

# Division of Endocrinology

DIVISION PROFILE	
Number of Faculty	10
Number of Fellows	
Clinical Fellows	6
Research Fellows	5
Number of Support Personnel	41
Annual Total Grant Support (direct)	\$2,396,775
Annual Total Industry Contracts (direct)	\$203,807
Number of Peer Reviewed Publications	15
Patient Encounters	
Outpatient	6,479
Inpatient	2,238

## FACULTY LISTING

**Stuart Handwerker, MD**, Professor of Pediatrics, Division Director  
**Philippe Backeljauw, MD**, Associate Professor of Pediatrics  
**Steven D. Chernausek, MD**, Professor of Pediatrics, Associate Director  
**Lawrence M. Dolan, MD**, Professor of Pediatrics, Director, Clinical Diabetes Center  
**Deborah Elder, MD**, Assistant Professor of Pediatrics  
**Jonathan Katz, PhD**, Associate Professor of Pediatrics, Director, Diabetes Research Center  
**David J. Klein, PhD, MD**, Associate Professor of Pediatrics  
**David Repaske, PhD, MD**, Associate Professor of Pediatrics  
**Susan Rose, MD**, Professor of Pediatrics  
**Bo Wang, DVM, PhD**, Assistant Professor of Pediatrics

## STAFF PHYSICIAN LISTING

**Peggy Stenger, DO**, Staff Physician

## OVERVIEW

The major activities in the Division of Endocrinology included patient care, basic and clinical research and the training of physician/scientists, graduate students and postdoctoral fellows for careers in academic medicine. During the past year, approximately 6,800 patient visits were made in the endocrine and diabetic clinics, and inpatient care was provided for approximately 1100 children. About 125 newly diagnosed patients with diabetes mellitus are admitted yearly; the total number of children followed in the diabetes clinic is about 1,400.

The major basic research projects performed during the past year included investigations of 1) the roles of IGF and IGF-binding proteins in bone development and growth; 2) the regulation of human placental and uterine decidual differentiation; 3) the regulation of human placental lactogen and prolactin gene expression; 4) the development of animal models to study the pathogenesis of type I diabetes mellitus; 5) the role of T-lymphocytes in the pathogenesis of type I diabetes mellitus; and 6) genomic analysis of risk factors in diabetes mellitus. Clinical research projects included investigations of 1) the use of low dose insulin injections in the prevention of insulin-dependent diabetes in genetically susceptible children; 2) the natural history and etiology of diabetic heart disease and nephropathy; 3) the epidemiology of type II diabetes mellitus in childhood; 4) the roles of growth hormone, IGF and IGF-binding proteins in normal growth and intrauterine growth retardation; and 5) the endocrine consequences of childhood cancer and head trauma.

In addition to participating in the teaching of medical students and house staff, the division was involved in the training of six postdoctoral fellows in pediatric endocrinology, one postdoctoral fellow in

Obstetrics/Gynecology, one PhD postdoctoral fellow seeking advanced research training in endocrinology, and four PhD postdoctoral fellows pursuing diabetes research training.



*Left to Right: (1<sup>st</sup> row) B. Wang, D. Elder, L. Dolan, S. Handwerger, S. Rose, D. Klein, P. Backeljauw, D. Repaske*

## HIGHLIGHTS

During the past decade, type 2 diabetes mellitus has increased dramatically in American teenagers, with a prevalence rate now approaching 1:1000. The disease in adolescents affects all ethnic groups and now accounts for about 20% of newly diagnosed diabetes in teenagers. The accelerated prevalence parallels the epidemic of childhood obesity and may be the most significant consequence of increased adiposity in young people. Because type 2 diabetes mellitus results in striking increases in morbidity and mortality, the recent epidemic of the disease in adolescents constitutes a major public health problem.

While dysfunction of the pancreatic beta cell and insulin resistance are critical factors in the development of type 2 diabetes in adults, relatively little is known about the pathophysiology of the disease in adolescents and young adults. Consequently, it is unclear whether the disease in adolescents represents a distinct form of diabetes or is simply an early manifestation of the condition seen in adults. Recently, Dr. Deborah Elder, in collaborations with Dr. Larry Dolan and Dr. David D'Allesio (Division of Endocrinology, Department of Medicine, University of Cincinnati), studied glucose, insulin and glucagon dynamics in a cohort of adolescent patients with type 2 diabetes and non-diabetic lean and obese controls. The major diabetes patients were severely insulin resistant compared to the lean and obese controls and had impaired insulin secretion relative to the degree of insulin resistance. However, in contrast to adult subjects with type 2 diabetes, the adolescent diabetic subjects had a first phase insulin response to intravenous glucose comparable to lean controls, and did not have hyperproinsulinemia (the precursor form of insulin) or hyperglucagonemia (another measure of beta cell function). This islet phenotype is in marked contrast to the classical findings in adults with T2DM, in whom first phase insulin secretion is very low; the proinsulin/insulin ratio is markedly elevated and glucagon secretion is excessive. These results therefore suggest that the pathophysiology of type 2 diabetes in youth is different than that in adults. The findings also suggest that the optimal therapy for the disease in adolescent patients may be distinct from that for adult patients.

Drs. You-Hong Cheng and Stuart Handwerger continued their investigations of the regulation of human placental development. They cloned and partially characterized the promoter for a newly-described gene called syncytin that codes for a glycoprotein that is critical early in placental differentiation when mononuclear cytotrophoblast cells fuse to form syncytiotrophoblast cells. In recently completed investigations, they

identified a region of the promoter that is essential for placenta-specific expression of the syncytin gene and showed that the activity of the region requires intact binding sites for GATA-2, GATA-3 and Sp1 transcription factors. These studies are of clinical importance since markedly decreased syncytin expression has been observed in placentas from women with pre-eclampsia, a common pathologic condition of pregnancy that is associated with a marked increase in fetal and neonatal morbidity and mortality. An understanding of the regulation of key genes involved in placental development may lead to new therapies for pre-eclampsia and other diseases associated with abnormalities in placental development and function.

## TRAINING

Nancy Crimmins	PL-IV	Cincinnati Children's Hospital
Alvina Kansra	PL-IV	Hurley Medical Center, MSU
Ori Eyal	PL-V	Dana Children's Hospital, Tel-Aviv Israel
Jefferson Lomenick	PL VI	Vanderbilt University Medical School
Sumana Sundararajan	PL-VI	New York Medical College and Westchester County Medical Center
Moshe Weiss	PL-VI	Jackson Memorial Hospital
Research Fellows:		
Judith Cain, PhD		University of Alabama, Birmingham
You-Hong Cheng, MD, PhD		University of Newcastle, Australia
Leo Grinius, PhD		Moscow State University, Russia
Vukkadapu S. Sankaranand, PhD		University of Mysore, India
Vijay Saxena, PhD		Chhatrapati Shahu Ji Maharaj University, India

## GRANTS, CONTRACTS AND INDUSTRY AGREEMENTS

### Grant and Contract Awards Annual Direct/Project Period Direct

Cain, J		
<b>Regulatory T Cells in the Control of Type I Diabetes</b>		
National Institutes of Health		
K01 DK 064836	08/30/03 – 06/30/06	\$82,173/\$251,716
Dolan, L		
<b>Landmarks in the Progression to Type II Diabetes</b>		
National Institutes of Health		
R01 DK 59183	09/30/00 – 08/31/05	\$727,525/\$2,941,004
<b>Childhood Diabetes: Prevalence, Incidence and Characteristics</b>		
Centers for Disease Control		
U48 CCU519239	09/30/00 – 9/29/05	\$387,110/\$678,220
<b>Understanding Social Status Impact on Adolescent Health</b>		
National Institutes of Health (Brandeis University subcontract)		
R01 HD 41527	07/01/02 – 01/31/07	\$45,358/\$162,644
<b>Understanding the Sociobiological Translation: Subjective Social Standing in Adolescents</b>		
William T Grant Foundation (Brandeis University subcontract)		
	02/01/03 – 01/31/05	\$23,437/\$37,214
<b>Type 1 Diabetes Genetics Consortium</b>		
Benaroya Research Institute		
	01/01/04 – 08/31/07	\$20,600/\$82,400

Handwerger, S		
<b>Decidual Prolactin in Normal and Pathological Pregnancies</b>		
National Institutes of Health R01 HD 15201	04/01/03 – 03/31/08	\$225,000/\$1,125,000
<b>The Physiology of Placental Lactogen</b>		
National Institutes of Health R01 HD 07447	04/01/02 – 03/31/07	\$225,000/\$1,125,000
Katz, J		
<b>Cincinnati Mouse Diabetes Phenotype Center</b>		
National Institutes of Health (University of Cincinnati subcontract) U24 DK 59630	07/01/01 – 06/30/06	\$77,608/\$388,050
<b>Functional Genomics of THL-Mediated Diabetes in NOD Mice</b>		
Juvenile Diabetes Research Foundation	06/01/02 – 05/31/05	\$241,026/\$737,194
<b>Using Genomics to Understand Autoimmune Diabetes</b>		
National Institutes of Health R01 DK 62274	06/01/02 – 05/31/07	\$183,438/\$950,002
Wang, B		
<b>Spatiotemporal Control of Insulinitis in NOD Mice</b>		
American Diabetes Association	01/01/04 – 12/31/08	\$158,500/\$758,500
<b>Current Year Direct</b>		<b>\$2,396,775</b>
<b>Industry Contracts</b>		
Backeljauw, P		
Astra Zeneca Pharmaceuticals		\$5,787
Genetech, Inc.		\$562
Pharmacia		\$12,512
Chernausek, S		
Novo Nordisk Pharmaceuticals		\$12,108
Pharmacia & Upjohn Company		\$25,422
Dolan, L		
American Diabetes Association		\$30,050
Klein, D		
Eli Lilly & Co.		\$62,766
Rose, S		
Pharmacia		\$54,600
<b>Current Year Direct Receipts</b>		<b>\$203,807</b>
<b>TOTAL</b>		<b>\$2,600,582</b>

## PUBLICATIONS

1. **Backeljauw PF, Rose SR**, Lawson M. Clinical management of menstruation in adolescent females with developmental delay. *The Endocrinologist* 2004;14(2):87-91.
2. Lomenick JP, Jackson WA, **Backeljauw PF**. Amiodarone-induced neonatal hypothyroidism: a unique form of transient early-onset hypothyroidism. *J Perinatol* 2004;24(6):397-9.
3. Abuzzahab MJ, Schneider A, Goddard A, Grigorescu F, Lautier C, Keller E, Kiess W, Klammt J, Kratzsch J, Osgood D, Pfaffle R, Raile K, Seidel B, Smith RJ, **Chernausek SD**. IGF-I receptor mutations resulting in intrauterine and postnatal growth retardation. *N Engl J Med* 2003;349(23):2211-22.
4. Cavallo A, Daniels SR, **Dolan LM**, Khoury JC, Bean JA. Blood pressure response to melatonin in type 1 diabetes. *Pediatr Diabetes* 2004;5(1):26-31.
5. Cavallo A, Daniels SR, **Dolan LM**, Bean JA, Khoury JC. Blood pressure-lowering effect of melatonin in type 1 diabetes. *J Pineal Res* 2004;36(4):262-6.
6. Goodman E, Adler NE, Daniels SR, Morrison JA, Slap GB, **Dolan LM**. Impact of objective and subjective social status on obesity in a biracial cohort of adolescents. *Obes Res* 2003;11(8):1018-26.
7. Cheng YH, **Handwerger S**. Identification of an enhancer of the human activating protein-2alpha gene that contains a critical Ets1 binding site. *J Clin Endocrinol Metab* 2003;88(7):3305-11.
8. Cheng YH, Aronow BJ, Hossain S, Trapnell B, Kong S, **Handwerger S**. Critical role for transcription factor AP-2alpha in human trophoblast differentiation. *Physiol Genomics* 2004;18(1):99-107.
9. Cheng YH, Richardson BD, Hubert MA, **Handwerger S**. Isolation and characterization of the human syncytin gene promoter. *Biol Reprod* 2004;70(3):694-701.
10. **Klein DJ**, Aronson Friedman L, Harlan WR, Barton BA, Schreiber GB, Cohen RM, Harlan LC, Morrison JA. Obesity and the development of insulin resistance and impaired fasting glucose in black and white adolescent girls: a longitudinal study. *Diabetes Care* 2004;27(2):378-83.
11. Van Staveren WC, Steinbusch HW, Markerink-Van Ittersum M, **Repaske DR**, Goy MF, Kotera J, Omori K, Beavo JA, De Vente J. mRNA expression patterns of the cGMP-hydrolyzing phosphodiesterases types 2, 5, and 9 during development of the rat brain. *J Comp Neurol* 2003;467(4):566-80.
12. Eyal O, **Rose SR**. Autoimmune thyroiditis during leuprolide acetate treatment. *J Pediatr* 2004;144(3):394-6.
13. **Rose SR**. Endocrinopathies in childhood cancer survivors. *The Endocrinologist* 2003;13(6):488-495.
14. **Rose SR**, Schreiber RE, Kearney NS, Lustig RH, Danish RK, Burghen GA, Hudson MM. Hypothalamic dysfunction after chemotherapy. *J Pediatr Endocrinol Metab* 2004;17(1):55-66.
15. Wilson TA, **Rose SR**, Cohen P, Rogol AD, **Backeljauw P**, Brown R, Hardin DS, Kemp SF, Lawson M, Radovick S, Rosenthal SM, Silverman L, Speiser P. Update of guidelines for the use of growth hormone in children: the Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee. *J Pediatr* 2003;143(4):415-21.