



UNIVERSITY OF PENNSYLVANIA  
SCHOOL OF MEDICINE  
HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA  
DIVISION OF ENDOCRINOLOGY, DIABETES, AND METABOLISM  
FELLOWSHIP TRAINING PROGRAM

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The **University of Pennsylvania** was founded by Benjamin Franklin in 1740. The Medical School was founded in 1765, making it the oldest school of medicine in North America. The Penn campus is located in University City, just across the Schuylkill River from Center City Philadelphia. It is home to all of the undergraduate, graduate and professional schools (including Medicine, Nursing, Veterinary Medicine, and Dental Medicine as well as the Law School and the Wharton School of Business). Furthermore, the Children's Hospital of Philadelphia and the Veterans Administration Medical Center are adjacent to the campus. This close proximity of associated divisions, departments, and schools facilitates interaction among the various biomedical disciplines, faculty and trainees. The 725-bed Hospital of the University of Pennsylvania serves both primary and tertiary care functions providing an ideal patient balance for trainees to gain clinical experience.

### **FELLOWSHIP PROGRAM IN ENDOCRINOLOGY, DIABETES, AND METABOLISM**

The goal of the fellowship program in Endocrinology, Diabetes, and Metabolism at the University of Pennsylvania is to train outstanding endocrinologists for academic careers. This is accomplished by providing:

1. Broad and intensive clinical exposure and teaching
2. Training in and opportunities for teaching and academic presentations
3. Post-doctoral level training in basic and/or clinical research

For most fellows, the first year is devoted predominantly to clinical training. Fellows spend 12 months doing in-patient consultations as well as participating in a mixture of out-patient clinics. During this first year, fellows still have sufficient time to plan and initiate a research project on a part-time basis. After completion of the first year, fellows still participate in divisional conferences and clinics, but the primary emphasis becomes the fellow's individual research project, supervised by a faculty mentor. The minimum length of fellowship training is two years, but most fellows preparing for research careers in academic medicine complete a total of three (or more) years. These additional research years can generally be accommodated within the program, and many fellows have been successful in obtaining grant support for their own projects.



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HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA  
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FELLOWSHIP TRAINING PROGRAM

## **CLINICAL TRAINING**

During the fellow's clinical training, he/she evaluates patients with a wide range of endocrine disorders: thyroid diseases (including fine needle aspiration of thyroid nodules and radioactive iodine therapy for hyperthyroidism and thyroid cancer), metabolic bone disorders (osteoporosis, osteomalacia, Paget's disease), hyper- and hypocalcemia, hyperandrogenism in women, sexual dysfunction and infertility, diabetes mellitus, male hypo-gonadism, endocrine causes of hypertension (Cushing's syndrome, hyperaldosteronism, pheochromocytoma), and pituitary dysfunction.

**Outpatient Experience:** Because Endocrinology is largely an outpatient subspecialty, a major portion of the clinical effort in the fellowship program is devoted to evaluation and treatment of patients in an ambulatory care setting. Approximately 350 general endocrine and 500 diabetic outpatients are seen per month. This busy outpatient practice allows fellows to see a large number of new patients, varied both in the reason for consultation and the complexity of the endocrine problem. Patients are referred from primary care practices throughout the Delaware Valley, from within the Penn Healthcare System, and from surrounding states for second/third opinions

***First year*** fellows attend two endocrinology clinics per week, during which they work closely with faculty seeing new patients and coordinating follow-up care. In addition to general endocrine clinics, subspecialty clinics are devoted to pituitary, and nodular thyroid disease. In the second and subsequent years of the fellowship program, fellows are required to maintain one continuity clinic. Fellows may also choose electives where they attend pediatric, lipid, and reproductive endocrinology clinics.

***First year*** fellows attend one diabetes clinic per week, during which they work with attending faculty, as well as with the on-site diabetes teaching nurse, nurse practitioner, nutritionist, and podiatrist. Fellows are also encouraged to attend a diabetic retinopathy clinic. Fellows interested in obtaining additional training in diabetes may choose to participate in diabetes clinic in the second and subsequent years in the fellowship program.

**Inpatient Experience:** The consult team is comprised of an attending, a first year fellow, medical residents and 4th year medical students taking the Endocrine elective. In conjunction with a faculty-attending physician, the fellow assumes primary responsibility for the in-patient consults and helps with teaching rotating medical students and residents.

***First year*** fellows spend twelve months on the endocrinology/diabetes in-patient consult service. Consults obtained by the medicine, surgery, and other admitting services are referred to the endocrinology consult service. The fellow presents the cases to the attending, and decisions are made for initial and follow-up care as a team with medical students and medical house-staff on rotation. Didactic Endocrinology Rounds are held three times a week with the endocrinology attending alternating with Diabetes Rounds, held twice a week with the diabetes attending. All first year fellows attend both conferences.



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SCHOOL OF MEDICINE  
HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA  
DIVISION OF ENDOCRINOLOGY, DIABETES, AND METABOLISM  
FELLOWSHIP TRAINING PROGRAM

## **DIDACTIC TRAINING**

The Division faculty conduct consult rounds that focus on disease etiology and management. In addition, both endocrine and diabetes attendings give didactic presentations on the “theme of the month” (e.g., Endocrine--thyroid, adrenal, male reproductive; Diabetes--insulin resistance, oral agents, dyslipidemias). This program ensures that fellows receive formal instruction in a full curriculum as designated.

The Endocrine Clinical Conference is held on Wednesday at lunch. This conference is jointly attended by faculty and fellows of the Division of Endocrinology, Diabetes, and Metabolism at HUP and the Endocrinology Division at the Children’s Hospital of Philadelphia. Once a month, this is a clinical-pathological conference, in which fellows present patients who had either endocrine biopsies or surgery and the pathology is reviewed. Once a month this conference is devoted to pediatric endocrinology presented by our colleagues at CHOP. On the remaining 2-3 Wednesdays per month, the endocrine consult fellow presents challenging or instructive cases with review of the pertinent literature.

Endocrine Grand Rounds occur monthly. Outstanding speakers throughout the country are invited to present a talk on a clinically relevant topic. This formal lecture is followed by informal case presentations to the visiting professor in his/her area of expertise, with ample time for discussion.

Journal club is held once a month, where both an attending and fellow each present recent literature and present a paper of interest to the group. In this forum, the fellow learns to read and evaluate critically the clinical endocrinology literature.

The Thursday diabetes clinic is followed by a bi-monthly Diabetes Conference at noon. This provides a forum for case presentation and discussion of interesting, challenging, and instructive cases alternating with more formal didactic sessions presenting basic concepts in clinical and molecular diabetology and metabolism.

On Thursday afternoons, fellows attend the Combined Division of Endocrinology, Diabetes, and Metabolism and University of Pennsylvania Diabetes Center Seminar Series. Here, Penn faculty and outstanding invited faculty from throughout the country present innovative basic scientific work involving molecular diabetology and endocrinology. Fellows are also required to attend Medical Grand Rounds on Tuesday mornings, which frequently addresses a topic relevant to endocrinology and diabetes.

## **RESEARCH TRAINING**

The research component of the fellowship is designed to provide trainees with an intensive introduction to the principles and techniques of clinical or laboratory investigation. Divisional research training grants allow our fellows to pursue this on a full time basis and opportunities are available for fellows both within and outside of the Division of Endocrinology Diabetes and Metabolism. During the first year of the fellowship, trainees become familiar with the research interests of faculty members, both through informal interactions and their presentations in Research Conference. Fellows are also encouraged to meet individually with faculty members to discuss research interests.



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SCHOOL OF MEDICINE  
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DIVISION OF ENDOCRINOLOGY, DIABETES, AND METABOLISM  
FELLOWSHIP TRAINING PROGRAM

## **RESEARCH TRAINING (CONT.)**

After deciding on a topic and preceptor, fellows prepare a research proposal with the guidance of the preceptor. This provides useful experience in developing an experimental plan and preparing a grant application, and also helps to formally define the fellow's project. Appropriate proposals are submitted to the N.I.H. for individual National Research Service Awards by the middle of the first year.

Fellows present their work in the Division's research seminar and are encouraged to submit abstracts of their work for presentation at national meetings. Research training may be supplemented by formal graduate courses at the University. Past fellows have taken courses in fields as diverse as Clinical Study Design, Eukaryotic Genetics, and Biomedical Statistics.

For those specifically interested in clinical research, the University of Pennsylvania Medical Center offers fellows opportunities for training in clinical epidemiology (leading to an M.S. in epidemiology) in a program pioneered and directed by Brian Strom. As well as an outstanding introduction to patient oriented clinical investigation in a year-long course run by the Clinical Research Center.

## **RESEARCH PROJECTS**

### **DIVISION OF ENDOCRINOLOGY, DIABETES, AND METABOLISM**

Research interests of Endocrinology Diabetes and Metabolism faculty and investigators in other divisions or departments who conduct research related to Endocrinology are summarized below.

#### **Rexford S. Ahima, M.D., Ph.D** **Assistant Professor of Medicine**

Research in my lab focuses on the interrelationship between energy stores and regulation of energy balance by the brain. Obesity is a highly prevalent condition in the United States, and an important risk factor for cardiovascular disease, diabetes and cancer. Our understanding of the physiology of energy homeostasis and the pathogenesis of obesity has been greatly enhanced by the recent discovery of the adipocyte hormone, leptin, and neural targets in the brain. Contrary to the prevailing view of the adipocyte as merely a specialized cell for the storage of excess energy in the form of triglycerides, there is increasing evidence that adipose tissue plays a more active role in energy homeostasis. The levels of leptin and other products secreted by adipose tissue are dependent on the status of energy balance, and appear to serve as important signals linking energy stores to peripheral and central homeostatic mechanisms. Adipose-derived hormones, cytokines and other factors have profound effects on adipocytes and peripheral targets e.g liver and pancreas, and also regulate feeding behavior, thermogenesis and neuroendocrine function through action in the central nervous system. Leptin, PAI-1, components of the renin-angiotensin system, TNF-alpha and other adipocyte hormones may also mediate the well-known complications of obesity.



UNIVERSITY OF PENNSYLVANIA  
SCHOOL OF MEDICINE  
HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA  
DIVISION OF ENDOCRINOLOGY, DIABETES, AND METABOLISM  
FELLOWSHIP TRAINING PROGRAM

**Rexford S. Ahima, M.D., Ph.D.**  
**Assistant Professor of Medicine**

(continued)

**Current and planned projects:**

1. The role of adipose-derived hormones, proinflammatory cytokines and complement factors in adipogenesis.
2. The potential involvement of these factors in the metabolic and endocrine dysfunction in obesity.
3. Interactions between adipose-derived hormones/cytokines and neural targets in the hypothalamus and other brain regions involved in energy balance.
4. Effects of adipocyte hormones/cytokines on neural development and plasticity.

**Selected References:**

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2. Ahima, R.S., Flier, J.S.: The Adipocyte as an Endocrine Organ. *Trends in Endocrinol. & Metab.* 11:327-332, 2000
3. Ahima, R.S., Hileman, S.M.: Postnatal regulation of hypothalamic neuropeptide expression by leptin: implications for energy balance and body weight regulation. *Regul. Pept.* 92:1-7, 2000
4. Ahima, R.S., Osei, S.Y.: Molecular regulation of eating behavior: new insights and prospects for therapeutic strategies. *Trends Mol. Med.* 7:205-213, 2001

**Morris J. Birnbaum, M.D., Ph.D.**  
**Professor of Medicine**  
**Director, Diabetes Research Programs**

**Regulation of Glucose Transport by Insulin**

Research in Dr. Birnbaum's laboratory is directed towards understanding events that mediate the actions of insulin on metabolism and growth. Relevant areas of investigation include hormone action, signal transduction, membrane protein trafficking and the control of cell growth. Insulin and IGF-1, which both initiate a signaling pathway well-conserved throughout evolution, have been implicated in the control of nutrient homeostasis, organismal size, cell survival, and ageing. Yet the precise molecular mechanisms that mediate these effects remain largely unknown. Elucidation of protein kinase cascades rapidly activated by insulin led to the identification of a serine-threonine protein kinase, called Akt or protein kinase B, as crucial to many of the actions of insulin. Work is now underway in Dr. Birnbaum's laboratory using both genetic and biochemical strategies to clarify the role of Akt in many biological processes taking advantage of tissue culture cells, mice and fruit flies as model systems.



UNIVERSITY OF PENNSYLVANIA  
SCHOOL OF MEDICINE  
HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA  
DIVISION OF ENDOCRINOLOGY, DIABETES, AND METABOLISM  
FELLOWSHIP TRAINING PROGRAM

**Morris J. Birnbaum, M.D., Ph.D.**  
**Professor of Medicine**  
**Director, Diabetes Research Programs**

(continued)

**Current and Planned Projects**

1. Define the mechanism by which GLUT4 is sorted to a hormone-responsive organelle and translocated to the cell surface.
2. Clarify the role of Akt in insulin action and secretion.
3. Understand the mechanism by which insulin/IGF-1 through Akt regulates cell growth.

**References**

1. Verdu, J., Buratovich, M. A., Wilder, E.L., and Birnbaum, M.J. (1999) Cell-autonomous regulation of cell and organ growth in *Drosophila* by Akt/PKB. *Nature Cell Biol.*, 1: 500-506.
2. Birnbaum MJ. (2001) Diabetes. Dialogue between muscle and fat. *Nature.* 409:672-3.
3. Mu, J., Brozinick, J.T., Valladares, O., Bucan, M., and Birnbaum, M.J. (2001) A Role for AMP-activated Protein Kinase in Contraction and Hypoxia Regulated Glucose Transport in Skeletal Muscle. *Molecular Cell* 7:1085-1094.
4. Cho, H., Mu, J., Kim, J. K., Thorvaldson, J. L., Chu, Q., Crenshaw, E. B., Kaestner, K. H., Bartolomei, M. S., Shulman, G. I., Birnbaum, M. J. (2001) Insulin Resistance and Diabetes Mellitus in Mice Lacking Akt2/PKB. *Science* 292: 1728-1731.
5. Lawrence, J. T. R. and Birnbaum, M. J. (2001) ADP-Ribosylation Factor 6 Delineates Separate Pathways Used by Endothelin-1 and Insulin for Stimulating Glucose Uptake in 3T3-L1 Adipocytes. *Mol. Cell. Biol.* 21(15):5276-5285.

**Seth N. Braunstein, M.D., Ph.D.**  
**Associate Professor of Medicine**  
**Director, Clinical Diabetes Programs**

Dr. Braunstein has a large clinical Diabetes practice. His interests include treatment of complications related to diabetes, treatment of diabetes in pregnancy and young adults and intensive treatment programs. Current research is focused on new treatment strategies for complications of diabetes and industry-sponsored programs in the use of inhaled insulin, other new insulin analogs, a computer-analysis of retinal photographs, and the use of insulin in combination with oral agents. Dr. Braunstein is a PI in the NIH-sponsored EDICT trial and the Look AHEAD trial.



UNIVERSITY OF PENNSYLVANIA  
SCHOOL OF MEDICINE  
HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA  
DIVISION OF ENDOCRINOLOGY, DIABETES, AND METABOLISM  
FELLOWSHIP TRAINING PROGRAM

**Seth N. Braunstein, M.D., Ph.D.**  
**Associate Professor of Medicine**  
**Director, Clinical Diabetes Programs**

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2. The DCCT Research Group, Baseline Analysis of Renal Function in the Diabetes Control and Complications Trial, *Kidney Int.* 43: 668-674, 1974.
3. Grunwald J, Brucker A, Braunstein SN, Schwartz S, Baker L, Petrig B, and Riva C, Strict Metabolic Control and Retinal Blood Flow in Diabetes Mellitus, *Br. J. Ophthalmol.* 78: 598-604, 1994.

**Lewis A. Chodosh, M.D., Ph.D.**  
**Assistant Professor of Medicine and Molecular & Cellular Engineering**

Research in Dr. Chodosh's laboratory focuses on mammary gland development and its relationship to endocrine risk factors for breast cancer. The emphasis of this research stems from epidemiologic studies demonstrating that breast cancer risk is influenced by the timing of reproductive endocrine events as illustrated by the observation that women who have their first child early in life have a significantly lower lifetime risk of developing breast cancer. Using murine mammary gland development as a model system, current approaches towards understanding the relationship between development and carcinogenesis in the breast include: 1) defining the molecular and cellular changes that occur in the breast during stages of development that influence breast cancer risk; 2) studying the role played by three novel protein kinases identified in our laboratory in mammary epithelial differentiation, development and carcinogenesis; and 3) using inducible transgenic and knockout models for breast cancer coupled with oligonucleotide microarray expression profiling to study the process of mammary carcinogenesis.

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2. Chodosh LA, D'Cruz CM, Gardner HP, Ha SI, Marquis ST, Rajan JV, Stairs DB, Wang JY, and Wang M. Mammary gland development, reproductive history and breast cancer risk. *Cancer Research* 59:1765s-1772s, 1999.
3. Gardner HP, Belka GK, Wertheim GBW, Hartman JL, Ha SI, Gimotty PA, Marquis ST, and Chodosh LA. Developmental role of the SNF1-related kinase Hunk in pregnancy-induced changes in the mammary gland. *Development* 127:4493-4509, 2000.



UNIVERSITY OF PENNSYLVANIA  
SCHOOL OF MEDICINE  
HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA  
DIVISION OF ENDOCRINOLOGY, DIABETES, AND METABOLISM  
FELLOWSHIP TRAINING PROGRAM

**Lewis A. Chodosh, M.D., Ph.D.**

**Assistant Professor of Medicine and Molecular & Cellular Engineering**

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4. Gardner HP, Ha SI, Reynolds C, and Chodosh LA. The CaM kinase, *Pnck*, is spatially and temporally regulated during murine mammary gland development and may identify an epithelial cell subtype involved in breast cancer. *Cancer Research*, 60:5571-5577, 2000.
5. D'Cruz CM, Gunther EJ, Hartman J, Sintasath L, Moody SE, Boxer RB, Cox JD, Ha SI, Belka GK, Golant A, Cardiff RD and Chodosh LA. MYC induces mammary tumorigenesis by means of a preferred pathway involving spontaneous *Kras2* mutations. *Nature Medicine*, 7:235-239, 2001.
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7. Master SR, Hartman JL, D'Cruz CM, Moody SE, Keiper EA, Ha SI, Belka GK and Chodosh LA. Functional microarray analysis of mammary development reveals a novel role in adaptive thermogenesis. (Submitted).

**Nancy E. Cooke, M.D.**

**Professor of Medicine and Genetics**

**Molecular Endocrinology of the Growth Hormone and Vitamin D Binding Protein Gene Families**

Research in Dr. Cooke's laboratory focuses on defining the molecular basis for high-level, tissue-specific, developmentally-controlled expression of the human growth hormone/chorionic somatomammotropin gene cluster *in vivo*. These studies utilize transgenic mice as the model system and are focussed on delineating the mechanism by which the growth hormone locus control region (LCR) functions. A second area of research concerns the vitamin D binding protein (DBP), a member of the albumin and alpha-fetoprotein gene family. Current aims include functional mapping of the DBP gene regulatory elements; specifically determining how DBP gene regulation occurs at the level of chromatin. The phenotype of a DBP<sup>-/-</sup> mouse model that has been generated by targeted homologous recombination at the DBP locus is also being characterized.

**Current and Planned Projects**

1. Regulation of the growth hormone cluster of genes: studies to evaluate the mechanism of action of the growth hormone locus control region in directing developmental and tissue-specific gene regulation; chromatin mapping; mutagenesis and *in vivo* analyses of expression during development by timed recombination-activated gene expression.
2. Biological consequences of DBP deficiency in a mouse model: alterations in vitamin D metabolism, alterations in macrophage activation, and G-actin metabolism *in vivo*. Studies on the action of vitamin D analogues in the DBP null mouse are also being studied.



UNIVERSITY OF PENNSYLVANIA  
SCHOOL OF MEDICINE  
HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA  
DIVISION OF ENDOCRINOLOGY, DIABETES, AND METABOLISM  
FELLOWSHIP TRAINING PROGRAM

**Nancy E. Cooke, M.D.**  
**Professor of Medicine and Genetics**  
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#### **Growth hormone**

1. Su Y, Liebhaber SA, Cooke NE. The human growth hormone gene cluster locus control region supports position-independent pituitary- and placenta-specific expression in the transgenic mouse. *J. Biol. Chem.* 275: 7902-8113, 2000.
2. Elefant F, Cooke NE, Liebhaber SA. Targeted Recruitment and Spreading of Histone Acetyltransferase Activity by a Locus Control Region. *J. Biol. Chem.* 275: 13827-13834, 2000.
3. Elefant F, Su Y, Liebhaber SA, Cooke NE. Patterns of histone acetylation suggest dual pathways for gene activation by a bifunctional locus control region. *EMBO J.* 24: 6814-6822, 2000.

#### **DBP**

1. Song Y-H, Ray K, Liebhaber SA, Cooke NE. Vitamin D binding protein gene transcription is regulated by the relative abundance HNF-1<sub>alpha</sub> and HNF-1<sub>beta</sub>. *J. Biol. Chem.* 273:28408-28418, 1998.
2. Safadi F, Thornton P, Magiera HM, Hollis B, Gentile M, Haddad JG, Liebhaber SA, Cooke NE. Osteopathy and resistance to vitamin D toxicity in mice null for vitamin D binding protein. *J. Clin. Invest* 103:239-251, 1999.
3. Song Y-H, Naumova A, Liebhaber SA, Cooke NE. Physical and meiotic mapping of the region of human chromosome 4q11-q13 encompassing the vitamin D binding protein (DBP/Gc-globulin) and albumin multigene cluster. *Genome Research* 9:581-587, 1999.

**Nayyar Iqbal M.D.**  
**Assistant Professor**

Research in Dr. Iqbal's laboratory focuses on the study of free fatty acids and certain cytokines (like TNF-alpha) in insulin resistance. In addition to the study in vivo insulin sensitivity and resistance, the hyperinsulinemic clamp techniques are utilized.

### **Current and Planned Projects**

1. Changes in insulin sensitivity after high protein /high fat versus ADA recommended diet in obesity and type 2 diabetes.
2. Long term effects of insulin pumps in type 1 DM-a retrospective study.

### **Selected References**

1. Iqbal N, Zayed M, Boden G. Thalidomide impairs insulin action on glucose uptake and glycogen synthesis in patients with type 2 diabetes mellitus. (submitted for publication in *JCEM*)
2. Boden G, Chen X, Iqbal N. Acute lowering of plasma free fatty acids lowers insulin secretion rate in diabetic and normal subjects. *Diabetes* 1998.



UNIVERSITY OF PENNSYLVANIA  
SCHOOL OF MEDICINE  
HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA  
DIVISION OF ENDOCRINOLOGY, DIABETES, AND METABOLISM  
FELLOWSHIP TRAINING PROGRAM

**Mitchell A. Lazar, M.D., Ph.D.**  
**Professor of Medicine and Genetics**  
**Chief, Division of Endocrinology, Diabetes, and Metabolism**

**Nuclear Hormone Receptors in Gene Expression and Physiology**

Receptor for small lipophilic hormones, such as thyroid hormone and retinoic acid, regulate gene expression by binding to and altering the transcription of target genes. We are studying the mechanisms by which the receptors regulate gene transcription. In the absence of hormone, receptors interact with corepressor molecules to repress transcription; hormone ligand leads to coactivator recruitment and activation of transcription. The receptor complexes contain histone modifying activities that may be drug targets. We are dissecting the molecular and cellular biology of these transcription complexes. Understanding the mechanisms underlying tissue- and target gene-specificity of hormone action will allow improved patient care and facilitate the development of new rational therapies for a variety of diseases, including myeloid leukemias whose pathogenesis has been linked to corepressor biology.

We are also studying the molecular mechanisms of nuclear receptors called PPARs. PPAR ligands actively promote fat cell differentiation. Excitement has been generated by the observation that PPAR ligands include a promising new class of antidiabetic drugs called thiazolidinediones (TZDs), including pioglitazone (Actos<sup>®</sup>), and rosiglitazone (Avandia<sup>®</sup>). These drugs enhance the actions of insulin, which is critical because diabetes is a major cause of morbidity and mortality in the U.S. and more than 95% of diabetics have type 2 diabetes, associated with obesity and severe resistance to the action of insulin. The mechanism whereby PPAR activation leads to increased insulin sensitivity is not known. We are studying the regulation of gene expression by PPAR in vitro and in vivo. Mouse models of PPAR gene mutations have been created and are being analyzed for susceptibility to obesity and diabetes. We have also identified and are currently characterizing novel target genes for PPAR ligands. One of these is a novel, adipocyte-secreted protein called resistin that may play a role in the link between obesity and diabetes.

**Current and Planned Projects**

1. Discovery and characterization of proteins involved in regulation of transcription by hormone receptors.
2. Elucidation of the molecular mechanisms underlying the ability of PPAR to induce adipocyte differentiation and enhance sensitivity to insulin.

**Selected References**

1. Reginato MJ, **Lazar MA**. Mechanisms by which thiazolidinediones potentiate insulin action. *Trends in Endocrinology and Metabolism* 10:9-13, 1998. (Review)
2. Zhang J, **Lazar MA**. The mechanism of action of thyroid hormones. *Ann Rev Physiol* 62:439-466, 2000. (Review)
3. Shao D, Rangwala SM, Bailey ST, Krakow SL, Reginato MJ, **Lazar MA**. Interdomain communication regulating PPAR ligand binding. *Nature* 396:377-380, 1998. (Original research)



UNIVERSITY OF PENNSYLVANIA  
SCHOOL OF MEDICINE  
HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA  
DIVISION OF ENDOCRINOLOGY, DIABETES, AND METABOLISM  
FELLOWSHIP TRAINING PROGRAM

**Mitchell A. Lazar, M.D., Ph.D.**  
**Professor of Medicine and Genetics**  
**Chief, Division of Endocrinology, Diabetes, and Metabolism**  
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4. Hu X, **Lazar MA**. The CoRNR motif controls the recruitment of corepressors by nuclear hormone receptors. *Nature* 402:93-96, 1999. (Original research)
5. Huang EY, Zhang J, Miska E, Guenther MG, Kouzarides T, **Lazar MA**. Nuclear receptor corepressors partner with class II histone deacetylases in a Sin3-independent repression pathway. *Genes & Development* 14:45-54, 2000. (Original research)
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**Susan J. Mandel, M.D., M.P.H.**  
**Assistant Professor of Medicine**  
**Associate Chief for Clinical Affairs**

**Clinical Thyroidology**

Thyroid Function and Reproduction/Pregnancy: Normal thyroid function is crucial to both conception and gestation. The presence of thyroid autoantibodies in women with normal thyroid function is associated with an increased risk of miscarriage. However, it is unclear whether the miscarriages are related to thyroid dysfunction during gestation, for which the antibodies may be a direct marker, or whether the presence of antithyroid antibodies is a clue to the existence of a more generalized autoimmunity. During pregnancy, data from thyroxine-replaced hypothyroid women indicate that thyroid hormone production increases about 45% and then decreases after delivery. Early pregnancy can also aggravate Graves' hyperthyroidism.

Nodular Thyroid Disease: Palpable thyroid nodules are extremely common and are found in ~6% of women and ~3% of men over the age of 50; if detected by ultrasound, the prevalence approaches 50%. However, the clinical significance of subcentimeter nodules is unclear. Although evaluation of nodules over 1cm in euthyroid patients includes fine-needle aspiration, the long-term clinical management of such patients varies.

**Current and Planned Projects**

1. Evaluation of thyroid function during pregnancy and miscarriage
2. Assessment and management of gestational Graves' disease
3. Develop disease management protocol for nodular thyroid disease
4. Cost-effectiveness analysis of thyroid nodule evaluation



UNIVERSITY OF PENNSYLVANIA  
SCHOOL OF MEDICINE  
HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA  
DIVISION OF ENDOCRINOLOGY, DIABETES, AND METABOLISM  
FELLOWSHIP TRAINING PROGRAM

**Susan J. Mandel, M.D., M.P.H.**  
**Assistant Professor of Medicine**  
**Associate Chief for Clinical Affairs**  
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1. Mandel SJ, Larsen PR, Seely EW, Brent GA. 1990. Increased need for thyroxine during pregnancy in women with primary hypothyroidism. N Engl J Med. 323:91-6.
2. Mandel SJ, Brent GA, Larsen PR. 1993. Levothyroxine therapy in patients with thyroid disease. Ann Intern Med. 119:492-502.
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4. Marqusee E, Hill JA, Mandel SJ. 1997. Thyroiditis after pregnancy loss. J Clin Endocrinol Metab. 82:2455-57.

**Stanley S. Schwartz, M.D.**  
**Associate Professor of Medicine**

**Clinical Disease Management, Endocrinology, Internal Medicine**  
**Clinical Use of Information System**  
**Diabetes Disease Management**

Dr. Schwartz maintains a large clinical practice in diabetes and its complications at the Hospital of the University of Pennsylvania. He also practices general endocrinology and has a busy internal medicine consultative service for perioperative patients. He is the associate director for clinical systems' to HUP Health Information Services for "Clinical Computing." Dr. Schwartz is the principal investigator for EDIC, an NIH sponsored trial for following DCCT patients.

**Current and Planned Projects**

1. Continue EDIC
2. Assist Dr. Braunstein in clinical drug studies
3. Develop clinical information systems in Diabetes Disease Management
4. Co-PI, SHOW Trial, for Obesity and Diabetes



UNIVERSITY OF PENNSYLVANIA  
SCHOOL OF MEDICINE  
HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA  
DIVISION OF ENDOCRINOLOGY, DIABETES, AND METABOLISM  
FELLOWSHIP TRAINING PROGRAM

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### **Peter J. Snyder, M.D.** **Professor of Medicine**

### **Diseases of the Pituitary-Testicular Axis**

Dr. Snyder's research is focused on two major areas. One area is gonadotroph adenomas, the most common pituitary macroadenoma. These secrete gonadotropins and their subunits, but they are clinically silent, in that the hormonal secretory products do not result in a recognizable syndrome, so they usually do not present until they become so large as to cause neurologic symptoms. The second area of research is the delivery and the effects of testosterone.

### **Current and Planned Projects**

1. The pathogenesis of gonadotroph adenomas.
2. The effect, in men, of testosterone on the trabecular architecture of bone as determined by magnetic resonance microimaging.
3. The effect, in women, of estradiol on the trabecular architecture of bone.

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UNIVERSITY OF PENNSYLVANIA  
SCHOOL OF MEDICINE  
HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA  
DIVISION OF ENDOCRINOLOGY, DIABETES, AND METABOLISM  
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**Francis Sterling, M.D.**  
**Professor of Medicine**  
**Director of Medical Student Education**

Dr. Sterling practices diabetology and endocrinology at the Veterans' Administration Medical Center and at the Hospital of the University of Pennsylvania. His primary interest is patient care and he directs the division's teaching program for Penn medical students and house-staff. He has deservedly won numerous prestigious awards for his excellent teaching.

**Doris A. Stoffers, M.D., Ph.D.**  
**Assistant Professor of Medicine**

Research in Dr. Stoffers' laboratory focuses on pancreas development and its relationship to the pathophysiology of diabetes mellitus. Diabetes mellitus (DM) results from a failure of pancreatic islet  $\beta$ -cells to produce sufficient insulin to meet the requirements of peripheral tissues. A reduction in  $\beta$ -cell mass plays a critical role in the pathogenesis of both type 1 and type 2 DM.  $\beta$ -cell development is regulated by a hierarchy of transcription factors. Genetic studies link monogenic forms of diabetes (formerly called MODY; maturity onset diabetes of the young) to mutations in several pancreatic transcription factors. One of these factors, IPF-1, plays critical roles in early pancreas development and in insulin gene regulation in the differentiated  $\beta$  cell. The relevance of these findings to common late onset type 2 diabetes is illustrated by the discovery of IPF-1 mutations in approximately 5% of type 2 diabetics in certain populations. We have also demonstrated that chronic *in vivo* administration of the incretin hormone GLP-1 upregulates IPF-1 expression and expands the mass of insulin producing beta cells in the pancreas. Interest in the specific molecular mechanisms of IPF-1 is thus further raised by consideration of IPF-1 as a regulatory target for the induction of new  $\beta$  cells (neogenesis) *in vivo* and *in vitro*. These concepts form the foundation for the main projects ongoing in the laboratory as summarized briefly below:

1. Investigating the molecular mechanisms whereby specific IPF-1 mutations lead to type 2 diabetes, using molecular techniques, yeast two hybrid screening and knock-in mutant mouse models.
2. Investigating the biological and molecular mechanisms by which GLP-1 regulates endocrine pancreatic growth using mutant mouse models, by examining signal transduction mechanisms, and by identifying target genes using cDNA microarrays as well as candidate gene approaches.
3. Testing the utility of GLP-1 as a growth/anti-apoptotic factor in islet transplantation models and in the rat intrauterine growth retardation model that develops diabetes during adulthood.
4. Creating genetic mouse models to investigate the interdependence of the exocrine and endocrine pancreas and to determine precursor/progeny relationships in the mouse pancreas *in vivo*.



**Doris A. Stoffers, M.D., Ph.D.**  
**Assistant Professor of Medicine**

(continued)

5. Evaluating other novel candidate cell growth factors.
6. We also maintain an ongoing interest in the molecular genetic basis of MODY and congenital pancreatic malformation.

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