

Endocrinology

Division Details

RESEARCH AND TRAINING DETAILS

Faculty	17
Joint Appointment Faculty	3
Research Fellows and Post Docs	3
Total Annual Grant Award Dollars	\$1,484,496
Total Annual Industry Award Dollars	\$169,754
Total Publications	56

CLINICAL ACTIVITIES AND TRAINING

Clinical Fellows	9
Inpatient Encounters	4,421
Outpatient Encounters	15,658



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Research Highlights

Philippe Backeljauw, MD

On July 24-26, 2016, [Dr. Philippe Backeljauw, MD](#), clinical professor of pediatrics, and the fellowship program director in the Division of Endocrinology, organized an international consensus meeting in downtown Cincinnati. The [International Turner Syndrome Clinical Care Guidelines Meeting](#) brought together more than sixty experts from a variety of pediatric and adult disciplines to develop evidence-based recommendations for the clinical management of girls and women with Turner syndrome. Turner syndrome individuals deal with a variety of co-morbidities, such as growth failure, infertility, and congenital heart disease, among many other health issues. Turner syndrome has a prevalence of 1 in 2,000 live female births. The consensus meeting was unique in several aspects: it was fully funded by several professional societies and the National Institutes of Health (NIH)—and was not supported by the pharmaceutical industry. In addition, the organizers, Dr. Backeljauw and his co-chair, [Dr. Claus Gravholt, MD, PhD](#), ([Aarhus University](#), Denmark), invited input from several patient advocate organizations. The results of the meeting will lead to improved clinical care for Turner syndrome patients throughout their entire lifespan, and several publications expected as a result from the proceedings. Dr. Backeljauw sees patients through the [Turner Syndrome Center](#) and the [Adult Turner Syndrome Center](#), while continuing research on the co-morbidities of Turner syndrome.

Nancy Crimmins, MD, MS

The Divisions of Endocrinology and [Gastroenterology, Hepatology and Nutrition](#) have collaborated on a quality improvement project to better care for patients with both type 1 diabetes and celiac disease. The risk of developing celiac disease in patients with type 1 diabetes is five to seven times greater than the general population, and celiac disease can lead to increased risk of hypoglycemia, poor growth, and nutritional deficiencies in patients with type 1 diabetes. Working with the [James M. Anderson Center for Health Systems Excellence](#), we created a new screening and clinic care algorithm that is widely accepted by both divisions. Since the creation of the

algorithm, screening for celiac disease at diagnosis of type 1 diabetes increased from a baseline of <5% to >90% within six months. Furthermore, [Dr. Nancy Crimmins, MD](#), associate professor of pediatrics in the Division of Endocrinology; [Dr. Danny Mallon, MD, MSHPEd](#), assistant professor of pediatrics in the Division of Gastroenterology, Hepatology and Nutrition; and Jess Gahl, a diabetes educator and dietitian with celiac expertise, have created a monthly clinic to see patients with both type 1 diabetes and celiac disease. The aim is to streamline care for this population, and to create a registry to optimize outcomes and facilitate future research and quality improvement efforts. Families have offered very positive feedback, citing reduced hospital visits and better coordination of care.

Andrew Dauber, MD, MMSc

The Genetic Basis of Growth Disorders

As the director of the [Cincinnati Center for Growth Disorders](#), [Dr. Dauber's](#) research focuses on identifying novel genetic etiologies for children with severe growth disorders. Dr. Dauber, MD, MMSc, and his colleagues, receive referrals from physicians all around the globe. The Center recruits these patients onto their research protocol, and then uses cutting edge genomic technologies to identify novel gene mutations. Recently, their group identified the first human mutations in PAPP2, a gene involved in regulating the bioavailability of IGF-1, the key mediator of growth hormone action. Further studies are ongoing to characterize the clinical features and pathophysiology of sub-cohorts of children with short stature due to specific molecular defects.

Deborah Elder, MD

[Dr. Elder's](#) academic interest in beta-cell function has led to her role as endocrinology director of the Pancreatic Care Center ([PCC](#)) and Total Pancreatectomy Islet Cell Auto Transplantation ([TPIAT](#)) Program. The mission of the PCC is to be leaders in delivering world class healthcare to children with pancreatic disease through a comprehensive multidisciplinary management that puts patient's outcomes at the forefront of the desired center goals. Because a euglycemic environment is a favorable predictor of insulin independence after TPIAT, Dr. Elder has positioned to use state of the art technology in glucose management in this population. Hospital policy, written and approved for the use of a continuous glucose monitoring (CGM) device, aids in glucose management. In addition, to improved safety against hypoglycemia while striving for tight blood glucose control, families receive insulin pumps at the time of discharge. We have presented our experience using CGM in the TPIAT pediatric population at several endocrinology and gastroenterology scientific meetings. A manuscript entitled, *Post-operative Continuous Glucose Monitoring Following Pancreatectomy with Islet Auto Transplantation* is in preparation. Further academic endeavors will include predictors of insulin independence after TPIAT which will include the assessment of insulin and c-peptide production after a mixed-meal challenges pre- and post-TPIAT. We are also investigating the role of genetic factors in differentiating chronic pancreatitis from other forms of pancreas inflammation. The collection of data is also underway to assess the quality of life in relation to diabetes care.

Iris Gutmark-Little, MD

[Dr. Gutmark-Little's](#) research aims to elucidate the mechanisms of acquired aortic pathology in girls and women with Turner syndrome. This group of patients known to have a significantly elevated mortality as the result of cardiovascular disease includes aortic dissection. However, the underlying pathophysiology is not understood. This work, funded by the Chain of Love Foundation, has been in collaboration with [Aarhus University](#) and the [Department of Aerospace Engineering and Engineering Mechanics](#) at the [University of Cincinnati](#). Dr. Gutmark-Little, MD, and her interdisciplinary team have developed computerized tools that enable the noninvasive study of aortic blood flow. They are characterizing how this flow changes over time in diseased TS aortae, and how it contributes to progressive aortic pathology. These tools include a software that is able to automatically measure aortic diameter continuously over the entire aortic span. They have shown that this technique is more sensitive, robust, and accurate to measure changes in aortic dimension over time than the currently used manual method. They have correlated these changes in aortic dimension with indices of aortic blood flow. They have also recently shown areas of high stresses on the aortic wall (reflective of both changes in aortic dimension and aberrant blood flow) that would predispose an area of the aortic wall to fracture and therefore dissection.

Vivian Hwa, PhD

As the Basic Research arm of the Cincinnati Center for Growth Disorders, Dr Hwa's group is involved in a number of projects stemming from genes/variants identified by WES (whole exome sequencing) analysis in patients with monogenic growth disorders. These include defects in genes along, and beyond, the GH-IGF-I (growth hormone-insulin-like growth factor-I) axis. Highlights: (a) novel dominant-

negative mutations were recently identified in the GHR (GH receptor) and STAT5B genes, which are genes in which mutations are classically autosomal recessive; highlighted are the discoveries of more than one dominant-negative mechanism exerted by the heterozygous STAT5B variants; (b) a CRISPR/Cas knock-in mouse model of the group's recently described human missense PAPP2 mutation, has been successfully generated (Transgenic Core) and currently being characterized. Purification of recombinant human PAPP2 (important for IGF-I bioavailability) is underway, targeted for PK and PD studies in mouse models; (c) CRISPR/Cas knock-in zebrafish models, together with reconstitution studies, are being employed to validate pathophysiological significance of top WES-identified candidate variants/genes.

Sarah Lawson, MD

The need for a change in insulin administration has been a growing concern, with insulin carrying one of the highest error rates among high risk drugs at Cincinnati Children's Hospital Medical Center. Insulin misuse in a hospital setting can lead to significant morbidity and mortality, prolong hospital stay, and increased admission cost. Pre-intervention Cincinnati Children's data revealed a lag in time from blood glucose check to insulin administration, a lack of understanding on insulin dosing and administration on all levels, and an inappropriate delegation of responsibility with insulin management. These problems have led to the overall increase in insulin errors at Cincinnati Children's.

Combined efforts of endocrine, pharmacy, and nursing management have led to standardization of insulin throughout the hospital. Quality improvement methodology, initial testing and hospital spread of standardized insulin administration has led to a reduction in insulin errors and blood glucose variability. Specifically, on tested units, there has been a reduction in time from blood glucose check to insulin administration by 24 minutes, efficiency in bedside insulin administration (15 minutes per insulin injection saved by bedside staff), reduction in hyperglycemia by 50%, and a reduction in blood glucose variability by 60%. Feedback includes an improved fund of knowledge on insulin dosing and administration among staff, more efficient patient care, increased comfort with insulin handling, and improved patient satisfaction.

Takahisa Nakamura, PhD

Dr. Nakamura's research continues to focus on the role of RNA networks in the pathogenesis of obesity. Dr. Nakamura's group has shown that disruption of microRNA (miRNA) processing machinery is associated with obesity and development of metabolic diseases such as type 2 diabetes (T2D) and non-alcoholic fatty liver disease (NAFLD). In a NIH RO1 funded study, Dr. Nakamura and colleagues will further investigate how new miRNA-based pathways in the liver regulate systemic glucose and lipid metabolism and demonstrate that the therapeutic effects of the anti-diabetic drug metformin involve the pathways. This study would uncover novel mechanisms of RNA networks that could be therapeutic targets aimed at reversing metabolic diseases.

Susan Rose, MD

Our work is focused on providing both short and long term care to pediatric cancer survivors and anticipating endocrine problems before they arise. The cure rate for pediatric malignancies is increasing, and most patients who have childhood cancer survive and enter adulthood. Surveillance for late endocrine effects after cancer therapy is required to ensure early diagnosis and treatment and to optimize physical, cognitive and psychosocial health. Even as cancer treatment modalities change, potential endocrine problems are numerous and include growth hormone deficiency, hypothyroidism (primary or central), adrenocorticotropin deficiency, hyperprolactinemia, precocious puberty, hypogonadism (primary or central), altered fertility and/or sexual function, low bone mineral density, metabolic syndrome, and hypothalamic obesity. Optimal endocrine care for survivors of childhood cancer should be delivered in a multidisciplinary setting, providing continuity from acute cancer treatment to long-term follow-up of late endocrine effects throughout the lifespan. Additionally, we endeavor to research the effect of cancer treatment on growth, thyroid disease, hypopituitarism, fertility, and bone health in cancer survivors and have recently co-authored an article in Nature Reviews Endocrinology describing the myriad of endocrine complications in pediatric cancer patients. We hope that this publication will be helpful globally in guiding endocrine care of survivors.

Amy Sanghavi Shah, MD, MS

Understanding the Role of HDL Subspecies in Adolescents with Type 2 Diabetes

In this National Institutes of Health (NIH) funded study, [Dr. Amy Sanghavi Shah, MD, MS](#), in collaboration with [Dr. W. Sean Davidson, PhD](#), at the [University of Cincinnati](#), aim to determine how adolescent onset type 2 diabetes alters HDL subspecies and their functions rendering the so called "good cholesterol" non-atheroprotective. This project combines molecular laboratory techniques and noninvasive cardiovascular imaging tools to identify HDL subspecies, study their functions in vitro, and understand the functional implications on atherosclerosis development. The goal is to identify the most cardioprotective HDL subspecies and understand how type 2 diabetes alters them. Developed therapies will then enhance, increase or improve these HDL particles in the body.

Significant Publications

Smego AR, Backeljauw P, Gutmark-Little I. Buccally Administered Intranasal Desmopressin Acetate for the Treatment of Neurogenic Diabetes Insipidus in Infancy. *J Clin Endocrinol Metab.* 2016 May;101(5):2084-8.

This manuscript describes a novel treatment approach, orally administered intranasal DDAVP for infants with neurogenic diabetes insipidus including dosing parameters and outcomes.

de Bruin C, Dauber A. Insights from exome sequencing for endocrine disorders. *Nat Rev Endocrinol.* 2015 Aug;11(8):455-64.

Whole-exome sequencing has emerged as a fast and effective tool for the elucidation of genetic defects underlying both rare and common human diseases. Within the field of endocrinology, exome sequencing has led to major advancements in our understanding of many disorders including adrenal disease, growth and puberty disorders and type 2 diabetes mellitus, as well as a multitude of rare genetic syndromes with prominent endocrine involvement. In this Review, we provide an overview of these new insights and discuss the role that exome sequencing we expect to have in endocrine research and future clinical practice.

Rose SR. Hormone Therapy in Fanconi Anemia. *Expert Opin Orphan D.* 2015; 3:831-42

Children with Fanconi anemia (FA) have unrepaired chromosomal breakage that leads to chronic risk for cancer, requirement for bone marrow transplant, and endocrine deficiencies. I wrote this article to alert practitioners to endocrine testing that can allow hormone treatments. Hormone replacement may improve quality of life in these children and young adults. About 80% of children and adults with FA have at least one endocrine abnormality, and benefit from thyroid hormone therapy as well as vitamin D therapy. Some benefit from growth hormone therapy. Metformin may be beneficial if overweight develops, in view of underlying insulin deficiency in FA. Early gonadal failure may occur. Individuals with FA should be routinely screened for endocrine abnormalities, and when found to have hormone deficiencies, treat them with standard endocrine therapy.

Shah AS, Dabelea D, Fino NF, Dolan LM, Wadwa RP, D'Agostino R Jr, Hamman R, Marcovina S, Daniels SR, Urbina EM. Predictors of Increased Carotid Intima-Media Thickness in Youth With Type 1 Diabetes: The SEARCH CVD Study. *Diabetes Care.* 2016 Mar;39(3):418-25.

Carotid intima media thickness (IMT) is a non-invasive cardiovascular imaging technique used to detect early atherosclerosis. Youth with type 1 diabetes have shown to have a higher carotid IMT compared to their peers without diabetes. However, the risk factors that predict a higher carotid IMT are not known. In this study Dr. Amy Sanghavi Shah, MD, MS, in the Division of Endocrinology, Dr. Elaine Urbina, MD, MS, in the Division of Cardiology, and their collaborators in the SEARCH for Diabetes in Youth Study studied 298 youth with type 1 diabetes at baseline, and then five years later. Researchers assessed body mass index (BMI) z score, lipids, blood pressure, hemoglobin A1c and smoking status at both visits, and measured carotid IMT at follow-up. Over five years, all cardiovascular risk factors worsened. However, only higher body mass index over time can be an important determinant of carotid IMT. This study highlights the importance of body weight as a risk factor for the development of atherosclerosis, and the need to maintaining a normal body weight in youth with type 1 diabetes.

Division Publications

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2. Aulinger B, Vahl T, Prigeon R, D'Alessio D, Elder D. **The Incretin Effect in Obese Adolescents with and without Type 2 Diabetes: Impaired or Intact?** *Am J Physiol-Endoc M.* 2016; 310:E774-E81.
3. Backeljauw PF, Bondy C, Chernausek SD, Cernich JT, Cole DA, Fasciano LP, Foodim J, Hawley S, Hong DS, Knickmeyer RC, Kruszka P, Lin AE, Lippe BM, Lorigan GA, Maslen CL, Mauras N, Page DC, Pemberton VL, Prakash SK, Quigley CA, et al. **Proceedings from the Turner Resource Network Symposium: The Crossroads of Health Care Research and Health Care Delivery.** *Am J Med Genet A.* 2015; 167A:1962-71.
4. Baron J, Savendahl L, De Luca F, Dauber A, Phillip M, Wit JM, Nilsson O. **Short and Tall Stature: A New Paradigm Emerges.** *Nat Rev Endocrinol.* 2015; 11:735-46.
5. Bauer A, Francis G, Waguespack S, Zimmerman D, Krishnan S, Breidbart E, Viswanathan P, McDonough R, Barger K, Yan Y. **How Can We Apply the New American Thyroid Association Treatment Guidelines for Children and Adolescents with Thyroid Cancer to Improve Patient Management? Novel Insights into Clinical Experience.** *US Endocrinology.* 2016; 12:39-51.
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Grants, Contracts, and Industry Agreements

Annual Grant Award Dollars

Investigator	Title	Sponsor	ID	Dates	Amount
Nancy Abigail Crimmins, MD	CTLA-A Ig (Abatacept) for Prevention of Abnormal Glucose Tolerance and Diabetes in Relatives At-Risk for Type 1 Diabetes Mellitus	National Institutes of Health (University of South Florida)	TN18	4/1/2016 - 6/30/2017	\$5,590
Nancy Abigail Crimmins, MD	Long Term Investigative Follow-up in Trial Net (LIFT)	National Institutes of Health (University of South Florida)	USF - Crimmins,Nancy	3/10/2014 - 6/30/2017	\$1,750
Nancy Abigail Crimmins, MD	Anti-CD3 MAB (Teplizumab) for Prevention of Diabetes in Relatives At-Risk for Type 1 Diabetes Mellitus	National Institutes of Health (University of South Florida)	USF - Crimmins,Nancy	2/27/2015 - 6/30/2017	\$10,530
Nancy Abigail Crimmins, MD	The Type 1 Diabetes TrialNet Protocol TN-07, Oral Insulin for Prevention of Diabetes in Relatives at Risk for Type 1 Diabetes Mellitus	National Institutes of Health (University of South Florida)	USF - Crimmins,Nancy	7/1/2015 - 6/30/2017	\$16,200
Andrew Dauber, MD	Rare Genetic Variants as Novel Causes of Idiopathic or Syndromic Short Stature	National Institutes of Health	K23 HD073351	2/15/2015 - 5/31/2017	\$129,870
Lawrence M Dolan, MD	SEARCH for Diabetes in Youth Registry Study, Phase 4: Ohio Center	Ctr for Disease Control and Prevention	U18DP006134	9/30/2015 - 9/29/2020	\$360,686
Lawrence M Dolan, MD	Limited Competition for the Continuation of the SEARCH for Diabetes in Youth Cohort Study (UC4) - SEARCH for Diabetes in Youth Cohort Study	National Institutes of Health (Wake Forest University Health Sciences)	UC4 DK108175	9/25/2015 - 9/24/2020	\$359,376

Iris Gutmark Little, MD	Assessment of Risk for Progression of Aortic Dilatation in Turner Syndrome using Computational Fluid Dynamics	Chester County Community Foundation	CCCF - Gutmark-Littl	4/1/2014 - 8/31/2017	\$35,000
Vivian Hwa, PHD	Roles of STAT5b in IGF-1 Production and Human Growth	National Institutes of Health	R01 HD078592	9/1/2014 - 6/30/2019	\$315,607
Amy Sanghavi Shah, MD	Understanding the Role of HDL Subspecies in Adolescents with Type 2 Diabetes	National Institutes of Health	K23 HL118132	4/15/2014 - 3/31/2019	\$191,362
Nicole M Sheanon, MD	Training Program - Molecular Epidemiology in Children's Environmental Health (MECEH)	National Institutes of Health (University of Cincinnati)	T32 ES010957	7/30/2014 - 7/29/2015	\$4,309
Halley M Wasserman, MD	Training Program - Molecular Epidemiology in Children's Environmental Health (MECEH)	National Institutes of Health (University of Cincinnati)	T32 ES010957	7/1/2014 - 6/30/2016	\$54,216
Total Annual Grant Award Dollars					\$1,484,496

Annual Industry Award Dollars

Investigator	Industry Sponsor	Amount
Philippe Ferdinand Backeljauw, MD	Novo Nordisk Pharmaceuticals	\$94,978
Susan Rose, MD	TOLMAR Inc.	\$74,776
Total Annual Industry Award Dollars		\$169,754