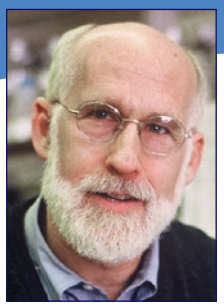
Division of Experimental Medicine



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 40 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 continues to make progress evaluating the pathogenesis of Kaposi's sarcoma. They evaluated the role of the G protein coupled receptor (GPCR) in transformation, and found an interaction between the Kaposi's sarcoma-associated herpesvirus GPCR and an important physiological GPCR, the cannabinoid receptor type 2 (CB2). Moreover, with Dr. Hava Avraham, they observed in murine models that cannabinoids could mobilize hematopoietic progenitors from the marrow into the circulation.

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.

Hava Avraham, PhD, studies the role of Src kinases in Neu-induced tumorigenesis. Amplification of the HER-2/neu (ErbB-2) gene is observed in approximately 30% of human breast cancers, correlating with a poor clinical prognosis. Src kinases are also involved in the etiology of breast cancer, and their activation

Research Funding • AY'07

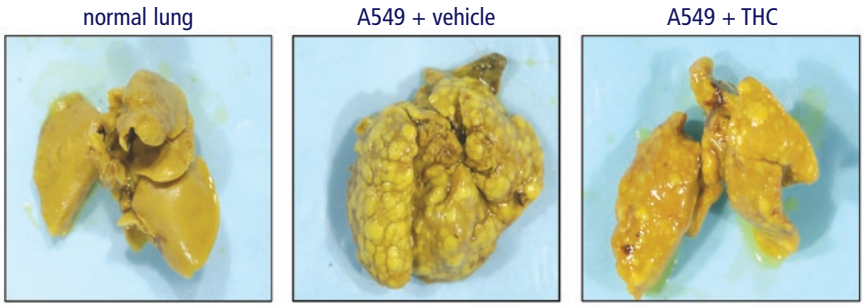
Federal Direct	1,654,610
Federal Indirect	1,159,487
Other Direct	1,935,331
Other Indirect	2,005

was suggested to be necessary for Neu-induced oncogenesis. Blocking Neu-induced Src activity without altering Src expression levels had no significant effects on Neu-mediated mammary tumorigenesis *in vivo*. This contradicts the current paradigm that activation of Src kinases is essential for Neu-induced oncogenesis.

Shalom Avraham, MD, PhD, 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 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.



Tetrahydrocannabinal (THC) treatment inhibits the metastases of lung tumors in SCID mice. A549 lung cancer cells were injected intravenously into immunodeficient SCID mice. Experimental mice were given THC (5 mg/kg body weight) daily for 28 days. THC-treated mice showed significantly reduced metastatic lesions.

Ramesh Ganju, PhD, is defining and elucidating novel HIV-induced and CXCR4/CCR5-mediated apoptotic signaling mechanisms in primary cells isolated from healthy and HIV-infected individuals, and determining how these signaling cascades could be altered to prevent the loss of immune cells during HIV infection. In addition, the chemokine receptor CXCR4 and its ligand CXCL12 play a critical role in breast cancer metastasis. The Ganju laboratory is defining novel signaling pathways mediated by CXCR4 that regulate the CXCL12-induced chemotaxis, chemoinvasion, and adhesion of breast cancer cells, and developing innovative strategies to block the CXCR4-mediated metastasis of breast cancer cells.

Dr. John Ladias' laboratory uses techniques of structural biology to answer several biological questions. The cystic fibrosis transmembrane conductance regulator (CFTR) is an ATP-regulated chloride channel that determines the rate of electrolyte and fluid transport in the apical membrane of epithelial cells. One project focuses on the structural analysis of cytoplasmic CFTR domains and their complexes with regulatory proteins, using X-ray crystallography and NMR spectroscopy. A second focuses on the structural analysis of the common human subunits of RNA polymerases and the elucidation of their roles in the molecular architecture and function of human RNA polymerase II.

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.

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. Jerome Groopman received the 2006 Victor Cohn Prize for Excellence in Medical Science Reporting by the Council for the Advancement of Science Writing for his articles in *The New Yorker* magazine that combine sensitivity to patients' concerns with a thoughtful analysis of issues and controversies in medicine.

Faculty

Hava Avraham, PhD

Shalom Avraham, MD, PhD

Ramesh Ganju, PhD

Jerome Groopman, MD

John Ladias, MD

Huchun Li, PhD

In-Woo Park, PhD

Seyha Seng, PhD

Ernest Tewilliger, PhD

Radoslaw Zagozdzon, MD, PhD

Xuefeng Zhang, PhD

Selected Publications

Anand AR, Ganju RK. HIV gp120-mediated apoptosis of T-cells is regulated by membrane tyrosine phosphatase CD45. *J Biol Chem* 2006; 281:12289-12299.

Tfelt-Hansen J, Hansen JL, Smajilovic S, Terwilliger EF, Haunso S, Sheikh SP. The calcium receptor is functionally expressed in rat neonatal ventricular cardiomyocytes. *Am J Physiol Heart Circ Physiol* 2006; 290:H1165-1171.

Lee BC, Avraham S, Immamoto A, Avraham HK. Identification of the nonreceptor tyrosine kinase MATK/CHK as an essential regulator of immune cells using Matk/CHK-deficient mice. *Blood* 2006; 108:904-907.

Lee TH, Seng S, Avraham H, Li H, Kennel S, Avraham S. Regulation of integrin expression and activation by VEGF in human brain microvascular endothelial cell: Role of alpha6 in angiogenesis. *J Biol Chem* 2006; 281:40450-40460.

Tiburu EK, Karp ES, Birrane G, Strupp JO, Chu S, Lorigan GA, Avraham S, Avraham H. 31P and 2H relaxation studies of helix VII and the cytoplasmic helix of the human cannabinoid receptors utilizing solid-state NMR techniques. *Biochemistry* 2006; 45:7356-7365.

Lee T, Seng S, Sekine M, Hinton C, Fu Y, Avraham HK, Avraham S. Vascular endothelial growth factor mediates intracrine survival in human breast carcinoma cells through internally expressed VEGFR-1/Flt-1. *PLoS Med* 2007; 4:e186.

Jiang S, Seng S, Avraham HK, Avraham S. Process elongation of oligodendrocytes is promoted by the kelch-related protein MRP2/KLHL1. *J Biol Chem* 2007; 282:12319-12329.

Park IW, Reddy MVR, Reddy EP, Groopman JE. Evaluation of novel cell cycle inhibitors in mantle cell lymphoma. *Oncogene* 2007; 26:5635-42.

Baek K, Brown RS, Birrane G, Ladias JAA. Crystal structure of human cyclin K, a positive regulator of cyclin-dependent kinase 9. *J Mol Biol* 2007; 366:563-573.

Birrane G, Varma AK, Soni A, Ladias JAA. Crystal structure of the BARD1 BRCT domains. *Biochemistry* 2007, June 6, epub before print.