Mission

The Division of Pediatric Endocrinology, Diabetes, and Metabolism supports the tripartite goals of exceptional teaching, world-acclaimed research, and superb patient care for children with all hormonal disorders, including growth, thyroid, adrenal, gonadal, calcium, diabetes, and carbohydrate-related metabolic disorders. The division's core missions are to:

- Maintain and surpass its record of excellence in patient care
- Teach medical students, residents, and fellows and train the next generation of pediatric endocrinologists
- Conduct state-of-the-art research focused on understanding and treating endocrine disorders and diabetes
OVERVIEW OF DIVISION

The faculty and fellows continue to be nationally and internationally recognized for their clinical expertise and their research endeavors. Six members of the division were listed again in the survey of “best doctors” in the United States and Pittsburgh. Development of satellite and outreach clinics combined with regional referrals and those from other centers resulted in a steady increase in patient numbers. Members of the faculty and division nurses continue to receive invitations to be speakers and panel members, expert committee members, and journal reviewers. Two new fellows started their clinical and research training in the program this year, and two fellows graduated from the program. Starting July 2018, the number of trainees will increase to three fellows per year.

Radhika Muzumdar is chief of the division and an associate professor of pediatrics and cell biology. Her research focuses on growth hormone (GH); insulin-like growth factors (IGFs) and their binding partners; and the effects of novel
mediators of glucose homeostasis, energy metabolism, and aging. One mediator is humanin, a mitochondria-associated peptide recognized for its effects on cell survival. Muzumdar found that it has a marked effect on insulin sensitivity and that it increases insulin secretion through enhancement of beta-cell glucose metabolism. Her laboratory discovered a role for humanin in regulating hepatic lipid fluxes through the hypothalamus. She continues her studies on humanin, aging, life span, cardiovascular health, and diabetes at Children’s Hospital of Pittsburgh of UPMC. She is joined by Zhenwei Gong, a research assistant professor studying the role of humanin in augmenting existing therapies for diabetes and the effects of humanin and analogs on lipid metabolism, cellular processes of autophagy, and oxidative stress. Muzumdar and Gong investigate the role of a novel acyl CoA dehydrogenase enzyme, ACAD10, and an inflammation-associated protein, Aim 2, on glucose metabolism and energy homeostasis. Muzumdar serves as a standing member on the National Institutes of Health (NIH) Study Section on Aging Systems and Geriatrics, in addition to being a reviewer for international and national granting agencies, including the U.S. Food and Drug Administration.

Dorothy Becker is a grant reviewer and a member of NIH and national diabetes committees. She continues as the principal investigator examining the prediction and prevention of type 1 diabetes in the Research Project Grant (R01) and three multicenter Opportunities for Collaborative Research at the Clinical Center (U01) programs. Becker is the U.S. principal investigator and a member of the International Executive Committee of a large primary prevention diabetes study, “Trial to Prevent Insulin-Dependent Diabetes in the Genetically at Risk: Nutritional Primary Prevention of Type 1 Diabetes (TRIGR).”

Henry Dong is NIH funded to study the role of forkhead box O (FoxO) transcription factors in glucose and lipid homeostasis. He is funded by the American Diabetes Association (ADA) to study the role of hepatic insulin on glucose homeostasis.

Ingrid Libman continues her research of the epidemiology of both type 1 and type 2 diabetes. She explores the complications of type 1 diabetes and the effects of obesity and insulin resistance in children with features of both type 1 and type 2 diabetes. She studies innovative, technology-based approaches to improve care of children with diabetes. Her findings have been the foundation for several awarded grants. She is youth/pediatric diabetes chair, ADA Scientific Sessions Meeting Planning Committee, 2016–2018.

Kara Hughan, through her K23 project, is investigating the mechanisms of macrovascular disease related to insulin resistance. She received the EnVision award from the Cystic Fibrosis Foundation. Becker, Silva Arslanian, Oscar Escobar, Libman, and Selma Witchel were co-investigators on several other NIH- and foundation-supported grants.

Escobar Luigi Garibaldi continues with national GH and gonadotropin-releasing hormone analog studies.

The division has continued its high level of research productivity, with 39 active research studies, sustained by the NIH, foundation grants, and several pharmaceutical grants. The grants have supported the peer-reviewed publications and chapters in textbooks in the appended bibliographic list (2015–2017).

The faculty are recognized for their teaching skills. Mark Sperling has been a very successful editor of the Pediatric Diabetes Journal, a journal he established. Sperling, Muzumdar, and Witchel are on the editorial panel of Frontiers of Pediatric Endocrinology. In addition, Muzumdar, Becker, Sperling, Dong, Witchel, Libman, and Arslanian have taken part in scientific peer review of NIH grants, have chaired sessions at major scientific meetings, and have been invited to give several national and international lectures. Witchel has been active nationally and internationally on committees related to androgen excess disorders. Muzumdar and Witchel are chairs of the Research Affairs Council and Education Council for the Pediatric Endocrine Society (PES). Hecht-Baldauff and Libman are involved in the Education Council and Diabetes Special Interest Group at the PES.

This year, five trainees participated in the Pediatric Endocrine Fellowship Training Program under the overall directorship of Witchel. The research training portion of the program is supported by a T32 training grant from the NIH and is directed by Muzumdar, who also oversees the David Nicholas Fellowship. Baldauff, Garibaldi, and Escobar assist Witchel with the fellowship clinical education program and teach residents and students. The division’s fellows received competitive grants for their research projects and presented their work at national meetings.
CLINICAL ACTIVITIES

Flint, associate clinical director, and Garibaldi have continued to expand the clinical program, adding more satellite and outreach clinics to meet the demands of a growing patient population. They maintain the division’s delivery of team care and intensive diabetes therapy in satellite and outreach sites. Libman, as the director of diabetes, and Ismail, as clinical director of diabetes, have continued to expand access to the transition program, which is a vital component of diabetes care for patients who graduate from high school and move on to college or the workforce. The division pioneered and refined the retinopathy screening via fundus photography, which has the potential to become the standard of care.

The Weight Management and Wellness Center has been incorporated into the division of endocrinology. Patients who call for appointments are now triaged more efficiently into regular endocrine clinics, diabetes clinics, or endocrine wellness clinics, which provide intensive nutritional support for patients with weight concerns.

Faculty, fellows, 11 full-time advanced practice providers, and the diabetes team keep pace with the large and ever-increasing outpatient clinical service, as shown in the figure below. The division supports a vibrant inpatient service, including frequent consultations throughout Children's Hospital of Pittsburgh and Magee-Womens Hospital. The number of new diabetes patients, already on the rise over the past decade from about 160 to 250 per year, increased by 20% this year. Patients are educated by the division's superb team of diabetes educators and dietitians. The diabetes educators deliver traditional diabetes teaching for all patients with new-onset type 1 or type 2 diabetes and staff diabetes clinics at all sites. They initiate and provide training with increasingly sophisticated devices, such as insulin infusion pumps and glucose sensors. To meet the needs of patients, the team established a technology clinic, where a diabetes educator with expertise in advances in diabetes technology advises patients and families. The diabetes educators maintain a daytime call-in service for the approximately 2,200 patients with diabetes. The division recently added extended hours of telephone support for the hours from 5 to 11 p.m. This should improve patient care and satisfaction considerably, as evening is a peak time for diabetes-related calls. The division also provides most of the medical staff for the ADA-sponsored diabetes camp each summer.

The endocrine clinical and teaching nurse team has grown to seven full-time nurses to accommodate growing patient numbers and the need for dynamic endocrine testing. The nurses perform more than 1,000 tests per year, by scheduled appointment. Additionally, during the past year, the division introduced same-day testing to offer the advantage of dynamic testing at the time of patient encounter. The nurse team facilitates physician workflow while improving patient satisfaction and quality of care.

The multidisciplinary approach to the care of children with chronic endocrine disorders includes a Diabetes Center led by Libman, Ismail, Muzumdar, and Becker, with the education coordinated by Karen Kelly. In addition to the transition program, the diabetes subdivision offers a specialized diabetes care program, including the recently initiated post-transplant diabetes clinic and program with Garibaldi and Flint, as well as the cystic fibrosis–related program with Hughan, Witchel, and Ismail. The division continues to actively participate in the autologous islet cell transplant program in collaboration with the Transplant Division at Children's Hospital and UPMC Presbyterian Hospital for children and young adults who undergo total pancreatectomy for severe, chronic pancreatitis; this is one of very few such pediatric programs in the United States.

The division offers specialized and disease-focused services as follows: the Growth Center, led by Escobar; the Center for Disorders of Sexual Development, under the direction of Witchel; a multidisciplinary Thyroid Center, under the direction of Pushpa Viswanathan, Witchel, and Gurtunca; a Lipid Clinic, under the direction of Flint; the Pittsburgh Endocrine Gender Center for gender non-conforming youth, under the direction of Witchel; and an endocrine surveillance and follow-up clinic and program for cancer survivors in collaboration with the Division of Oncology/Hematology, under the leadership of Gurtunca.
Muzumdar has found that humanin analog administered prior to or following ischemia protects the myocardium following ischemia-reperfusion injury and improves cardiac function in mice. Muzumdar has tested the cardioprotective effects of humanin analogs in swine models of ischemia and reperfusion. The studies, performed in collaboration with David Lefer, director of the National Heart, Lung, and Blood Institute (NHLBI) Consortium for Preclinical Assessment of Cardioprotective Therapies at Louisiana State University Health Sciences Center at New Orleans, demonstrated that humanin offers cardioprotection in swine models of myocardial ischemia and reperfusion. Muzumdar received a grant from the Pittsburgh Foundation to conduct the preliminary studies, which are the basis of an R01 with multiple principal investigators that was submitted this year. She is also collaborating with Eric Goetzman’s laboratory to understand the mechanisms behind humanin-mediated cardioprotection, through studies on substrate flux and metabolism.
Ischemia/reperfusion is associated with significant oxidative stress. Recently, Muzumdar’s laboratory found that humanin analog protects against oxidative stress through critical upregulation of key antioxidant enzymes in a tyrosine kinase–dependent manner. Because oxidative stress is intimately linked to the cellular recycling process of autophagy, Muzumdar and Gong studied the effects of humanin on autophagy and, particularly, chaperone-mediated autophagy, in collaboration with Ana Maria Cuervo at AECOM. A manuscript describing the observations was recently accepted for publication in the *Journal of Cellular Biology*.

Endogenous levels of humanin decline with age. Humanin and its potent analogs have been shown to have beneficial effects in many age-related diseases, including Alzheimer’s disease, stroke, diabetes, myocardial ischemia and reperfusion, atherosclerosis, amyotrophic lateral sclerosis, and certain types of cancer. An association between humanin levels, the GH/IGF axis, and lifespan was demonstrated in various mouse models with mutations in the GH/IGF axis. Muzumdar is currently collaborating with Ghazi’s laboratory to study the effects of humanin on healthy aging and lifespan in a *Caenorhabditis elegans* model.

Muzumdar’s laboratory also studies the regulation of energy and glucose homeostasis. A knockdown of a gene called *Absent in Melanoma 2* (*Aim 2*), a tumor suppressor gene and a part of the inflammasome, results in spontaneous obesity and impaired glucose tolerance. The effects seem to be mediated through upregulation of *ifi202b*, an interferon-related protein. The findings are especially significant, as human obesity is associated with upregulation of *ifi202b*. The studies were funded through a Cochrane Weber grant and are the focus of an R01 submitted with Gong.

In collaboration with Vockley and Goetzman, Muzumdar is studying the role of ACAD 10, a novel acyl CoA dehydrogenase in glucose homeostasis, and has shown that absence of ACAD10 in certain mouse background leads to a phenotype of obesity and insulin resistance. This is interesting, as polymorphisms in the ACAD 10 gene have been reported in Pima Indians, a population at high risk for obesity and type 2 diabetes. Knockout of the gene also results in a novel phenotype of hypoglycemia on fasting, with no evidence of defects in fatty acid oxidation. This collaboration is ongoing and has resulted in publications and funding from NIH, the Endocrine Fellows Foundation, and a Cochrane Weber grant.

In addition to the NIH, Muzumdar has received grant support from multiple funding agencies, including the PES, American Federation for Aging Research (AFAR), Beck Foundation, and Endocrine Fellows Foundation for her work on the roles of GH/IGF/IGFBP-3 in glucose homeostasis, as well as the role of humanin in insulin secretion and myocardial infarction.

She is on several national and international study sections, including the NIH, AFAR research council, United States–Israel Binational Science Foundation, Israeli Science Foundation, Binational Science Foundation between Israel and Italy, Marsden Fund (New Zealand), and Wellcome Trust (United Kingdom). She serves as a standing member of the NIH Aging Systems and Geriatrics Study Section. She chairs the Research Advisory Council of the PES and serves on AFAR’s National Scientific Advisory Council. She has chaired sessions and been an invited speaker at national and international endocrine meetings. She is a reviewer for numerous reputed journals and national meetings. She continues to be an active member of the PES, with leadership roles.

Muzumdar is the principal investigator of the Research Training in Pediatric Endocrinology Program. The goal of the T32 training grant is to provide state-of-the-art training in the molecular, cellular, physiologic, genetic, and biochemical aspects of pediatric endocrinology to ensure that the physician-scientists who graduate from the program are well prepared for productive academic careers in translational research related to pediatric endocrinology.

**ADVISORY COMMITTEE MEMBERSHIPS/STUDY SECTIONS**

- Chair, Clinical and Translational Research Registry Subcommittee, PES
- Chair, Research Affairs Council, PES
- National Mentoring Initiative, PES
- International Research Collaborations Subcommittee, PES
- Invited member, Research Advisory Council, PES
- Invited member, Committee on National Mentoring Initiative, PES
- Moderator, scientific sessions, ADA
- Ad hoc member, Integrative Physiology of Obesity and Diabetes Study Section, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NIH
- Mentor, Endocrine Society
- Standing member, Aging Systems and Geriatrics Study Section, National Institute on Aging, NIH
Natalie Hecht Baldauff, DO

RESEARCH
Natalie Hecht Baldauff’s research focuses on the role of adiponectin in new-onset type 1 diabetes and noninvasive maximization of fertility in a peri-pubertal population of patients with Klinefelter syndrome.

Dorothy J. Becker, MBBCh, FCP (paed)

RESEARCH
Dorothy J. Becker’s major interests are the prediction and prevention of type 1 diabetes and its complications. Her efforts are supported by several grants.

Research Training in Pediatric Endocrinology. The goal of the T32 training grant is to provide state-of-the-art training in the molecular, cellular, physiologic, genetic, and biochemical aspects of pediatric endocrinology to ensure that the physician-scientists who graduate from the program are well prepared for productive academic careers in translational research related to pediatric endocrinology. Becker serves as senior transition consultant.

Juvenile Diabetes Mellitus: Epidemiology and Etiology. This is a 37-year study funded by the NIH until this year that evaluates the immunologic, genetic, and environmental determinants of the risk of insulin-dependent diabetes mellitus in children and families of children with probands with type 1 diabetes. It is a prospective biannual study of T-cell markers of autoimmunity and viral infection and assessments of insulin resistance in genetically at-risk, first-degree relatives with islet cell antibodies and diabetes end points. Becker is principal investigator.

TrialNet (Prediction and Prevention of Type 1 Diabetes). TrialNet is an NIH collaborative study (Pittsburgh being one of the original centers) in the United States and Europe to examine the risks and mechanisms of
autoimmune progression. Data will be used to plan and implement intervention strategies to maintain beta-cell function in patients with new-onset type 1 diabetes and to prevent diabetes in first-degree relatives at high risk.

TRIGR. Pittsburgh is a major center and the coordinating center for the United States for this double-blind, randomized, controlled trial involving subjects with an affected first-degree relative and risk-associated human leukocyte antigen genotypes. This is an international, multicenter consortium involving 73 centers in 15 countries; it is funded by the NIH and Canadian Institutes of Health. The six- to eight-month intervention to compare the effects of either hydrolyzed casein or standard cow milk-based weaning formula has been completed. All subjects are being followed for 10 years for measurements of serological markers of intact cow milk exposure, autoantibodies predictive of diabetes (the end point at age 6 years), and the clinical and/or metabolic indices of diabetes (the end point at age 10 years). A large, cross-linked repository of stored sera, DNA, and cryopreserved peripheral blood mononuclear cells allows independently funded ancillary and mechanistic studies related to the natural history of prediabetes and the hypothesis to be tested. Becker is principal investigator.

The Environmental Determinants of Diabetes in the Young. This is an NIH-funded, multicenter, epidemiologic study of the environmental pathogenesis of autoimmunity in first-degree relatives of subjects with type 1 diabetes. Pittsburgh is a satellite. Becker is co-investigator.

Slow or Nonprogressive Autoimmunity to the Islets of Langerhans (SNAIL Study). This multicenter study in the United Kingdom; Germany; Pittsburgh, Pa.; and Denver, Colo., is exploring factors that slow the progression of diabetes autoimmunity from multiple autoantibodies to clinical diabetes.

Adolescents With and Without Diabetes: Transition to Emerging Adulthood. The goal of this NIH-funded research is to examine the impact of insulin-dependent diabetes on quality of life over the transition from adolescence into adulthood as compared to nondiabetic individuals. This study will concentrate on the follow-up of graduates of the diabetes program for analyses of psychosocial behaviors and risk factors and evaluation of their relationship with metabolic control and diabetes-related complications. Becker is co-investigator.

Epidemiology of Diabetes Complications. Led by Trevor Orchard, this long-term study evaluates the risk factors and trajectory of diabetes complications in a long-term cohort of type 1 diabetes patients who graduated from the program more than 30 years ago.

ADVISORY COMMITTEE MEMBERSHIPS
• Diabetes Advisory Committee, Children’s Hospital of Pittsburgh
• National Diabetes Data Group
• Data and Safety Monitoring Board, DirectNet, NIH
• Abstract reviewer, scientific sessions, International Society for Pediatric and Adolescent Diabetes
• Abstract reviewer, scientific sessions, Pediatric Academic Societies

EDITORSHIPS
• Associate editor, Pediatric Diabetes
• Associate editor, Diabetes in America, third edition
• International Society for Pediatric and Adolescent Diabetes e-learning

PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS
• ADA
• Endocrine Society
• PES
• Society for Pediatric Research
• International Society of Pediatric and Adolescent Diabetes
• European Association for the Study of Diabetes
• American Pediatric Society
• Juvenile Diabetes Research Federation

HONORS
• Best Doctors, Pittsburgh Magazine, 2017
• Best Doctors in America, Woodward/White, Inc.

H. Henry Dong, PhD

RESEARCH
H. Henry Dong is conducting research focusing on insulin signaling in glucose and lipid metabolism and beta-cell function in obesity and type 2 diabetes.

Mechanism of Beta-Cell Compensation and Beta-Cell Failure. Type 2 diabetes results from beta-cell failure, culminating in the inability of cells to compensate for insulin resistance in at-risk subjects with obesity. Beta-cell compensation is an adaptive mechanism by which cells increase insulin secretion to overcome insulin resistance or oxidative stress for maintaining euglycemia in obesity. Failure of beta cells to compensate for insulin resistance or oxidative stress contributes to insulin insufficiency and overt diabetes. Likewise, beta-cell compensation, accompanied by increased insulin synthesis and secretion, occurs in women during pregnancy. Impaired beta-cell compensation
Predisposes at-risk subjects to develop gestational diabetes. Dong’s research is positioned to characterize the genetic factor(s) responsible for coupling beta-cell compensation with nutrient signals to elucidate the underlying mechanism of beta-cell failure in diabetes. His goal is to delineate the insulin-Akt/PI3K-Akt/FoxO pathway in regulating beta-cell function and mass in obesity and type 2 diabetes. The project is funded by NIH grant R01 NIDDK DK098437.

**Pathophysiology of Insulin Resistance and Diabetic Dyslipidemia.** Hypertriglyceridemia is a hallmark of metabolic syndrome and is characterized by a triad plasma lipid profile (i.e., increased triglyceride and low-density lipoprotein levels and decreased high-density lipoprotein levels). Due to its proatherogenic potential, hypertriglyceridemia is considered an independent risk factor for coronary artery disease. The pathophysiology of hypertriglyceridemia is incompletely understood. Its close association with adiposity and type 2 diabetes implicates insulin resistance as a causative factor in the development of hypertriglyceridemia. However, factors that mechanistically link insulin resistance to the pathogenesis of hypertriglyceridemia are incompletely characterized. Dong’s group has identified FoxO1 as a key player in regulating triglyceride metabolism. FoxO1 regulates triglyceride metabolism via apolipoprotein C-III and microsomal triglyceride transfer protein—two rate-limiting steps in very-low-density lipoprotein (VLDL)-triglyceride hydrolysis and VLDL-triglyceride secretion. This research is funded by NIH grants R01 DK066301 and R01 DK087764. For clinical translation, Dong’s team has uncovered two lead compounds via screening 540,000 compounds for FoxO1 inhibitors. His laboratory is poised to validate FoxO1 as a potential therapeutic target for improving lipid metabolism and ameliorating hypertriglyceridemia in obesity and diabetes, with the NIH pending grant 1R01DK100312.

Dong has also received the ADA’s Career Development Award.

**ADVISORY COMMITTEE MEMBERSHIPS**
- Standing member, Cellular Aspects of Diabetes and Obesity Study Section, NIDDK, NIH, 2015–2019
- Standing member, Research Administrative Committee of Children’s Hospital of Pittsburgh

**EDITORSHIPS**
- Editorial Board, *Molecular Metabolism*
- Editorial Board, *Journal of Geriatric Cardiology*
- Editorial Board, *Immunology, Endocrinology, and Metabolic Agents*

**MAJOR LECTURESHIPS AND SEMINARS**
- “FoxO1 in Insulin Action and Lipid Metabolism,” University of California, Berkeley, San Francisco, Calif., April 2017
- “FoxO1 in Insulin Resistance and Diabetic Dyslipidemia” A&M University, College Station, Texas, April 2017
- “FoxO1 in Beta-Cell Mass and Function Regulation” Vanderbilt University, Nashville, Tenn., January 2017
- “What Causes Beta-Cell Failure in Type 2 Diabetes?” University of New Mexico, Albuquerque, N.M., September 2016

**PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS**
- American Heart Association
- ADA
- New York Academy of Sciences
- American Society of Gene Therapy

Oscar Escobar, MD

**RESEARCH**
As director of the Growth Center, Oscar Escobar’s primary focus is on his clinical research regarding the treatment of growth disorders in children.

**National Norditropin Registry.** The primary goal of this study is to evaluate the long-term safety and efficacy of Norditropin. The growth-hormone study is based on data collected in an observational setting. The study came to an end in December 2016. Escobar served as local principal investigator.

**Central Precocious Puberty Registry: A Multicenter, Observational Study of Pediatric Females With Central Precocious Puberty Receiving Supprelin LA.** The primary goal of this study is to categorize the recovery of the hypothalamic-pituitary-gonadal axis after discontinuation of treatment with Supprelin LA, an implantable gonadotropin-releasing hormone analog. The study is based on data collected in an observational setting. Escobar is local principal investigator.

**The VELOCITY Clinical Study—14VR4: Versartis Long-Acting Growth Hormone in Children with GH Deficiency.** This study is a phase 3, randomized, one-year, open-label, multicenter, noninferiority trial in prepubertal children.
with GH deficiency. The primary goal is to assess the efficacy and safety of VRS-317 in prepubertal children with GH deficiency compared to daily GH. It is sponsored by Versartis, Inc.; Escobar is the local principal investigator.

The VISTA Study-13VR3: Vesartris Long-Acting Growth Hormone Somavaratan in Children with GH Deficiency. This is an open-label, long-term safety study of long-acting human growth hormone Somavaratan (VRS-317) in prepubertal children with GH deficiency. It is sponsored by Versartis, Inc.; Escobar is local principal investigator.

**PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS**
- Endocrine Society
- ADA
- Colombian Association of Endocrinology
- Colombian Association of Pediatric Endocrinology
- PES

**HONORS**
- America’s Top Doctors, Castle Connolly Medical, Ltd., 2017
- Best Doctors, Pittsburgh Magazine, 2017

**Amanda Flint, MD**

**RESEARCH**
Amanda Flint’s research focuses on type 2 diabetes.

**PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS**
- Endocrine Society
- PES

**Luigi Garibaldi, MD**

**RESEARCH**
Luigi Garibaldi is the local co-principal investigator in the following data-collection studies.

- National Norditropin Registry, sponsored by Novo Nordisk
- Central Precocious Puberty Registry, sponsored by ENDO Pharmaceuticals
- VELOCITY study, sponsored by Versartis Pharmaceuticals
- VISTA study

**ADVISORY COMMITTEE MEMBERSHIPS**
- Diabetes Advisory Committee, Children’s Hospital of Pittsburgh
- Institutional Data and Safety Monitoring Board, University of Pittsburgh

**Zhenwei Gong, PhD**

**RESEARCH**
Zhenwei Gong’s major research interest is the role of humanin in metabolic disorders, with emphasis on the effects of humanin on lipid metabolism and whole-body glucose homeostasis. Humanin improves whole-body glucose homeostasis by regulating insulin sensitivity and increasing glucose-stimulated insulin secretion from the beta cells. Using a high-fat, diet-induced obesity mouse model, he has demonstrated that treatment with humanin decreases weight gain, visceral fat, and hepatic
triglyceride accumulation. The decrease in hepatic triglyceride accumulation is due to induced activity of hepatic microsomal triglyceride transfer protein and increased hepatic triglyceride secretion. In addition, intracerebroventricular infusion of humanin acutely increases triglyceride secretion from the liver, whereas vagotomy blocks the effects of intracerebroventricular humanin on hepatic triglyceride secretion. Furthermore, vagotomy also blocks hepatic triglyceride secretion induced by intravenous administration of humanin. Finally, he has shown that the central effects of humanin on hepatic triglyceride flux are mediated through the melanocortin system. He continues to define the roles of humanin in central regulation of lipid metabolism.

Gong is also interested in studying the effects of humanin in cardiovascular disease. While studying the mechanisms by which humanin protects cardiomyocytes from stress-induced cell death, he found that humanin activates chaperone-mediated autophagy (CMA). He demonstrated that this effect occurs in cardiomyocytes, fibroblasts, and neuronal cells. Treatment with humanin increases long-lived protein turnover and prevents the cells from oxidative stress–induced cell death. Humanin lost its protective effects on these cells with knockdown of lysosome-associated membrane glycoprotein 2A, suggesting that the protective effect is CMA dependent. His current focus is to identify the underlying mechanisms by which humanin activates CMA.

The third ongoing project for Gong is to study the role of a tumor suppressor, Absent in Melanoma (AIM2), in energy homeostasis. Gong has found that knockdown of AIM2 in mice induces spontaneous obesity and insulin resistance. This is at least partially due to the increased adipogenesis in WAT and BAT dysfunction–induced decrease in thermogenesis and subsequently reduced energy expenditure. Notably, he also has found that the effects of AIM2 in energy homeostasis are independent of its role in the inflammasome, as caspase1 activity and serum levels of IL-1β are not changed in AIM2–/- mice under physiological conditions when AIM2 inflammasome is inactivated. He is investigating the potential mechanisms by which AIM2 regulates energy metabolism and insulin sensitivity.

**EDITORSHIPS**
- Review editor, *Frontiers in Pediatric Endocrinology*

**PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS**
- ADA

**LECTURESHIPS AND SEMINARS**
- “Role of Humanin in Autophagy,” special seminar in the School of Life Science, Northeast Normal University, Changchun, China, October 2016
- “Mitochondria Signaling, Cellular Homeostasis,” department seminar, Dalian Polytechnic University, Liaoning, China, November 2016

**Nursen Gurtunca, MD**

**PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS**
- South African Medical Society
- American Pediatric Society
- PES
- Endocrine Society

**Kara Hughan, MD**

**RESEARCH**

Kara Hughan’s translational research is focused on metabolic and hormonal factors associated with cardiometabolic disease.

**Nitrite Modulation of Hypertension, Platelet Activation, and Endothelial and Mitochondrial Function.** This translational study aims to examine the effects of chronic oral nitrite therapy on blood pressure, endothelial function, and insulin sensitivity and whether it modulates mitochondrial energetics, oxidative stress, and redox signaling in platelets and skeletal muscle. The study is funded by NIH K23 NHLBI grant HL124051-01A1 and the McKamish Family Fund. Hughan is principal investigator.

**An Open-Label Study of Oral Nitrite in Adults With Metabolic Syndrome and Hypertension.** This study aims to investigate the effects of oral inorganic nitrite on the cardiometabolic and hormonal disturbances in metabolic syndrome and hypertension, targeting a population of overweight/obese adults with metabolic syndrome and hypertension at risk to develop insulin resistance and endothelial dysfunction. The study is supported by a University of Pittsburgh Clinical and Translational Science Institute award; the University of Pittsburgh Vascular Medicine Institute; and McKamish, Inc. Hughan is principal investigator.

**Postprandial Glycemia in the Free-Living Condition and Cardiometabolic Risk in Obese Youth.** This study aims to assess the relationship between postprandial glycemia in free-living conditions via continuous glucose monitoring and cardiometabolic risk in obese youth. Hughan is principal investigator.
Treatment Options for Type 2 Diabetes in Adolescents and Youth 2 (TODAY2). This is a multicenter, cooperative, NIH-funded trial regarding the treatment of youth with type 2 diabetes. It continues to follow the original TODAY study subjects to understand the persistence of the effects of the different treatment regimens used in TODAY, to track the continued evolution of beta-cell function, and to describe the development of vascular complications and risk factors for complications. Hughan is co-investigator.

Nitrite Benefits to Mediate Fatigability in Older HFpEF Patients. This National Institute on Aging/NIH-funded, randomized, controlled, double-blinded trial of oral nitrite therapy in older (> 70 years) HFpEF patients proposes there are intrinsic physiological components of HFpEF pathophysiology that predispose to fatigability, a concept defined specifically as a deterioration in function over time (performance fatigability) and subjective tiring from an exercise stimulus (perceived fatigability). The study will evaluate the pleiotropic benefits of oral inorganic nitrite, including enhanced performance of skeletal muscle (strength and metabolism) and vasomotor responses (systemic and pulmonary arterial). Hughan is co-investigator.

Cystic Fibrosis (CF) Foundation’s EnVision CF: Emerging Leaders in CF Endocrinology Award. This award, funded by the CF Foundation, trains Hughan and 15 other emerging U.S. endocrinologists caring for patients with CF and related endocrine conditions. In addition to Hughan providing designated pediatric endocrine-related patient care within the division’s CF Care Center, this proposal includes the opportunity to submit CF and related endocrine disorder research projects. Hughan is principal investigator.

A Randomized, Double-Blind Study With an Open-Label Extension Comparing the Effect of Once-Weekly Dulaglutide With Placebo in Pediatric Patients With Type 2 Diabetes Mellitus (Assessment of Weekly Administration of LY2189265 in Diabetes-PEDiatric Study). This phase III study, sponsored by Eli Lilly and Company, aims to test the hypothesis that dulaglutide (0.75 mg and 1.5 mg, pooled) given subcutaneously once a week for 26 weeks to children and adolescents with type 2 diabetes mellitus who have inadequate glycemic control, despite diet and exercise, with or without metformin or basal insulin, is superior to placebo in the treatment of type 2 diabetes mellitus, as measured by baseline to week 26 change in hemoglobin A1c. Hughan is co-investigator.

An Open-Label, Randomized, Multicenter, Single-Dose, Parallel-Group Trial to Evaluate Pharmacokinetics and Pharmacodynamics of Empagliflozin in Children and Adolescents From 10 to Less Than 18 Years of Age With Type 2 Diabetes Mellitus. In this phase I trial sponsored by Boehringer-Ingelheim Pharmaceuticals, Inc., Hughan completed eight subjects at Children’s Hospital out of the 27 subjects completed internationally. Hughan is site principal investigator.

MAJOR LECTURESHIPS AND SEMINARS
- “Pediatric Endocrine Emergencies,” Allegheny Health Network/Drexel University College of Medicine, Emergency Medicine Residency Lectureship, Pittsburgh, Pa., August 2016
- “Mitochondrial Function in Cystic Fibrosis,” EnVision webinar program broadcast to EnVision CF trainees and mentors, Cystic Fibrosis Foundation, November 2016
- “Diabetes Through the Ages—Special Consideration in the Care of Infants and Toddlers With Diabetes,” American Association of Diabetes Educators Western Pennsylvania Local Networking Group, Pittsburgh, Pa., November 2016
- “Mitochondrial Function in Cystic Fibrosis,” Pediatric Endocrine Research Conference, Children’s Hospital, Pittsburgh, Pa., February 2017

PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS
- PES
- ADA
- Endocrine Society
- Vascular Medicine Institute, University of Pittsburgh School of Medicine
- Nitric Oxide Society

ADVISORY COMMITTEE MEMBERSHIPS
- Children’s Hospital Pediatric Endocrine Fellowship Curriculum Committee, Accreditation Council for Graduate Medical Education
- Children’s Hospital Pediatric Endocrine Fellowship Interview Committee, Accreditation Council for Graduate Medical Education
- Comorbidity Assessment Committee, TODAY2

HONORS
- EnVision CF: Emerging Leaders in CF Endocrinology Program, Cystic Fibrosis Foundation
Heba Ismail, MBBCh, MSc, PhD

Heba Ismail joined the division in December 2017 as the new clinical director of the diabetes program.

RESEARCH

Ismail’s research focuses on the pathogenesis and treatment of type 1 diabetes mellitus, with emphasis on the use of technology in the management of type 1 diabetes.

*Nutrition Education Through Mobile Gaming for Young Patients With Type 1 Diabetes*. This is a study to assess the effect of using a neuropsychology-based gaming application on the food choices and consumption of children with type 1 diabetes as compared to conventional, standard diet teaching. Ismail is principal investigator.

*Bridges Education Innovation Project Grant: A Day in the Life of a Patient With Diabetes Mellitus: An Experiential Learning*. This is a study to assess an innovative method of education using role-playing as a form of experiential learning. The goal is to familiarize pediatric trainees with diabetes technology as well as enhance a culture of empathy. Ismail is principal investigator.

*TrialNet (Prediction and Prevention of Type 1 Diabetes)*. This is a collaborative study of 14 centers in the United States and five in Europe to plan and implement intervention strategies to maintain beta-cell function in patients with new-onset type 1 diabetes and prevent diabetes in first-degree relatives at high risk. Ismail is sub-investigator.

MAJOR LECTURESHIPS AND SEMINARS

- “Glucose and C-Peptide Secretion Patterns,” endocrine grand rounds, Indiana University, October 2017

PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS

- ADA
- Endocrine Society
- PES

HONORS

- Young Investigator Award, TrialNet award in recognition of research efforts

Ingrid Libman, MD, PhD

RESEARCH

Ingrid Libman’s research has focused on the etiology, prevention, and treatment of type 1 diabetes mellitus, with emphasis on the effect of obesity in type 1 diabetes. She directs the Diabetes Transition Program, which aims to provide the best care and to research the best ways to support and guide successful transition for young patients with diabetes mellitus. She is involved in the development and testing of age-appropriate shared decision-making tools to educate about the importance of prevention and screening for complications of diabetes. She works on numerous multicenter studies of type 1 and type 2 diabetes.

*Transition to Adulthood for Adolescent Patients With Type 1 Diabetes Mellitus*. This three-year project funded by the Children’s Hospital Foundation David Paul Diabetes Transition Care Research Initiative will develop and test a series of educational modules for patients and families as the patient transitions from pediatric to adult care and management of type 1 diabetes. Libman is principal investigator.

*Availability of a Program to Screen for Retinopathy in Children With Type 1 Diabetes: Does It Improve Compliance?* The overall goal of this project, funded by the Beckwith Foundation, is to design, integrate, and evaluate a shared decision-making approach, including appropriate tools, to engage children with type 1 diabetes in understanding the importance of yearly screening for diabetic retinopathy and what can be done to prevent or delay the complication. Libman is co-principal investigator.

*Are Current Screening Guidelines for Complications in Youth With Type 1 Diabetes Appropriate?* This study is funded by the University Partnership Program Academic Foundation. Libman is principal investigator.

*Novel Biomarkers for Early Diabetic Nephropathy in Children With Type 1 Diabetes*. This study is funded by the Cochrane Weber Endowment. Libman is co-investigator.

*A Shared Decision-Making Approach to Engage Youth With Type 1 Diabetes in Cardiovascular Disease Prevention*. This study, funded by the Cochrane Weber Endowment, aims to design, integrate, and evaluate a shared decision-making approach, including appropriate tools, to engage children with type 1 diabetes in understanding the importance of yearly screening for cardiovascular disease risk factors and what can be done to prevent or delay this complication. Libman is co-principal investigator.

*A Day in the Life of a Patient With Diabetes Mellitus: An Experiential Learning*. The objective of this proposal, funded by the Bridges Education Innovation Award, is to have residents and endocrine fellows “experience” living with diabetes, using insulin pumps and glucose testing to familiarize themselves with the different clinical scenarios and diabetes technology and ensure a culture of empathy. Libman is co-investigator.
Type 1 Diabetes Exchange Project. This multicenter study funded by the Leona M. and Harry B. Helmsley Charitable Trust aims to create a registry and biobank of individuals with type 1 diabetes mellitus to address pertinent clinical issues and conduct exploratory and hypothesis-generating analyses. Libman is principal investigator at the Pittsburgh center.

Research on Emerging Adults Changing Health. The goal of this NIH-funded research in collaboration with Carnegie Mellon University is to examine the impact of insulin-dependent diabetes on quality of life over the transition from adolescence into adulthood as compared to nondiabetic individuals. The study will concentrate on the follow-up of graduates of the diabetes program for the analyses of psychosocial behaviors and risk factors and the evaluation of their relationship with metabolic control and diabetes-related complications. Libman is co-investigator.

TrialNet (Prediction and Prevention of Type 1 Diabetes). This is a collaborative study of 14 centers in the United States and five in Europe to plan and implement intervention strategies to maintain beta-cell function in patients with new-onset type 1 diabetes and prevent diabetes in first-degree relatives at high risk. Libman is co-investigator.

SNAIL Study. The aim of this multicenter study, funded by JDRF, is to identify and characterize “slow progressors” from several longitudinal studies of type 1 diabetes. Libman is co-investigator.

TODAY2. This is a multicenter, cooperative, NIH-funded trial regarding treatment of youth with type 2 diabetes. It continues to follow the original TODAY study subjects to understand the persistence of the effects of the different treatment regimens used in TODAY, to track the continued evolution of beta-cell function, and to describe the development of vascular complications and risk factors for complications. Libman is co-investigator.

ADVISORY COMMITTEE MEMBERSHIPS
• Youth/pediatric chair, Scientific Sessions Planning Committee, ADA
• Chair, Diabetes in Youth Interest Group, ADA
• Member, Organizing Committee, International Meeting of Pediatric Endocrinology, to be held in Buenos Aires, Argentina, 2021
• Member, Training Council, PES
• Member, Diabetes Special Interest Group, PES
• Invited member, Eunice Kennedy Shriver National Institute of Child Health and Human Development’s Initiative to Advance Pediatric Therapeutics, NIH

Comorbidities Assessment Committee, TODAY study
Ancillary Studies Committee, TODAY study
Member and reviewer, Institutional Review Board, University of Pittsburgh
Member, Diversity Committee, Institute of Clinical Research Education, Clinical and Translational Science Institute, University of Pittsburgh

EDITORSHIPS
• Editorial Board (international), Latin ADA Journal
• International Editorial Board, Revista Medica de Rosario

MAJOR LECTURESHIPS AND SEMINARS
• “Double Diabetes or Type 1.5: How Frequent Is It and How to Treat?” invited speaker, International Society for Diabetes in Adolescents and Youth 2016 Congress, Valencia, Spain, October 2016
• “Type 2 Diabetes Mellitus in Children and Youth: Myth or Reality?” invited speaker, Latin ADA Congress, Bogota, Colombia, November 2016
• “Prevention and Treatment of Type 1 Diabetes in Youth: What Is New?” invited speaker, Latin ADA Congress, Bogota, Colombia, November 2016

PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS
• ADA
• Latin ADA
• European Association for the Study of Diabetes
• International Society for Pediatric and Adolescent Diabetes
• Society for Pediatric Research
• PES

HONORS
• Best Doctors, Pittsburgh Magazine, 2017
• Best Doctors in America, Woodward/White, Inc., 2017
• Outstanding Patient Award, Children’s Hospital, 2016
• America’s Top Doctors, Castle Connolly Medical, Ltd., 2017

Pushpa Viswanathan, MD

RESEARCH
As codirector of the Thyroid Center, Pushpa Viswanathan’s primary clinical research focus is treatment of thyroid disorders and thyroid cancers in children. Viswanathan’s current research involves clinical and prognostic evaluation of pediatric thyroid disease.

ADVISORY COMMITTEE MEMBERSHIPS
• Co-chair, Multidisciplinary Thyroid Center, Children’s Hospital of Pittsburgh
• Patient Experience Outpatient Committee, Children’s Hospital of Pittsburgh
PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS
• Endocrine Society
• American Academy of Pediatrics
• ADA

Selma F. Witchel, MD

RESEARCH
Selma Witchel’s research projects address androgen excess, glucocorticoid receptors, and gender questioning in children and adolescents.

Persistent Symptoms of Hyperandrogenism in Girls With a History of Premature Adrenarche or Adolescent Hyperandrogenism. The goal of this project is to ascertain outcome data for girls with a history of premature adrenarche or adolescent hyperandrogenism to test the hypothesis that these girls have an increased risk to develop polycystic ovary syndrome (PCOS). The project has been expanded to include investigation of the novel bioactive adrenal steroid hormones in normal adrenarche, premature adrenarche, adolescent hyperandrogenism, and congenital adrenal hyperplasia.

Substance Use Disparities Among Transgender Youth. The overarching goal of this study is to systematically examine substance use and associated health disparities among transgender and gender-questioning youth.

Noninvasive Maximization of Fertility in a Peripubertal Population of Patients With Klinefelter Syndrome. The goal of this pilot project funded by the Clinical and Translational Science Institute is to determine whether sperm can be detected in the urine or in semen samples of adolescent or young adult patients, as well as whether there is a correlation between the presence of sperm and the physical/endocrine end points routinely assessed in these patients.

Role of Glucocorticoids in Prenatal Brain Development. The goal of this project is to investigate the developmental consequences of premature glucocorticoid exposure on the developing brain. Initial studies have found that dexamethasone exposure alters the development trajectory of the brain.

ADVISORY COMMITTEE MEMBERSHIPS
• Research Advisory Committee, Children’s Hospital of Pittsburgh
• Chair, Disorders of Sexual Differentiation Committee, Children’s Hospital of Pittsburgh
• Co-chair, Multidisciplinary Thyroid Center, Children’s Hospital of Pittsburgh
• CARES Foundation Advisory Board

EDITORSHIPS
• Editorial Board, Journal of Clinical Endocrinology and Metabolism

MAJOR LECTURES AND SEMINARS
• “Biology of Gender,” Midwest PES meeting, Chicago, Ill., March 2016
• “Sex Steroids and Gender Identity—The Endocrinologists’ Perspective,” Pittsburgh TransPride Conference, Pittsburgh, Pa., September 2016
• “Biology of Gender,” pediatric endocrinology grand rounds, University of Michigan, Ann Arbor, Mich., December 2016
• “Premature Adrenarche and PCOS,” Endocrinology Research Conference, University of Michigan, Ann Arbor, Mich., December 2016

PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS
• Endocrine Society
• PES
• Society for Pediatric Research
• American Academy of Pediatrics
• ADA
• Androgen Excess and PCOS Society
• European Society for Pediatric Endocrinology

HONORS
• Best Doctors, Pittsburgh Magazine, 2017
• America’s Top Doctors, Castle Connolly Medical, Ltd.
2015


2016


Zhang T, Dong HH. FoxO1—a conductor of insulin signaling to glucose and lipid metabolism. In: Ntambi JM (Ed.), Hepatic De Novo Lipogenesis and Regulation of Metabolism. Switzerland: Springer International Publishing; 2016.


2017


Corticosteroids mediate autophagy.


Humanin is an endogenous activator of chaperone-mediated autophagy.


Witchel SF. Puberty: Gonadarche and adrenarche. In Strauss and Barbieri (Eds.), Yen and Jaffe’s Reproductive Endocrinology (8th ed.) Elsevier Saunders; 2017.


