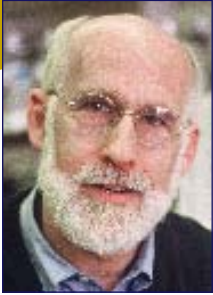


Division of Experimental Medicine



Jerome E. Groopman, MD,
Chief

● Overview

The mission of the Division of Experimental Medicine is to perform laboratory research that provides insights into developing clinical therapies for patients with unmet needs. The Division has diversified considerably from its initial focus on HIV and on hematopoiesis, moving into the areas of solid tumor biology, vascular biology, cannabinoid biology, and neurobiology.

The Division currently numbers 28 scientists and support personnel and occupies the third floor of the Harvard Institutes of Medicine building. Staff are divided into six research teams, each headed by a faculty member. Although each team has its own set of projects, collaborations are frequent and expertise and reagents are shared.

● Research Activities

Dr. Jerome Groopman's laboratory is studying novel pathways in angiogenesis mediated by G-protein coupled receptors that modulate the response to vascular endothelial growth factors. These novel receptors include GPR55 and what is termed the putative abnormal cannabinoid receptor. Initial studies indicate signaling via these receptors promotes cell survival and protects against apoptosis by mediators like endotoxin. In addition, with Dr. Hava Avraham, they observed in murine models that cannabinoids could mobilize hematopoietic progenitors from the marrow into the circulation. The mechanism has not yet been deciphered, and is a major aim of recently submitted NIH proposal. They have also initiated studies of cannabinoid regulation of endothelial cells, addressing whether cannabinoids may protect hematopoietic progenitors from radiation-induced damage.

Dr. Groopman is studying cell cycle inhibitors as potential therapeutics in lymphoma, particularly mantle cell lymphoma that has a signature genetic abnormality with over-expression of cyclin D. In collaboration with Onconova, they have screened a number of compounds and identified two metachemically similar styryl sulfones.

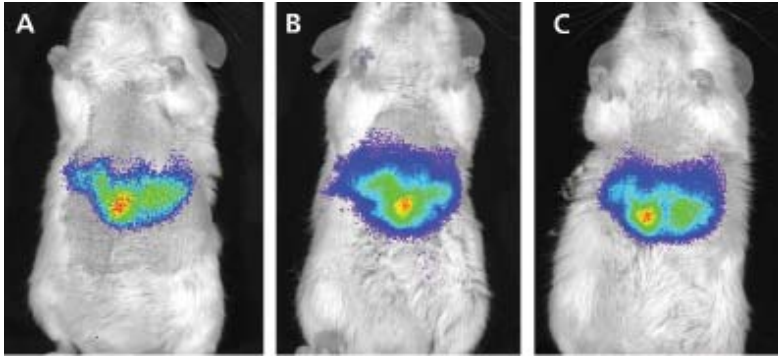
Research Funding • AY'07

Federal Direct	604,878
Federal Indirect	411,039
Other Direct	2,111,448
Other Indirect	55,853

Dr. Hava Avraham studies the role of BRCA mutations and how they affect transcriptional factors and the cell cycle in breast cancer. She also is characterizing how angiogenic receptors like VEGFR1 participate in breast cancer metastasis. She continues to decipher pathways of growth and spread mediated by surface ERB receptors and downstream molecules in breast cancer.

Dr. Shalom Avraham is investigating whether the deregulation and alteration of structure and function of the nuclear matrix protein NRP/B contribute significantly to brain tumor development, using molecular and cellular techniques and animal models. Mayven and MRP2, members of the kelch-related protein family, were cloned and characterized by the group. Their findings strongly suggest that Mayven and MRP2 are required for process elongation in oligodendrocytes by playing a central role in the dynamics of cytoskeletal rearrangement, leading to process extension. The

biological functions of the MRP2 and Mayven proteins and their structure-function relationship in oligodendrocytes *in vitro* and *in vivo* are being investigated in the lab, as well as their roles in the genesis of brain tumors.



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- Imaging of bioluminescent signals in healthy live mice following delivery of a viral gene vector developed in Dr. Terwilliger's lab, in which long-term expression of a Luciferase gene is restricted to liver hepatocytes. Imaging was performed using the Xenogen IVIS 50 at BIDMC's Small Animal Imaging Facility.

A: low dose i.v., day 23; B: high dose i.v., day 26; C: high dose i.p., day 24.

The integrity of the blood-brain barrier (BBB) is critical for normal brain function. BBB dysfunction has been associated with HIV-1 Associated Dementia (HAD), which occurs in a significant portion of individuals infected with HIV-1. The role of brain endothelium in the pathogenesis of HIV-1 related neurological pathology is being studied in the lab, specifically, by investigating whether the HIV-1 envelope glycoprotein, Gp120, may interact with brain endothelium and cause cell injury. Dr. Avraham's laboratory has also studied the role of VEGF in modulating brain endothelial cell permeability, migration and activation and enhancing breast cancer cell migration to the brain.

Dr. John Ladias' laboratory uses techniques of structural biology to answer several biological questions. His group has provided new information about the structure of proteins and nucleic acids that are believed important in the development of schizophrenia, Alzheimer's disease, breast cancer and AIDS.

Dr. Ernest Terwilliger's group addresses basic and clinical issues in tissue regeneration and viral pathology. These studies employ gene vectors derived from Adeno Associated Viruses (AAV) or other agents to promote healing or restoration of function resulting from injury or degenerative conditions. Most of these projects include basic as well as applied components with therapeutic endpoints, and incorporate the development of novel viral vectors. Current areas of emphasis are upon targets in the CNS (brain as well as spinal cord) following injury such as stroke, and the field of orthopedics (bone and cartilage). A newer project area growing from the group's interest in manipulation of gene expression in the liver is the use of gene vectors and RNA interference that target hepatocytes. This project is a collaborative undertaking with Dr. Barbara Kahn in the Division of Endocrinology and Dr. Seth Karp in the Division of Transplantation.

● *Educational Programs*

A regular seminar series held on a weekly basis includes all members of the division. Fellows present their ongoing work and learn how to analyze and defend data. On other occasions, they lead a journal club, critically assessing published work relevant to their fields. In addition, there is training of postdoctoral fellows as well as undergraduates in laboratory research.

● *Awards and Honors*

Dr. Groopman was elected as a Fellow of the American Association for the Advancement of Science in 2007 and the AAAS Fellows Rosette and certificates were presented in 2008. He was also inducted as a member of the American Academy of Arts & Sciences in 2008. Dr. Groopman's fourth book, "How Doctors Think" received the Best Wellness Book Award in 2007 from Books for a Better Life. His book also received The Quill Book Award in 2007 in the Health/Self-Improvement category. He was named Knowles Scholar in recognition of undergraduate teaching at Harvard College in 2008.

● Faculty

Hava Avraham, PhD	Seyha Seng, PhD
Shalom Avraham, MD, PhD	Ernest Terwilliger, PhD
Gabriel Birrane, PhD	Jianfeng Xu, MD, PhD
Jerome Groopman, MD	Radoslaw Zagozdzon, MD, PhD
John Ladas, MD	Xuefeng Zhang, PhD
Huchun Li, PhD	

● Selected Publications

- Cucchiari M, Thurn T, Weimer A, Kohn D, Terwilliger EF, Madry H. Restoration of extracellular matrix in human osteoarthritic articular cartilage by overexpression of the transcription factor Sox9. *Arthritis Rheum* 2007; 56:158-67.
- Chattopadhyay N, Jeong K-H, Yano S, Huang S, Ren XH, Terwilliger EF, Kaiser UB, Vassilev PM, Pollak MR, Brown EM. Calcium-sensing receptor (CaR) stimulates chemotaxis and secretion of MCP-1 in GnRH neurons *in vitro*: Potential impact on reduced GnRH neuron population in CaR-null mice. *Am J Physiol Endocrinol Metab* 2007; 292:E523-32.
- Jiang S, Fu Y, Williams J, Wood J, Pandarinathan L, Avraham S, Makriyannis A, Avraham S, Avraham HK. Expression and function of cannabinoid receptors CB1 and CB2 and their cognate cannabinoid ligands in murine embryonic stem cells. *PLoS ONE* 2007; 2:e641.
- Meiyappan M, Birrane G, Ladas JAA. Structural basis for polyproline recognition by the FE65 WW domain. *J Mol Biol* 2007; 372:970-80.
- Tiburu EK, Bass C, Struppe JO, Lorigan GA, Avraham S, Avraham HK. Structural divergence among cannabinoids influences membrane dynamics: A 2H solid-state NMR analysis. *Biochim Biophys Acta* 2007; 768:2049-59.
- Zhang X, Wang JF, Kunos G, Groopman JE. Cannabinoid modulation of Kaposi's sarcoma-associated herpesvirus infection and transformation. *Cancer Research* 2007; 67:7230-37.
- Zhang X, Xu J, Lawler J, Terwilliger EF, Parangi S. AAV-mediated anti-angiogenic gene therapy with thrombospondin-1 type 1 repeats and endostatin. *Clin Cancer Res* 2007; 13:3968-76.
- Anderson SM, Famous KR, Sadri-Vakili G, Kumaresan V, Schmidt HD, Bass C, Terwilliger EF, Cha J-HJ, Pierce RC. Calcium/calmodulin-dependent protein kinase II (CaM-KII): A biochemical bridge linking accumbens dopamine and glutamate systems in cocaine seeking. *Nature Neurosci* 2008; 11:344-53.
- Preet A, Ganju RK, Groopman JE. Δ^9 -Tetrahydrocannabinol inhibits epithelial growth factor-induced lung cancer cell migration *in vitro* as well as its growth and metastasis *in vivo*. *Oncogene* 2008; 27:339-46.
- Tischkowitz M, Hamel N, Carvalho MA, Birrane G, Soni A, van Beers EH, Joosse SA, Wong N, Novak D, Quenneville LA, Grist S, kConFab Investigators, Nederlof PM, Goldgar DE, Tavtigian SV, Monteiro ANA, Ladas JAA, Foulkes WD. Pathogenicity of the BRCA1 missense variant M1775K is determined by the disruption of the BRCT phosphopeptide-binding pocket: a multi-modal approach. *Eur J Hum Genet* 2008; 16:820-32.