. Bachurski, et al. TEAD1 inhibits prolactin gene expression in cultured human uterine decidual cells

Although prolactin was originally described as a pituitary hormone that is critical for lactation, it is now known that prolactin is also expressed by many extrapituitary cells. These include decidualized human endometrial stromal cells

(decidual cells), which are the primary cells that line the uterus during pregnancy and are the site for the attachment of the blastocyst to the uterus. Previous studies by Dr. Handwerger's laboratory have shown prolactin expression from uterine decidual cells is regulated by a different promoter than that of pituitary cells. However, relatively little is known about the transcription factors that regulate the expression of prolactin by decidual cells. In this study, Dr. Handwerger and his colleagues demonstrated that transcription factor TEAD1 markedly inhibits activity of the decidual prolactin promoter. High levels of TEAD1 in human endometrial stromal cells prior to pregnancy prevent the cells from expressing prolactin. During pregnancy, a decrease in TEAD1 levels contributes to the induction of prolactin expression by these cells. A better understanding of prolactin production by the pregnant uterus is important since many studies strongly suggest physiological roles for prolactin in the mother and fetus.

Goodman, E., T.E. Graham, et al. The relationship of retinol binding protein 4 to changes in insulin resistance and cardiometabolic risk in overweight black adolescents

The physiologic mechanism that links obesity, insulin resistance, and adverse health outcomes is not known. However, recent data in animals suggests that retinol binding protein 4 (RBP4), traditionally known to transport retinol from storage sites in the liver to extra hepatic tissues, may affect insulin resistance. These data include but are not limited to a study in mice in which chronic elevation of RBP4 in plasma was associated with increased hepatic glucose production and down regulation of insulin signaling in muscle resulting in systemic insulin resistance. Data in humans are inconclusive.

We hypothesized that increased plasma RBP4 over three years of follow up will be associated with worsening insulin resistance. To test this hypothesis we used frozen plasma and data from the Princeton School District Study in black overweight adolescents. We chose to study blacks because blacks have a higher frequency of obesity and its sequelae and racial and ethnic variation in the relative contributions of insulin resistance to the development of type 2 diabetes may confound the relationship of RBP4 to insulin resistance.

Using a nested, retrospective design we identified 51 overweight post-pubertal blacks. The subjects were divided into tertiles based on those who had the greatest increasing in insulin resistance (top tertile) by HOMA-IR or greatest improvement in insulin resistance (lowest terrile) over the three years of the study. RBP4 increased in one third of the subjects. Logistic regression demonstrated that increased RBP4 was associated with a significantly higher odds ratio of worsening insulin resistance (IR) independent of age, gender, or adiposity. The odds ratios were 5.6 (weight, $p=0.024$), 6.0 (BMI, $p<0.025$), and 7.4 (waist circumference, $p=0.015$). Initial RBP4 (beta=0.81, $p=0.005$) and delta RBP4 (beta=0.56, $p<0.046$) also predicted change in triglycerides.

These associations suggest that RBP4 may be a mechanism through which obesity influences insulin resistance and hypertriglyceridemia in overweight, post-pubertal, black youth. In addition, RBP4 may be a risk marker for IR.

Division Highlights

David Klein, MD, PhD

Obesity rates have increased dramatically over the past 30 years, particularly in populations experiencing health disparities. The importance of developing evidence-based techniques to prevent childhood obesity and its consequences has been emphasized not only in the medical arena, but also in the political realm and lay press. A focus of Dr. Klein’s research has become obesity prevention in communities experiencing health disparities. He has conducted an obesity prevention program in the Commonwealth of the Northern Marianas Islands, a Pacific US protectorate that experiences a high occurrence of type 2 diabetes and obesity. The results of this intervention were recently published in the journal Nature Obesity. Mothers of 3rd grade children were educated about the role of obesity in the development of type 2 diabetes and how to prevent overweight by healthy lifestyle practices, using culturally sensitive techniques delivered by teachers in a program developed using community based participatory research. The program was successful in reducing the amount of obesity experienced by the students.

Closer to home, in the predominantly African American (AA) neighborhood of Avondale in Cincinnati, OH, Dr. Klein and his coworkers have tested and established an after school obesity prevention program in three elementary schools. Obesity rates were 21.6% amongst these students, which is much higher than in comparable Caucasian elementary schools. High school students from the predominantly AA Hughes High School for the Health Professions administered the program, whose curriculum was developed by a multi-disciplined team of health educators, medical professionals, AA students, and community members. These “peer educators” were able to prevent further increases in obesity rates in this community. The studies conducted by Dr. Klein are amongst the few successful obesity prevention program thus far reported and should lay the groundwork for larger endeavors addressing this important health problem.

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

Comprehensive Weight Management Center 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

Research collaboration

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 - 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 adolescent 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

Clinical Research on IGF-I Therapy Leads to FDA-Approval of Recombinant Human IGF-I

From the beginning of the 1990's, Dr. Backeljauw has been a principal investigator in the clinical studies that recently led to the FDA-approval of a second agent (next to GH) for growth promotion: recombinant human insulin-like growth factor I (IGF-I; mecasermin). IGF-I therapy is now approved for the treatment of short stature resulting from severe primary IGF-I deficiency (IGFD). Patients with primary IGFD have normal or increased GH concentrations, but low IGF-I, due to defects of the GH receptor or post-GH receptor signaling pathway. Long-term clinical research, in collaboration with investigators at the University of North Carolina, led to important advances in the understanding of the physiology of the GH-IGF-I axis, and opened the door for the therapeutic use of IGF-I. Final height data for initial study patients will be

presented at the combined LWPES/ESPE global meeting in New York, in September 2009.

As the director of the Turner Syndrome Center, Dr. Backeljauw follows more than 100 Turner syndrome (TS) patients. Collaborative efforts with physicians in Pediatric Cardiology and Developmental Pediatrics, amongst others, have led to the development of a successful multidisciplinary clinic, to provide excellence in clinical care for girls with this chronic disorder. A clinical/research database is in place, and some of the original research resulting from this has included the evaluation of the prevalence of ADHD in TS, and the prevalence of partial anomalous venous return in TS patients evaluated by cardiac MRI. The latter project was also accepted for oral presentation at the Global Pediatric Endocrinology Meeting in New York, September 2009. Additional research in development involves the study of aortic root dilatation by cardiac MRI, as well as arteriopathy through the use of non-invasive imaging techniques.

Division Publications

1. van der Kaay DC, de Jong FH, Rose SR, Odink RJ, Bakker-van Waarde WM, Sulkers EJ, Hokken-Koelega AC. Overnight levels of luteinizing hormone, follicle-stimulating hormone and growth hormone before and during gonadotropin-releasing hormone analogue treatment in short boys born small for gestational age. *Horm Res.* 2009; 71: 260-7.
2. Goodman E, Graham TE, Dolan LM, Daniels SR, Goodman ER, Kahn BB. The relationship of retinol binding protein 4 to changes in insulin resistance and cardiometabolic risk in overweight black adolescents. *J Pediatr.* 2009; 154: 67-73 e1.
3. Inge TH, Miyano G, Bean J, Helmrath M, Courcoulas A, Harmon CM, Chen MK, Wilson K, Daniels SR, Garcia VF, Brandt ML, Dolan LM. Reversal of type 2 diabetes mellitus and improvements in cardiovascular risk factors after surgical weight loss in adolescents. *Pediatrics.* 2009; 123: 214-22.
4. Handwerger S. The growth hormone gene cluster: physiological actions and regulation during pregnancy. *Growth Genet Horm.* 2009; 25: 1-8.
5. van der Kaay DC, Rose SR, van Dijk M, Noordam C, van Rheenen E, Hokken-Koelega AC. Reduced levels of GH during GnRH analogue treatment in pubertal short girls born small for gestational age (SGA). *Clin Endocrinol (Oxf).* 2009; 70: 914-9.
6. Walvoord EC, de la Pena A, Park S, Silverman B, Cuttler L, Rose SR, Cutler G, Drop S, Chipman JJ. Inhaled growth hormone (GH) compared with subcutaneous GH in children with GH deficiency: pharmacokinetics, pharmacodynamics, and safety. *J Clin Endocrinol Metab.* 2009; 94: 2052-9.
7. Urbina EM, Kimball TR, McCoy CE, Khoury PR, Daniels SR, Dolan LM. Youth with obesity and obesity-related type 2 diabetes mellitus demonstrate abnormalities in carotid structure and function. *Circulation.* 2009; 119: 2913-9.
8. Liu LL, Yi JP, Beyer J, Mayer-Davis EJ, Dolan LM, Dabelea DM, Lawrence JM, Rodriguez BL, Marcovina SM, Waitzfelder BE, Fujimoto WY. Type 1 and Type 2 diabetes in Asian and Pacific Islander U.S. youth: the SEARCH for Diabetes in Youth Study. *Diabetes Care.* 2009; 32 Suppl 2: S133-40.
9. Lomenick JP, Reifschneider KL, Lucky AW, Adams D, Azizkhan RG, Woo JG, Backeljauw PF. Prevalence of adrenal insufficiency following systemic glucocorticoid therapy in infants with hemangiomas. *Arch Dermatol.* 2009; 145: 262-6.
10. Brown RS, LaFranchi S, Rose SR. Patient information page from the hormone foundation. Congenital hypothyroidism. *J Clin Endocrinol Metab.* 2009; 94: 1835-6.
11. McGrady ME, Laffel L, Drotar D, Repaske D, Hood KK. Depressive symptoms and glycemic control in adolescents with type 1 diabetes: mediational role of blood glucose monitoring. *Diabetes Care.* 2009; 32: 804-6.
12. Kenny AP, Crimmins NA, Mackay DJ, Hopkin RJ, Bove KE, Leonis MA. Concurrent Course of Transient Neonatal Diabetes with Cholestasis and Paucity of Interlobular Bile Ducts: A Case Report. *Pediatr Dev Pathol.* 2009; : 1.
13. Mayer-Davis EJ, Ma B, Lawson A, D'Agostino RB, Jr., Liese AD, Bell RA, Dabelea D, Dolan L, Pettitt DJ, Rodriguez BL, Williams D. Cardiovascular disease risk factors in youth with type 1 and type 2 diabetes: implications of a factor analysis of clustering. *Metab Syndr Relat Disord.* 2009; 7: 89-95.
14. Maahs DM, Snively BM, Beyer J, Imperatore G, Bell R, Mayer-Davis EJ, Dolan LM, Pettitt DJ, Hirsch I, Rodriguez B, Dabelea D. Birth weight [corrected] and elevated albumin to creatinine ratio in youth with diabetes: the SEARCH for Diabetes in Youth study. *Pediatr Nephrol.* 2008; 23: 2255-60.
15. Eyal O, Blum S, Mueller R, Smith FO, Rose SR. Improved growth velocity during thyroid hormone therapy in children with Fanconi anemia and borderline thyroid function. *Pediatr Blood Cancer.* 2008; 51: 652-6.
16. Kazlauskaite R, Evans AT, Villabona CV, Abdu TA, Ambrosi B, Atkinson AB, Choi CH, Clayton RN, Courtney CH, Gonc EN, Maghnie M, Rose SR, Soule SG, Tordjman K. Corticotropin tests for hypothalamic-pituitary-adrenal insufficiency: a metaanalysis. *J Clin Endocrinol Metab.* 2008; 93: 4245-53.

17. Pettitt DJ, Lawrence JM, Beyer J, Hillier TA, Liese AD, Mayer-Davis B, Loots B, Imperatore G, Liu L, Dolan LM, Linder B, Dabelea D. Association between maternal diabetes in utero and age at offspring's diagnosis of type 2 diabetes. *Diabetes Care.* 2008; 31: 2126-30.
18. Kessler CA, Bachurski CJ, Schroeder J, Stanek J, Handwerger S. TEAD1 inhibits prolactin gene expression in cultured human uterine decidual cells. *Mol Cell Endocrinol.* 2008; 295: 32-8.
19. Patton SR, Dolan LM, Henry R, Powers SW. Fear of hypoglycemia in parents of young children with type 1 diabetes mellitus. *J Clin Psychol Med Settings.* 2008; 15: 252-9.
20. Repaske DR, Handwerger S. Making the transition from pediatric to adult endocrinology services. *Nat Clin Pract Endocrinol Metab.* 2008; 4: 492-3.

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 and Prevention
U01 DP 000248 — 09/30/05 - 09/29/10 — $362,000 / $2,261,046

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 — $28,249 / $93,372

SEARCH Nutrition Ancillary Study
National Institutes of Health (University of South Carolina)
R01 DK 077131 — 01/15/07 - 12/31/10 — $4,131 / $19,865

Understanding Social Status Impact on Adolescent Health
National Institutes of Health (Tufts University)
R01 HD 041527 — 02/01/08 - 01/31/12 — $126,066 / $590,052

Type 1 Diabetes Genetics Consortium
Benaroya Research Institute
3215 — 09/01/08 - 08/31/09 — $4,900 / $4,900

ELDER, D

Beta Cell Function In Adolescents With Type II Diabetes
National Institutes of Health
K23 DK 070775 — 09/01/05 - 08/31/10 — $117,500 / $582,500

HANDWERGER, S

Training In Developmental and Perinatal Endocrinology
National Institutes of Health
T32 HD 007436 — 05/01/06 - 04/30/11 — $218,920 / $905,850

The Physiology of Placental Lactogen
National Institutes of Health
R56 HD 007447 — 04/01/02 - 07/31/09 — $212,500 / $1,125,000

KATZ, J

Pulling Back the Covers on Insulitis - The Insulitis Reporter Mouse
Juvenile Diabetes Research Foundation
1-2006-744 — 09/01/06 - 08/31/09 — $150,000 / $365,310

A Novel Dendritic Cell Subset
Juvenile Diabetes Research Foundation
5-2008-944 — 09/01/08 - 08/31/09 — $100,000 / $100,000

Current Year Direct **$ 1,324,266**

Industry Contracts

Backeljauw, P
Eli Lilly and Company — $ 5,871

Tercica, Inc.	$ 154,701
Novo Nordisk Pharmaceuticals	$ 29,492
Klein, D	
American Diabetes Association	$ 3,850
Repaske, D	
Pfizer Inc.	$ 4,562
Rose, S	
Pfizer Inc.	$ 38,218
Genentech, Inc.	$ 8,710
Current Year Direct Receipts	**$ 254,404**
Total	**$1,569,670**