Division of Endocrinology, Diabetes and Metabolism



Barbara B. Kahn, MD, Chief

Overview

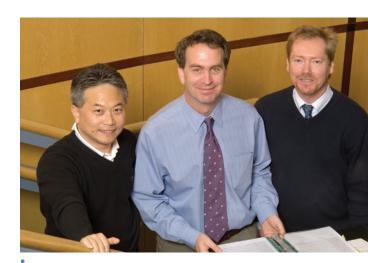
The mission of the Endocrinology, Diabetes and Metabolism Division is to provide clinical care, consultation and training, and to perform basic and clinical research in the areas of endocrinology and metabolism.

Clinical Activities

The clinical program is a joint venture with the Joslin Diabetes Center. This collaboration joins the nationally-known BIDMC endocrinology practice with the illustrious and world-renowned diabetes clinical practice at the Joslin. The combined program in Endocrinology, Diabetes and Metabolism ranked 12th in the nation in the 2006 US News & World Report of "Best Hospitals" in the U.S. Dr. James Hennessey is Director of the Clinical Endocrinology Program and Dr. Martin Abrahamson is the Medical Director of the Joslin Diabetes Center.

The greater size and overall strength of the combined clinical program have allowed for growth and development of clinical programs, including initiatives in obesity and nutrition. A full range of outpatient and inpatient endocrine services is available for problems such as diabetes, obesity, thyroid disease, metabolic bone disease (especially osteoporosis), calcium disorders, pituitary disease, adrenal disease, and reproductive and growth disorders. Consultation services are available in the Shapiro Clinical Center and Joslin Diabetes Center. This year, the Endocrine clinical strengths have grown with the addition of Alan Malabanan, MD, a specialist in metabolic bone disease, and Jim Hennessey, a noted thyroidologist. The highly successful Thyroid Nodule Clinic offers the coordinated

services of radiology, pathology, surgery, and endocrinology. The convenience of the combined services has led to increased patient volume and program expansion. The Osteoporosis Prevention and Treatment Center, directed by Dr. Harold Rosen, offers expert consultative services and state-of-the-art dual energy X-ray absorptiometry to diagnose patients with osteopenia and osteoporosis. The Division is also expanding its neuroendocrine-pituitary service in conjunction with neurosurgery.



Young-Bum Kim, PhD; Anthony Hollenberg, MD; Christian Bjorbaek, PhD

Quality Improvement

Among the Quality improvement activities of the Division are chart audits for quality of care and billing accuracy, monitoring the diagnostic outcomes of the thyroid nodule biopsy activities and assuring the safe use of osteoporosis medications in patients with declining renal function.

Educational Programs

The Division recruits three new subspecialty fellows yearly into a unified fellowship training program with the Joslin Diabetes Center. The director of the Fellowship Program is Evan Rosen, and the site directors are Eleftheria Maratos-Flier for BIDMC and William Hsu for the Joslin. The clinical year is conducted jointly with Brigham and Women's Hospital, and involves inpatient rotations at BIDMC and Brigham and Women's Hospital, continuity clinics in endocrinology and diabetes at both BIDMC and the Joslin, and sub-specialty clinics in pediatric endocrinology, lipids, reproductive endocrinology, metabolic bone disease, and obesity. A major aspect of the fellowship training is an in-depth research experience in one of the outstanding laboratories at BIDMC, Joslin or other Boston area research programs. Many graduates remain in academia. The program is supported by two NIH training grants. In addition to nine clinical fellows there are more than fifty postdoctoral research fellows working within the Endocrine Division research laboratories.

Research Activities

The Division has a highly successful, cutting-edge research portfolio which includes research initiatives supported by the National Institutes of Health, private foundations, and the pharmaceutical industry. The research includes clinical trials, *in vivo* physiology, adipocyte biology, cell signaling, gene transcription, mouse genetics, hormone action and resistance, insulin secretion, and basic investigations of gene structure and function.

Division investigators such as Jeff Flier, Barbara Kahn, Brad Lowell, Christian Bjorbaek, Terry Maratos-Flier, Christos Mantzoros and Evan Rosen are well-known for their research in diabetes, obesity, and energy metabolism. A particular strength is investigation of the molecular mechanisms for insulin resistance in diabetes and obesity. Specific studies relate to insulin signaling including the role of protein tyrosine phosphatases and suppressors of cytokine signaling, regulation of glucose

transport in insulin resistance and the role of novel adipocyte-secreted molecules in insulin resistance. Studies of insulin secretion focus on the role of uncoupling proteins. These investigators also have strong programs investigating the pathogenesis of obesity, including leptin biology and signaling, hypothalamic peptides

Research Funding • AY'07	
Federal DirectFederal Indirect	5,840,790 3,048,789
Other Direct Other Indirect	3,861,304 1,237,169

and appetite regulation, neuronal circuitry and regulation of adipogenesis. Techniques include sophisticated mouse genetics, viral vectors, state-of-the-art *in vivo* metabolic assessment of rodent models of obesity, electrophysiology, as well as patient-based studies.

The Division has a large NIH funded Program Project in Obesity Pathophysiology with a primary focus on the biology of the fat-derived hormone leptin, including the physiologic role of this hormone in the integration of energy balance, signaling pathways mediating the biological effects of leptin, leptin receptor biology, and mechanisms of leptin resistance. Other work using mouse genetics and gene targeting technologies investigates the basic mechanisms regulating energy expenditure and thermogenesis, including the biology of brown adipose tissue, novel uncoupling proteins and beta adrenergic receptors. Studies using neuron-specific knockout and knockin approaches are defining the functional neurocircuitry of body weight control. The Division has a second Program Project Grant from the American Diabetes Association which supports studies of the neuroendocrine regulation of hypothalamic function, including reproduction, growth, and the thyroid and stress axes.

Tony Hollenberg is a leader in the area of thyroid hormone action and nuclear receptor function. His group also studies the role of nuclear co-activator and co-repressor proteins and their involvement in cell signaling. Anny Usheva is exploring basic mechanisms of gene regulation at the transcription level. A specific interest is the effect of nutrition on transcription, and computational analyses are carried out in collaboration with the Theoretical Physics Division at the National Laboratory in Los Alamos.

Clinical and translational research activities of Christos Mantzoros' group, are focused on leptin physiology, the etiology and treatment of the HIV-associated metabolic syndrome, and the role of IGF-1 in the pathogenesis of malignancy.

Awards and Honors

Dr. Barbara Kahn received the George R. Minot Chair of Medicine at Harvard Medical School and a MERIT Award from the National Institutes of Health, and she was inducted into the Institute of Medicine of the National Academy of Sciences in 2006. In 2007, she received the Harold Rifkin Award from Albert Einstein College of Medicine. Dr. Christos Mantzoros was elected to the American Society of Clinical Investigation and received the Lilly Award from the North American

Association for the Study of Obesity in 2006 and the Center for Faculty Development Award for Excellence in Mentoring from Beth Israel Deaconess Medical Center in 2007.

Selected Publications

Badman MK, Pissios P, Kennedy AR, Koukos G, Flier JS, Maratos-Flier E. Hepatic fibroblast growth factor 21 is regulated by PPARalpha and is a key mediator of hepatic lipid metabolism in ketotic states. *Cell Metab* 2007; 5:426-437.

Bence KK, Delibegovic M, Xue B, Gorgun CZ, Hotamisligil GS, Neel BG, Kahn BB. Neuronal PTP1B regulates body weight, adiposity and leptin action. *Nature Med* 2006; 12:917-924.

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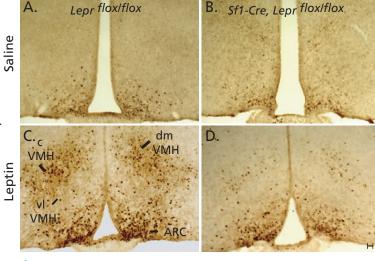
Dhillon H, Zigman JM, Ye C, Lee CE, McGovern RA, Tang V, Kenny CD, Christiansen LM, White RD, Edelstein EA, Coppari R, Balthasar

N, Cowley MA, Chua S Jr, Elmquist JK, Lowell BB. Leptin directly activates SF1 neurons in the VMH, and this action by leptin is required for normal body-weight homeostasis. *Neuron* 2006; 49:191-203.

Fulton S, Pissios P, Manchon RP, Stiles L, Frank L, Pothos EN, Maratos-Flier E, Flier JS. Leptin regulation of the mesoaccumbens dopamine pathway. *Neuron* 2006; 51:811-822.

Jimenez MA, Akerblad P, Sigvardsson M, Rosen ED. Critical role for Ebf1 and Ebf2 in the adipogenic transcriptional cascade. *Mol Cell Biol* 2007; 27:743-757.

Klöting N, Graham TE, Berndt J, Kralisch S, Kovacs P, Wason CJ, Fasshauer M, Schön MR, Stumvoll M, Blüher M, Kahn BB. Serum retinol binding protein is more highly expressed



Prad Lowell's laboratory has shown that neurons in the ventromedial hypothalamus (VMH) are involved in leptin action (Dhillon H et al. *Neuron* 2006;49:191-203). Leptin receptors in the VMH were targeted for ablation with *SF1-cre*. Knockout mice have a response to leptin in the arcuate nucleus (ARC) but not VMH. Knockout mice are obese and sensitive to a high fat diet, indicating that SF1 neurons play a role in leptin action.

Anti pSTAT3

in visceral than in subcutaneous adipose tissue and is a marker of intra-abdominal fat mass. *Cell Metabolism* 2007; 6:79-87.

Korner A, Pazaitou-Panayiotou K, Kelesidis T, Kelesidis I, Williams CJ, Kaprara A, Bullen J, Neuwirth A, Tseleni S, Mitsiades N, Kiess W, Mantzoros CS. Total and highmolecular-weight adiponectin in breast cancer: *In vitro* and *in vivo* studies. *J Clin Endocrinol Metab* 2007; 92:1041-1048.

Tong Q, Ye C, McCrimmon RJ, Dhillon H, Choi B, Kramer MD, Yu J, Yang Z, Christiansen LM, Lee CE, Choi CS, Zigman JM, Shulman GI, Sherwin RS, Elmquist JK, Lowell BB. Synaptic glutamate release by ventromedial hypothalamic neurons is part of the neurocircuitry that presents hypoglycemia. *Cell Metab* 2007; 5:383-393.

Zimon A, Erat A, Von Wald T, Bissell B, Koulova A, Choi CH, Bachvarov D, Reindollar RH, Usheva A. Genes invoked in the ovarian transition to menopause. *Nucleic Acids Res* 2006; 34:3279-3287.

Faculty

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