

Division Data Summary

Research and Training Details

Number of Faculty	12
Number of Joint Appointment Faculty	1
Number of Support Personnel	29
Direct Annual Grant Support	\$1,656,184
Direct Annual Industry Support	\$124,528
Peer Reviewed Publications	15

Clinical Activities and Training

Number of Clinical Fellows	10
Inpatient Encounters	2,605
Outpatient Encounters	11,724

Division Photo



Row 1: D Elder, N Crimmins
 Row 2: N Yayah Jones, I Gutmark-Little, A Sanghavi Shah
 Row 3: M Rutter, P Backeljauw, S Lawson
 Row 4: D Klein, L Dolan, J Katz

Significant Publications

Kim HK, Gottliebson W, Hor K, **Backeljauw P**, **Gutmark-Little I**, Salisbury SR, Racadio JM, Helton-Skally K, Fleck R. **Cardiovascular anomalies in Turner syndrome: spectrum, prevalence, and cardiac MRI findings in a pediatric and young adult population.** *American Journal of Roentgenology*. 196:454-50. 2011.

This paper provides a detailed description of the type and frequency of cardiovascular anomalies in Turner syndrome that may lead to premature morbidity and mortality.

Sherafat-Kazemzadeh R, Schroeder JK, Kessler CA, Handwerger S. **Parathyroid hormone-like (PTHLP) represses decidualization of human uterine fibroblast cells by autocrine/paracrine mechanism.** *Journal of Clinical Endocrinology and Metabolism*. 96:509-14. 2011.

PTHLP is found in large concentrations in human endometrial Stromal cells during decidualization. The role of PTHLP is not known. This paper demonstrates for the first time that PTHLP represses the induction of human decidualization, stimulates stromal cell apoptosis, and limits the extent of uterine stromal cell differentiation.

Katz JD, Ondr JK, Opoka RJ, Garcia Z, Janssen EM. **Cutting edge: merocytic dendritic cells break T cell tolerance to beta cell antigens in nonobese diabetic mouse diabetes.** *Journal of Immunology*. 15:1999-2003. 2010.

In this study Dr. Katz and his research team identified a critical sub-population of dendritic cells responsible for mediating peripheral tolerance to beta cell antigen in vivo.

Shah AS, **Dolan LM**, Gao Z, Kimball, Urbinia EM. **Clustering of risk factors: a simple method of detecting**

cardiovascular disease in youth. *Pediatrics*. 127:e312-8. 2011.

This paper demonstrates that clustering of risk factors is as reliable but simpler method for assessing cardiovascular risk than the Pathobiological Determinants of Atherosclerosis in Youth score, presently the accepted method of assessing cardiovascular risk.

Urbina EM, Kimball TR, Khoury PR, Daniels SR, **Dolan LM**. **Increased arterial stiffness is found in adolescents with obesity and obesity-related type2 diabetes.** *Journal of Hypertension*. 28:1692-8. 2010.

This manuscript establishes the presence of a progressive increase in vascular stiffness in youth from lean to obese to obese type 2 that cannot be explained by traditional cardiovascular risk factors.

Division Collaboration

Reproductive Sciences » S.K. Dey, MD; Sanjoy Das, PhD

Research

Neonatology & Pulmonary Biology » Cindy Bachurski, PhD; Jeffrey Whitsett, MD

Research

Biomedical Informatics » Bruce Aronow, PhD; Anil Jegga, MS, DVM

Research

Pathology » Jerzy Stanek, MD, PhD

Research

Molecular and Developmental Biology » James Wells, PhD

Research

Healthworks; Preventive Cardiology; Gastroenterology » Holly Ippisch, MD; Stavra Xanthakos, MD, MS; Robert Siegel, MD

Center for Better Health and Nutrition clinical collaboration

Center for Adherence in Psychiatry » Denny Drotar, PhD; Korey Hood, PhD

Research

Pulmonary » Mike Seid, PhD; James Acton, MD; Jamie Wooldridge, MD

Growth hormone therapy in patients with cystic fibrosis; Cystic fibrosis insulin study

General Pediatrics » Maria Britto, MD, MPH

Research

ICU » Derek Wheeler, MD

Research

Pharmacy » Anne Lesko, PharmD; Shannon Saldana, PharmD, MS, BCPP

Research

Adolescent Gyn; Urology » Lesley Breech, MD; Curtis Sheldon, MD

Clinical collaboration - Disorders of Sexual Differentiation Clinic

Gastroenterology » Lee Denson, MD

Study of the effects of growth hormone on patients with Crohn's disease

Emergency Medicine » Mike Gittelman, MD; Wendy Pomerantz, MD

Injury prevention project (RWJ sponsored) in an obesity prevention project in an area experiencing health disparities

Psychiatry » 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

Adolescent Medicine » 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

Rheumatology » Hermine Brunner, MD

NIH funded grant of Triptorelin therapy in lupus patients

Hematology Oncology; Hematology Oncology » Franklin Smith, MD; Richard Harris, MD; Stella Davies, MD; Parinda Mehta, MD

Funded study of oxadrolone therapy in children with Fanconi anemia

Research, database, and multicenter care of patients with Fanconi Anemia and other bone marrow failure syndromes

Mayerson Center » Kathi Makoroff, MD

Pfizer funded study shaken infants

Physical Medicine and Rehabilitation » Linda Michaud, MD

Pfizer funded study of endocrine function after traumatic brain injury

Neurology » Brenda Wong, MD

Development of research regarding Duchenne Muscular Dystrophy

Cardiology » 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

Epidemiology and Biostatistics » 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

Psychology and Behavioral Medicine » Scott Powers, PhD

Eating behaviors in individuals 16 years of age with type 1 diabetes

Surgery » Thomas Inge, MD, PhD

Bariatric surgery in youth: safety, efficacy, and effect on carbohydrate and cardiovascular outcomes

International Hypothalamic Obesity Registry

Faculty Members

Stuart Handwerger, MD, Professor

Professor of Cancer and Cell Biology

Research Interests Growth and thyroid disorders; perinatal endocrinology

Philippe Backeljauw, MD, Professor

Director, Cincinnati Turner Syndrome Center

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

Nancy Crimmins, MD, Assistant Professor

Research Interests Diabetes; obesity

Lawrence M Dolan, MD, Professor

Division Director, Robert and Mary Shoemaker Professor of Pediatrics

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

Deborah Elder, MD, Assistant Professor

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

Jonathan Katz, PhD, Associate Professor

Director, Diabetes Research Center

Research Interests

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

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

Research Interests Calcium disorders; endocrine function in childhood cancer survivors; endocrine function in muscular dystrophy

Peggy Stenger, DO, Assistant Professor

Research Interests Growth disorders; disorders of sexual development; pubertal disorders; disorders of the thyroid; goiter

Nana-Hawa Yayah Jones, MD, Assistant Professor

Research Interests Adherence/compliance in type 1 diabetes

Iris Gutmark-Little, MD, Assistant Professor

Research Interests Airway and great vessel disorders in Turner syndrome

Joint Appointment Faculty Members

Jessica Woo, PhD, Assistant Professor

Epidemiology

Significant Accomplishments

Turner Syndrome Research

The Turner Syndrome Center has investigated cardiovascular anomalies in Turner syndrome (TS) patients by cardiac MRI, including aortic abnormalities and partial anomalous pulmonary venous return (PAPVR). The prevalence of PAPVR was found to be 18 percent. Six of the newly diagnosed patients had not been diagnosed by echocardiogram. Another study found the prevalence of hypertension in TS girls to be under-recognized. More attention should be given to careful determination, interpretation and follow-up of blood pressure monitoring in TS girls, including a recommendation to manually perform all blood pressure measurements in TS girls. A prospective study comparing the prevalence of vasculopathy in TS patients showed evidence of increased arterial stiffness. This puts TS girls at greater risk for cardiovascular disease later in life. As a next step, measurements of TS-specific comorbidities will be evaluated in an attempt to determine the specific at-risk TS population. These studies underscore the importance of a multidisciplinary approach to TS care, together with the development of a large patient database. New studies being developed will focus on further evaluation of large vessel disease, assessment of airway dysfunction and studies looking at abnormalities of glucose metabolism.

Placental Development in Normal and Pathologic Pregnancies

Many pathologic conditions of pregnancy that result in infant morbidity and mortality, such as preeclampsia and intrauterine growth retardation (IUGR), are characterized by abnormal placental development. Research by Stuart Handwerger, MD, and his colleagues examines the roles for protein hormones, transcription factors and other signaling molecules in the development of normal and pathologic placentas. They postulate that a better understanding of the factors that regulate placental growth and development may lead to the discovery of therapeutic modalities that prevent or correct abnormal placental development and that improve fetal outcome. Their recent investigations have shown that placental development is critically dependent upon the transcription factors TFAP2A and NR2F2, both of which modulate cell structure, cell growth and hormone expression. The mRNA and protein levels of both transcription factors were shown to increase markedly during placental development; silencing the expression of either transcription factor was observed to markedly inhibit development. NR2F2 and TFAP2A were shown to form a positive feedback loop in which NR2F2 induces TFAP2A expression and TFAP2A in turn induces NR2F2. NR2F2 also potentiated the effect of retinoic acid on TFAP2A. Having demonstrated that TFAP2A and NR2F2 are critical for normal placental development, Handwerger, in collaboration with Jerzy Stanek, MD, PhD, and Rachel Sheridan, MD, of the Division of Pathology, recently observed by immunohistochemical analyses that TFAP2A protein levels in preeclampsia and IUGR placentas are markedly decreased compared to levels in gestational age-matched control placentas. Similar NR2F2 studies have not as yet been completed. Since these studies suggest that the abnormal placental development and function in preeclampsia and IUGR may be due, at least in part, to abnormalities in TFAP2A (and possibly NR2F2) expression, subsequent studies will examine whether correcting TFAP2A (and possibly NR2F2) expression in cultures of pathologic placentas will result in normal development.

Causes and Control of Type 1 Diabetes

Our research focuses on type 1 diabetes (T1D) by using a non-obese diabetic (NOD) mouse model. During the past year, our NIH-funded work has focused mainly on three areas: the role plasmacytoid dendritic cells and natural killer T cells play in establishing an immunoregulatory environment in mice that are protected from disease; the role merocytic dendritic cells play in breaking peripheral T cell tolerance to islet cell antigen (in collaboration with Edith Janssen, PhD, in the Division of Molecular Immunology); and the potential use of small molecule inhibitors of Bcl-2 family members in targeting diabetogenic CD4⁺ and CD8⁺ T cells for specific destruction to enhance long-term tolerance and to facilitate a novel therapeutic strategy to

re-establish tolerance in T1D patients (in collaboration with David Hildeman, PhD, in the Division of Immunobiology). Together these studies are designed to understand what normally controls T1D development, what underlies the basic response to beta cell antigens and, finally, what can be done to facilitate the restoration of normal beta cell function and glucose regulation in T1D patients.

Division Publications

1. Cunningham NR, Vesco AT, Dolan LM, Hood KK. **From caregiver psychological distress to adolescent glycemic control: the mediating role of perceived burden around diabetes management.** *J Pediatr Psychol.* 2011; 36:196-205.
2. Dabelea D, Dolan LM, D'Agostino R, Jr., Hernandez AM, McAteer JB, Hamman RF, Mayer-Davis EJ, Marcovina S, Lawrence JM, Pihoker C, Florez JC. **Association testing of TCF7L2 polymorphisms with type 2 diabetes in multi-ethnic youth.** *Diabetologia.* 2011; 54:535-9.
3. Ingerski LM, Anderson BJ, Dolan LM, Hood KK. **Blood glucose monitoring and glycemic control in adolescence: contribution of diabetes-specific responsibility and family conflict.** *J Adolesc Health.* 2010; 47:191-7.
4. Katz JD, Ondr JK, Opoka RJ, Garcia Z, Janssen EM. **Cutting edge: merocytic dendritic cells break T cell tolerance to beta cell antigens in nonobese diabetic mouse diabetes.** *J Immunol.* 2010; 185:1999-2003.
5. Kaulfers AM, Backeljauw PF, Reifschneider K, Blum S, Michaud L, Weiss M, Rose SR. **Endocrine dysfunction following traumatic brain injury in children.** *J Pediatr.* 2010; 157:894-9.
6. Kaulfers AM, Bean JA, Inge TH, Dolan LM, Kalkwarf HJ. **Bone loss in adolescents after bariatric surgery.** *Pediatrics.* 2011; 127:e956-61.
7. Kim HK, Gottliebson W, Hor K, Backeljauw P, Gutmark-Little I, Salisbury SR, Racadio JM, Helton-Skally K, Fleck R. **Cardiovascular anomalies in Turner syndrome: spectrum, prevalence, and cardiac MRI findings in a pediatric and young adult population.** *AJR Am J Roentgenol.* 2011; 196:454-60.
8. Kurtulus S, Tripathi P, Moreno-Fernandez ME, Sholl A, Katz JD, Grimes HL, Hildeman DA. **Bcl-2 allows effector and memory CD8+ T cells to tolerate higher expression of Bim.** *J Immunol.* 2011; 186:5729-37.
9. Shah AS, Dolan LM, Gao Z, Kimball TR, Urbina EM. **Clustering of risk factors: a simple method of detecting cardiovascular disease in youth.** *Pediatrics.* 2011; 127:e312-8.
10. Shah AS, Khoury PR, Dolan LM, Ippisch HM, Urbina EM, Daniels SR, Kimball TR. **The effects of obesity and type 2 diabetes mellitus on cardiac structure and function in adolescents and young adults.** *Diabetologia.* 2011; 54:722-30.
11. Sherafat-Kazemzadeh R, Schroeder JK, Kessler CA, Handwerger S. **Parathyroid hormone-like hormone (PTHrP) represses decidualization of human uterine fibroblast cells by an autocrine/paracrine mechanism.** *J Clin Endocrinol Metab.* 2011; 96:509-14.
12. Slaughter JL, Meinen-Derr J, Rose SR, Leslie ND, Chandrasekar R, Linard SM, Akinbi HT. **The effects of gestational age and birth weight on false-positive newborn-screening rates.** *Pediatrics.* 2010; 126:910-6.
13. Urbina EM, Dolan LM, McCoy CE, Khoury PR, Daniels SR, Kimball TR. **Relationship between elevated arterial stiffness and increased left ventricular mass in adolescents and young adults.** *J Pediatr.* 2011; 158:715-21.
14. Urbina EM, Khoury PR, McCoy C, Daniels SR, Kimball TR, Dolan LM. **Cardiac and vascular consequences of pre-hypertension in youth.** *J Clin Hypertens (Greenwich).* 2011; 13:332-42.
15. Urbina EM, Kimball TR, Khoury PR, Daniels SR, Dolan LM. **Increased arterial stiffness is found in adolescents with obesity or obesity-related type 2 diabetes mellitus.** *J Hypertens.* 2010; 28:1692-8.

Grants, Contracts, and Industry Agreements

Grant and Contract Awards

Annual Direct / Project Period Direct

DOLAN, L

SubClinical Cardiovascular Disease in Youth

National Institutes of Health(University of Colorado)

R01 DK 078542 09/22/09-08/31/11 \$197,323

SEARCH for Diabetes in Youth, Phase 3: Registry Study

Centers for Disease Control and Prevention

U18 DP 002709 09/30/10-09/29/15 \$428,578

T1D Exchange Registry

Jaeb Center for Health Research Foundation., Inc.

12/01/10-02/28/13 \$10,523

Understanding Social Status Impact on Adolescent Health

National Institutes of Health(Massachusetts General Hospital)

R01 HD 041527 05/31/10-01/31/12 \$256,200

KATZ, J

Dissecting Dendritic Cell Function in Autoimmune Diabetes

National Institutes of Health

R01 DK 078179 08/01/09-07/31/14 \$237,600

Dendritic Cells in the Breaking of Peripheral Tolerance in Type 1 Diabetes

National Institutes of Health

R01 DK 090978 09/20/10-08/31/13 \$185,000

CRIMMINS, N.

Type 1 Diabetes TrialNet

National Institutes of Health(George Washington University)

U01 DK 061055 06/16/11-06/30/12 \$24,813

RUTTER, M

DMD Insulin Growth Factor-1

Charley's Fund

11/01/10-10/31/12 \$254,000

SHAH, A

Role of High Density Lipoprotein Subspecies in Adolescents with Type 2 Diabetes

University of Cincinnati

01/26/11-06/30/11 \$11,140

SISLEY, S

Molecular Epidemiology in Children's Environmental Health Training Program

National Institutes of Health(University of Cincinnati)

T32 ES 010957 09/01/10-06/30/11 \$41,530

CNS NFkappaB Regulation of Peripheral Glucose Homeostasis

Endocrine Fellows Foundation

11/01/10-10/31/11 \$20,000

Current Year Direct \$1,656,184

Industry Contracts

BACKELJAUW, P

Eli Lilly and Company

\$7,998

Tercica, Inc.

\$29,543

Novo Nordisk Pharmaceuticals

\$30,025

HANDWERGER

Pfizer Inc.

\$3,311

KLEIN

Novo Nordisk Pharmaceuticals

\$31,801

ROSE

Pfizer Inc.

\$3,850

Current Year Direct Receipts**\$124,528**

Total**\$1,780,712**
