Endocrinology

RESEARCH AND TRAINING DETAILS

<table>
<thead>
<tr>
<th>Faculty</th>
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<td>Peer Reviewed Publications</td>
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CLINICAL ACTIVITIES AND TRAINING

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<th>Clinical Staff</th>
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<td>Clinical Fellows</td>
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<td>Outpatient Encounters</td>
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Research Highlights

Andrew Dauber, MD, MMSc

Dr. Dauber’s research focuses on genetic causes of extreme short stature. Dr. Dauber’s work has resulted in the identification of a number of new etiologies of severe growth disorders including a new paradigm in the growth hormone-
IGF-1 axis (factors affecting the bioavailability of IGF-1) resulting in short stature. For his work, Dr. Dauber has received numerous awards including the Early Investigator Award from the Endocrine Society, the Young Physician-Scientist Award from the American Society of Clinical Investigation, and the Young Investigator Award from the European Society of Pediatric Endocrinology. Dr. Dauber leads the Cincinnati Center for Growth Disorders, a research program spanning clinical, translational and basic research into growth disorders with a strong reliance on cutting edge genomic techniques.

Amy Sanghavi Shah, MD, MS

Dr. Shah’s research focuses on the development of premature cardiovascular disease in high-risk youth with an emphasis on the role of lipids and lipoproteins. Dr. Shah’s work combines vascular non-invasive imaging techniques with molecular laboratory studies to study the mechanisms by which high density lipoprotein subfractions contribute to the development and progression of early cardiovascular disease in youth with type 2 diabetes. Dr. Shah’s work is currently funded by a K23 career development award from the National Institutes of Health (NIH). For this work, Dr. Shah received the following honors: Young Investigator Award from the National Lipid Association and the Young Investigator Award for the International Society for Pediatric and Adolescent Diabetes (ISPAD).

**Significant Publications**


Adults develop type 2 diabetes due to a progressive loss of insulin production over many years. The development of T2DM in adults is a progressive process that manifests over years and perhaps decades. While it is clear that adolescents who develop T2DM are obese, insulin resistant, and have abnormalities in beta-cell function, the pathophysiology behind the transition from prediabetes to diabetes is not well understood. Our goal was to identify the key changes involved in the transition from normal glucose tolerance to diabetes, and our results support a rapid decline in beta-cell function as the key feature in this progression.


This three year randomized, multi-center, open-labelled study of the efficacy and safety of combined growth hormone and IGF-1 therapy in growth hormone sufficient children with short stature and low IGF-I concentration demonstrated that the therapy was safe. Over the three years of the study the combination therapy accelerated linear growth and sustained improvements in height standard deviation score compared to growth hormone monotherapy. These results provide a basis for further study of combined growth hormone and IGF-1 therapy to improve adult height in growth hormone sufficient subjects with (idiopathic) short stature.


Adults with Turner syndrome are at increased risk for premature cardiovascular disease including hypertension, vasculopathy, and aortic dilation and dissection. This study demonstrates for the first time the presence of vasculopathy (increased arterial thickness and stiffness) in young individuals with Turner syndrome. The presence of vasculopathy in youth with Turner syndrome suggests that studies of the natural history of vasculopathy may provide avenues for intervention to prevent or limit premature cardiovascular disease in individuals with Turner syndrome.
Division Publications


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**Faculty, Staff, and Trainees**

**Faculty Members**

- **Lawrence M Dolan, MD**, Professor
  - **Leadership** 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

- **Philippe Backeljauw, MD**, Professor
  - **Leadership** Director, Cincinnati Turner Syndrome Center
  - **Research Interests** Growth disorders; disorders of bone and calcium metabolism; Turner syndrome.

- **Sarah Corathers, MD**, Assistant Professor
  - **Research Interests** Transition to adult care; type 1 diabetes in adolescents and adults; quality improvement.
Nancy Crimmins, MD, MS, Associate Professor
Leadership Residency Elective Coordinator
Research Interests Diabetes; obesity.

Andrew Dauber, MD, MMSc, Assistant Professor
Leadership Program Director and Director of Translational Research, Cincinnati Center for Growth Disorders
Research Interests Genetic basis of growth disorders. His research group uses cutting edge genomic techniques to discover novel genetic etiologies of short stature as well as precocious puberty.

Deborah Elder, MD, Assistant Professor
Research Interests Diabetes; growth disorders; precocious puberty; calcium disorders.

Iris Gutmark-Little, MD, Assistant Professor
Research Interests Airway and great vessel disorders in Turner syndrome.

Stuart Handwerger, MD, Professor
Leadership Professor of Cancer and Cell Biology
Research Interests Growth and thyroid disorders; perinatal endocrinology.

Jonathan Howell, MD, PhD, Assistant Professor
Research Interests Using human stem cell derived intestinal tissue to understand human gut hormone development and function in order to facilitate new therapeutic options for diabetes.

Vivian Hwa, PhD, Associate Professor
Leadership Director of Basic Research, The Cincinnati Center for Growth Disorders
Research Interests Understanding the mechanism(s) of human growth failure resulting from mutations along, and beyond, the GH-IGF-I axis. Genes currently under investigation include STAT5B, GHR, IGF1R, CDKN1C, PAPPA2.

Sarah Lawson, MD, Assistant Professor
Research Interests Turner syndrome; septo-optic dysplasia; endocrine abnormalities related to oncology and its treatments.

Takahisa Nakamura, PhD, Assistant Professor
Research Interests Focus on endogenous dsRNA pathways to address questions concerning why and how inflammatory responses are initiated and thus involved in the pathogenesis of obesity.

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.

Amy Shah, MD, MS, Assistant Professor
Research Interests Type 2 diabetes; pre-diabetes; insulin resistance; obesity; lipid disorders.

Peggy Stenger, DO, Assistant Professor
Research Interests Disorders of bone and calcium metabolism; 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.

Joint Appointment Faculty Members

Jonathan Katz, PhD, Professor (Immunobiology)
Research Interests The immunology of type 1 diabetes mellitus.
Jane Khoury, PhD, Associate Professor (Biostatistics & Epidemiology)  
**Research Interests** Diabetes in pregnancy and effect on offspring; stroke.

James Wells, PhD, Professor (Developmental Biology)  
**Research Interests** Vertebrate gut development, stem cells, mammal.

**Trainees**
- Cassandra Brady, MD, PL-6, Vanderbilt University
- Christiaan de Bruin, MD, PhD, PL-5, University Medical Center, St. Radboud, Nijmegen
- Marjorie Golekoh, MD, PL-6, Cincinnati Children's Hospital Medical Center
- Vincent Horne, MD, PL-4, University of Missouri - Columbia
- Chijioke Ikomi, MD, PL-4, Metropolitan Hospital Centre, New York
- Pranati Jha, MBBS, PL-6, Albany Medical Center
- Jose Jimenez-Vega, MD, PL-5, University of Minnesota Medical School
- Christel Keefe, MD, PL-6, Cincinnati Children's Hospital Medical Center
- Arti Shah, MBBS, PL-6, University at Buffalo Program
- Nicole Sheanon, MD, PL-8, University of Massachusetts
- Allison Smego, MD, PL-5, Vanderbilt University
- Halley Wasserman, MD, PL-6, Cincinnati Children's Hospital Medical Center

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**Grants, Contracts, and Industry Agreements**

**Endocrinology**

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<td>Rare Genetic Variants as Novel Causes of Idopathic or Syndromic Short Stature</td>
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<td>National Institutes of Health</td>
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<td>K23 HD073351</td>
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| **Dolan, L**             |              |
| SEARCH for Diabetes in Youth, Phase 3: Registry Study - Ohio Center |              |
| Ctr for Disease Control and Prevention |              |
| U18 DP002709             | 9/30/2010-9/29/2015 | $421,894 |

Air Pollution, Subclinical CVD and InflammatoryMarkers in the SEARCH Cohort
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<td>Handwerger, S, Transcriptional Control of Human Placental Differentiation</td>
<td>National Institutes of Health</td>
<td>R01 ES019168</td>
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<td>Hwa, V, Roles of STAT5b in IGF-1 Production and Human Growth</td>
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<td>R01 HD065339</td>
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<td>Nakamura, T, Role of TRBP and its Phosphorylation in Obesity-induced Insulin Resistance and Type 2 Diabetes</td>
<td>Diabetes Action Research &amp; Education Fdn</td>
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<td>Shah, A, Understanding the Role of HDL Subspecies in Adolescents with Type 2 Diabetes</td>
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**Current Year Direct Receipts**

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<td>Current Year Direct</td>
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Whole Exome Sequencing Uncovers Defective Gene Linked to Severe Growth and Metabolic Disorder

A n emerging technology called whole exome sequencing — which enables researchers to sequence all 20,000 of the body’s genes at once rather than one gene at a time — has helped identify a defective gene that causes a rare condition marked by a spectrum of growth and metabolic disorders in children.

The defective XRCC4 gene, identified by Andrew Dauber, MD, MMSc, co-leader of the newly formed Cincinnati Center for Growth Disorders, includes a splice mutation that deletes 23 amino acids from the gene, interfering with the body’s ability to repair DNA damage.

XRCC4 was discovered by examining DNA from a Chilean brother and sister, both of whom were diagnosed with severe short stature, gonadal failure and early-onset metabolic syndromes that resulted in a gastrointestinal tumor in the sister, diabetes and other multi-system complications. The 39-year-old brother is still alive; the sister died at 36. Findings based on their tissues were published online March 5, 2015, in The Journal of Clinical Endocrinology & Metabolism.

“The body is constantly repairing damage that occurs to DNA, and this gene is part of the DNA damage repair process,” says Dauber. “We were able to show in skin cells from one of the patients that the cells were not able to execute the DNA damage repair process correctly.”

The finding creates deeper understanding of a spectrum of complications associated with the defective gene, and creates direct links among patient genome sequencing, translational biology in the lab, patient diagnosis and genetic counseling, he says.

“Our patients are among the oldest in the world to be identified, and because of this new understanding, the hope is that we’ll be better able to counsel them and their families about a variety of other issues that they might face, including predisposition to tumors, insulin resistance and other complications.”

PUBLISHED MARCH 5, 2015
The Journal of Clinical Endocrinology & Metabolism

Andrew Dauber, MD, MSc

Endocrinology

RESEARCH AND TRAINING DETAILS

Faculty 17
Joint Appointment Faculty 3
Support Personnel 27
Direct Annual Grant Support $1.4M
Direct Annual Industry Support $113,816
Peer Reviewed Publications 37

The body is constantly repairing damage that occurs to DNA, and this gene is part of the DNA damage repair process.

Growth charts (top) of two siblings from a rural family in Chile exhibit a novel syndrome consisting of severe short stature, microcephaly, hypergonadotropic hypogonadism, early-onset metabolic syndrome, and possible increased tumor susceptibility. Combined microarray analysis and whole exome sequencing detected an underlying XRCC4 mutation, a gene involved in the DNA damage repair process. The next figure shows Sanger sequencing of XRCC4 cDNA with the nucleotide c.246T highlighted demonstrating that the mutation results in a novel splice site causing deletion of 69 nucleotides.