Overview

The cancer therapeutics program in the Division of Clinical Pharmacology, Department of Medicine at Brown University and Rhode Island Hospital is bridging the gap between the research laboratory and the cancer patient. During the last two years our group of dedicated laboratory and clinical scientists have made significant strides in understanding the cellular basis of cancer, elucidating biochemical and molecular differences between normal and neoplastic cells, and improving the treatment options for patients with cancer.

Our cell biology group has gained insights into the molecular differences between normal and cancer cells that govern their responsiveness to anticancer therapy. For example, we have found that certain breast cancer cells produce a protein on their surface, designated GPR-30, that is capable of binding anti-estrogen drugs, such as tamoxifen, and subsequently inducing tumor growth. Studies are underway to define and identify the specific cell-signaling pathway(s) involved in this process as well as correlate the presence of this protein with lack of response to therapy. In parallel studies, our drug discovery group is designing and evaluating novel agents capable of specifically disabling GPR-30 and potentially improving the efficacy of tamoxifen-based therapy for breast cancer.

In a different disease model, our cell and molecular biologists have found that hormone-insensitive prostate cancer cells also express a protein, Raf kinase inhibitory protein (RKIP) that appears to be predictive for the effectiveness of camptothecin-based therapy. The expression of this protein also correlates with the sensitivity of colon cancer, mesothelioma and glioblastoma cells to camptothecin-based combinations. These studies have been expanded clinically where our group is participating, along with several Harvard-affiliated hospitals, in a multi-center Phase I/II clinical analysis of a novel, orally active, camptothecin analogue (gimatecan) in the United States. Results of these studies will be valuable in the future design of more effective cancer therapies.

Molecular biologists in our Division also are studying in detail the cell signaling interactions between competing apoptotic and survival/proliferation pathways. These scientists have found several, previously unappreciated, co-regulatory interactions between receptor-mediated cell death processes (ie. Fas) and cytokine-based proliferative pathways. Since the control of tumor cell apoptotic is the ultimate goal of therapy, it is anticipated that continued research to elucidate the interplay between the competing processes in cancer cells will lead to novel insights into methods to treat various forms of human cancer.

Our drug discovery group has identified a new chemotherapeutic agent, taurolidine, that is less toxic to normal cells and tissues but capable of specifically and rapidly killing cancer cells by inducing mitochondrial-mediated apoptosis. Clinically, we completed several clinical trials, in patients with advanced ovarian cancer and malignant brain tumors, and have obtained promising results.
Information from these early trials is being used to refine therapy delivery methods for future use in patients with cancer. At the same time, we are designing and evaluating novel analogues of taurolidine with the goal of increasing its cancer cell killing activity and chemical stability. Of interest, we have also recently observed that the combination of taurolidine and gimatecan may hold promise in the treatment of mesothelioma. A cooperative research and clinical program, with centers at Rhode Island Hospital, Columbia University, and Mount Sinai Hospital in New is being formed to expedite the laboratory and clinical studies to validate this clinical use. We also are using this same group of novel chemotherapeutic drugs to develop a novel method to ‘purge’ tumor cells from marrow or peripheral blood in cancer patients by specifically inducing tumor cell apoptosis. This ‘purged’ material can then be used in marrow transplant procedures after high dose chemotherapy to treat advanced cancers.

Funding for this research has been obtained from the U.S. government, private foundations and the pharmaceutical industry, including the T.J. Martell Foundation, the PhRMA Foundation, the American Cancer Society, the Department of Defense, and several pharmaceutical companies.

Faculty Members

**FULL-TIME FACULTY**

(Hospital and Foundation Based)

Paul Calabresi, M.D., Professor, Rhode Island Hospital, University Medicine Foundation

Devasis Chatterjee, Ph.D., Assistant Professor (Research), Rhode Island Hospital

James Darnowski, Ph.D., Associate Professor (Research), Rhode Island Hospital

Edward Filardo, Ph.D., Assistant Professor (Research), Rhode Island Hospital

Bai-Chuan Pan, Ph.D., Professor (Research), Rhode Island Hospital

Ming Chu, Ph.D., Professor Emeritus (Research), Rhode Island Hospital

**ADJUNCT FACULTY**

Wolfgang Oster, M.D., Adjunct Professor, Rhode Island Hospital

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National and International Honors and Recognition of Faculty

**Paul Calabresi, M.D., MACP**

- Laurea Honoris Causa (Honorary Degree in Medicine), University of Naples School of Medicine
- Distinguished Alumni Service Award, Association of Yale Alumni in Medicine
- Dedication of The Paul Calabresi Conference Room, Yale Cancer Center

**Invited presentations:**

- Keynote Speaker, 6th National Meeting of G.O.I.M., “Dalla Biologia Molecolare all’Accreditamento di Eccellenza” Naples, Italy
- Invited Lecture (Letta Magistrale), Gruppo Italiano per lo Studio e la Terapia del Mesotelioma Maligno (G.I.M.E.), Stresa, Italy
- Scientific presentation, “Antineoplastic effects of ST1481, a novel camptothecin, on human malignant mesothelioma” American Association for Cancer Research (AACR), San Francisco, CA
- Member and Past Chairman (1995), Board of Directors, New England Cancer Society
- Member, National Board of Trustees, Leukemia & Lymphoma Society
- Member, Board of Overseers, Tufts University School of Medicine
- Member, Board of Overseers, E. Bronson Ingram Center, Vanderbilt University, Nashville, TN
- Member, Editorial Board, Critical Reviews in Oncology/Hematology
- Guest Editor, Medicine and Health in Rhode Island
- Reviewer and former Member of the Editorial Board, New England Journal of Medicine
- North American Editor, International Journal of Multidisciplinary Oncology

**Devasis Chatterjee, Ph.D.**

- Member, American Association for Cancer research

**Invited presentations:**

- “Camptothecins as regulators of the FLIP-side of apoptosis,” T.J. Martell Foundation Research Symposium, October 2001


Ming Chu, Ph.D.
• Member, Biohazards and Laboratory Safety Committee, Rhode Island Hospital

James W. Darnowski, Ph.D.
• Member, CET-3 Study Section, Department of Defense Breast Cancer Research Program

Ad hoc reviewer:
• Cancer Research
• Biochemical Pharmacology
• Molecular Pharmacology
• Cancer
• Oncology Research
• Journal of the National Cancer Institute
• Leukemia Research
• Journal of Clinical Oncology
• Canadian National Cancer Institute

Invited presentations:
• “Therapeutic control of cell survival and apoptosis,” T.J. Martell Foundation for Cancer Research, October 2001
• “Taurolidine triggers receptor-mediated apoptosis in DU145 human prostate tumor cells,” Annual Meeting of the American Association for Cancer Research, April 2002
• “DU145 human prostate tumor cells undergo apoptosis following exposure to taurolidine,” Annual meeting of the New England Cancer Society, November 2001
• “STAT proteins are a target of caspase-mediated cleavage during staurosporin-induced apoptosis in the DU145 human prostate tumor cell model”, Annual Meeting of the American Association for Cancer Research, July 2003

Edward J. Filardo, Ph.D.
• Career Development Award, Department of Defense
• Consultant, Proctor and Gamble Pharmaceuticals

Ad hoc reviewer:
• Breast Cancer Research & Treatment
• Cancer Research
• FASEB

• Journal of Steroid Biochemistry & Molecular Biology
• Trends in Endocrinology & Metabolism Endocrinology
• European Journal of Biochemistry

Invited presentations:
• “GPR30: a novel estrogen receptor that promotes second messenger signaling as well as EGF-like effects in breast carcinoma cells,” Annual meeting of the New England Cancer Society, Nov. 2001
• “The search for membrane-associated steroid hormone receptors: rapid estrogen signaling via the orphan G-protein-coupled receptor, GPR30,” Divisions of Cardiovascular and Bone Metabolism Research, Procter and Gamble Pharmaceuticals, February 2002
• “Expression of GPR-30 in human tissues”, Divisions of Cardiovascular and Bone Metabolism Research, Procter and Gamble Pharmaceuticals, October 2002

Linda Nici, M.D.
• Writing Committee Member, Guideline for Pulmonary Rehabilitation Programs, American Society of Cardiovascular & Pulmonary Rehabilitation
• President, Board of Directors, Occupational and Environmental Center of RI
• Co-chair, American Thoracic Society on Pulmonary Rehabilitation
• Member, Task Force on Women & Girls, Tobacco & Lung Cancer, American College of Chest Physicians

Ad hoc reviewer:
• American Journal of Physiology: Lung Cellular & Molecular Physiology
• American Journal of Respiratory and Critical Care Medicine
• European Respiratory Journal – Cancer American Journal of Pathology

Invited Presentations:
• Keynote speaker, “Lung Disease, State of the Nation,” RI Nurses’ Alumni Annual Meeting, April 2002
Bai-Chuan Pan, Ph.D.
- Academic Consultant to the Shanghai Institute of Materia Medica, Academy of Sciences
- Chinese Academy of Science Prizes – First Class
- Chinese National Natural Science Prizes – Second Class
- Chinese National Natural Science Prizes – Third Class

Editorial boards:
- Acta Chimica Sinica (Journal of the Chinese Chemical Society)
- Scientia Sinica (Sciences in China)
- Kexue Tongbao (Communication of Sciences)

Research and Other Scholarly Activities

Faculty Members of Study Sections and Advisory Committees

Paul Calabresi, M.D., MACP
- Member, Scientific Advisory Board, Carter-Wallace, Inc.
- Chairman (1998-2001), Scientific Advisory Committee, Columbia University Comprehensive Cancer Center
- Chairman, Scientific Advisory Committee, TJ Martell Foundation
- Chairman, Clinical Pharmacology Advisory Committee, Pharmaceutical Manufacturers’ Association Foundation (PhRMA)
- Member, Steering Committee, National Dialogue on Cancer, Washington, D.C., Appointed by President George and Mrs. Barbara Bush
- Chairman, External Review Committee for the University of Wisconsin, Comprehensive Cancer Center
- Chairman, Director’s Advisory Board, Yale University Comprehensive Cancer Center, New Haven, CT
- Member, Scientific Advisory Board, Yale University Comprehensive Cancer Center, New Haven, CT
- President, Rhode Island Cancer Council, Appointed by Governor Lincoln Almond
- Member, Brown University Oncology Group (BrUOG)
- Chairman of Novel Agents Committee
- Member, Data Safety Monitoring Board
- Member, Lifespan Research Advisory Committee
- Member, Lifespan Cancer Committee
- Chairman, Institutional Review Board, Human Genome Project, Celera Genomics Corp.
- Member, National Cancer Legislation Advisory Committee Washington, DC — Appointed by President George Bush and Senator Diane Feinstein
- President, International Society for Geriatric Oncology
- Chairman, Scientific Advisory Board, Instituto Nazionale Tumori, Naples, Italy
- Member, Scientific Advisory Board, Alberta (Canada) Cancer Board
- Member, Diagnostic Advisory Board, Burrill & Co.
- Member, Experimental Therapeutics Program, Dana-Farber/Harvard Cancer Center

Teaching Activities

Teaching Responsibilities

Paul Calabresi, M.D., MACP
- Attending Rounds, Massachusetts General Hospital
- Faculty/Counselor to Brown/Dartmouth advanced transfer medical students: Wendy Gray, Allison Goldkamp, Julia Frew and Hannah Famiglietti
- Faculty, Visiting Research Fellows: Roberta Sarmiento and Andrea Sartore-Bianchi
- Faculty & Research Advisor, Paul Martin, M.D., First Year Resident, Brown Medical School
- Devasis Chatterjee, Ph.D.
  - Assisted Andrea Bianchi-Sartore, M.D., clinical research Fellow, with his research on the “Regulation of apoptosis in human colon and mesothelioma cells by RKIP”
- James W. Darnowski, Ph.D.
  - Faculty Leader, International Medical Fellow Research Group
    2001-2002 Roberta Sarmiento
    2002-2003 Andrea Bianchi
  - Mentor & Research Advisor, Arshad Asnudian, M.D., Candidate for MS/MD Degree, Brown Medical School
- Edward J. Filardo, Ph.D.
  - Research Mentor, 2001-2003 Jeffrey A. Quinn, MS
- Lisa Nici, M.D.
  - Faculty Leader, Affinity Group Prog. (Biomed 0551)
  - Co-Facilitator, Workshop on Racial Diversity
  - Lecturer, University of Rhode Island – PharmD Program Foundations of Human Disease (PHP/BMS 409)
  - Attending Physician, General Medicine Service, RIH and RISE Clinic The Miriam Hospital
PUBLICATIONS

Paul Calabresi, M.D.

• Calabresi, P., Goulette, FA and Darnowski, JW. 
  Taurolidine: cytotoxic and mechanistic evaluation of a novel antineoplastic agent. 

• Nici, L., Monfils, B and Calabresi, P. 
  Modulation of Bleomycin-induced Pulmonary Toxicity in the Hamster by L-Carnitine, 

• Shroyer, DP, Lukoff, H, King, T and Calabresi, P. 
  The effect of taurolidine on adherent and floating subpopulations of melanoma cells. 

• Graeber, CT, Quinn, JA, Kim, D, Steinhoff, MM, 
  Calabresi, P and Filardo, FJ. Estrogen receptor, Era and GPR30, a heptahelical receptor 
  that promotes the EGF-like effects of estrogen possess different tissue expression patterns. 
  Manuscript in preparation.

• Graeber, CT, Quinn, JA, Kim, D, Steinhoff, MM, 
  Calabresi, P and Filardo, FJ. Expression of GPR30, a G-protein-coupled receptor that 
  promotes the EGF-like effects of estrogen, in normal mammary epithelia and invasive mammary carcinoma. 
  Manuscript in preparation.

Devasis Chatterjee, Ph.D.

• Mukhopadhay, A., Bueso-Ramos, C., Chatterjee, D., 
  Pantazis, P., and Aggarwal, BB. Curcumin downregulates cell survival mechanism in human prostate 

• Urasaki, Y., Laco, GS., Pourquier, YP., Takebayashi, K., 
  Kohlhaagen, G., Gioffre, C., Chatterjee, D., Pantazis, P. and Pommier, Y. Characterization of a novel 
  topoisomerase I mutation from a camptothecin resistant prostate cancer cell line. 

• Chatterjee, D., Schmitz, I., Yeung, K., Krueger, A., 
  Kirchoff, S., Krammer, PH., Peter, ME., Wyche, JH. and Pantazis, P. Induction of apoptosis in 9-
  nitrocamptothecin-treated DU145 human prostate carcinoma cells correlates with de novo synthesis of 

• Yeung, KC., Rose, DW., Dhillon, A., Yaros, D., 
  Gustafsson, M., Chatterjee, D., McFerran, B., Wyche, J., Kolch., and Sedivy, JM. RKIP interacts with NIK 

• Chatterjee, D., Braastad, C., Darnowski, J., Pantazis, P., 
  Wyche, J., Sedivy, JM. and Yeung, KC. RKIP inhibits multiple cell signaling pathways and induces 

• Chatterjee, D., Goldman, M., Braastad, CD., Darnowski, J., 
  Wyche, JH., Pantazis, P. and Goodllick, L. Reduction of 9-nitrocamptothecin triggered apoptosis in DU145 

James Darnowski, Ph.D.

• Han, Z., Ribizzi, I., Darnowski, J., Pantazis, P., Wyche, JH. and Calabresi, P. 
  The novel antineoplastic drug Taurolidine induces apoptosis by a mitochondrial-dependent mechanism in the HL60 cell line. 

• Ribizzi, I., Darnowski, JW., Goulette, FA., Akhtar, MS., 
  Chatterjee, D. and Calabresi, P. Taurolidine: preclinical evaluation of a novel, highly selective, agent for bone 

• Han, Z., Wei, W., Dunaway, S., Darnowski, JW., Calabresi, P., 
  Sedivy, J., Hendrickson, EA., Balan, KV., Pantazis, P. and Wyche, JH. Role of p21 in apoptosis and senescence of human colon cancer cells treated with 

• Whartenby, KA., Darnowski, JW., Freeman, SM. and 
  Calabresi, P. A role for MAP kinase in the antitumor activity of a nucleoside analogue. Cancer Gene 

• Allegrini, G., Goulette, FA., Darnowski, JW. and 
  Calabresi, P. Thrombosphondin-1 plus irinotecan: a novel angiogenic-chemotherapeutic combination that inhibits the growth of advanced human colon 

• Darnowski, JW., Goulette, FA., Chatterjee, D., Cousens, LP. and 
  Calabresi, P. Mechanistic and antineoplastic evaluation of Taurolidine in the DU145 model of 

• Ribizzi, I., Darnowski, JW., Goulette, FA., Akhtar, MS. and 
  Calabresi, P. Synergistic cytotoxicity of azidothymidine (AZT) plus interferon-alpha2a (IFN) in 
  a human myelodysplastic syndrome cell line. Manuscript in preparation.

• Davol, PA., Goulette, FA., Frackelton, AR Jr. and 
  Darnowski, JW. Association of p53 protein with DNA polymerase beta: disruption by recombinant 

• Cousens, LP., Goulette, FA., Calabresi, P. and Darnowski, JW. 
  IFNa-stimulated signaling inhibits Fas ligand-induced apoptosis. Manuscript in preparation.

• Goulette, FA., Cousens, LP., Chatterjee, D., Braastad, C. and 
  Darnowski, JW. STAT protein expression is reduced in a caspase-dependent manner during staurosporine 
  induced apoptosis in the DU145 human prostate tumor cell model. Biochemical Pharmacol., submitted.
Edward Filardo, Ph.D.

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BASIC RESEARCH

Paul Calabresi, M.D.
• T.J. Martell - Administrative, T.J. Martell Foundation
• Assessment of the Potential Antineoplastic Activity of Taurodoline, Carter-Wallace Incorporated
• Modulation of Bleomycin Lung Injury by l-carnitine, Sigma Tau
• Evaluation of Taurodoline Pharmacokinetics, Carter-Wallace, Incorporated
• Assessment of the Antineoplastic Activity of ST1481 in Human Malignant Mesothelioma, Sigma Pharmaceutical Incorporated
• Analysis of the In Vitro Cytotoxic and In Vivo Antineoplastic Activity of ST184, Sigma-Tau Pharmaceuticals, Incorporated
• Assessment of Taurodoline Activity in In Vitro and Murine Models of Pancreatic Cancer and Melanoma, Carter-Wallace, Incorporated
• Assessment of Taurodoline Activity in In Vitro and Murine Models of Carcinoma of the Lung and Mesothelioma, Carter-Wallace, Incorporated
• Assessment of Taurodoline Activity in In Vitro and Murine Models of Carcinoma of the Breast, Carter-Wallace, Incorporated
• Assessment of Taurodoline Activity in In Vitro and Murine Models of Human Ovarian and Brain Cancer, Carter-Wallace, Incorporated
• Assessment of Taurodoline Activity in In Vitro and Murine Models of Prostate Cancer and Colon Cancer, Carter-Wallace, Incorporated
• Assessment of Taurodoline Activity in In Vitro and Murine Models of Leukemias, Lymphomas and Marrow-, Carter-Wallace, Incorporated

• Amifostine Cytotoxicity in a Human Myelodysplastic Cell Line, Pharmaceutical Research and Manufacturers of America Foundation, Inc

Devasis Chatterje, Ph.D.
• Regulation of Apoptosis in Human Prostate Cancer Cells by the Expression of RKIP, Lifespan

James Darnowski, Ph.D.
• Preclinical Studies of Taxotere and Ionizing Radiation in an Androgen-Sensitive and Androgen-Insensitive, Aventis Pharmaceuticals Products, Incorporated
• Development of Novel Therapies for Human Prostate Cancer, T.J. Martell Foundation

Edward Filardo, Ph.D.
• Estrogen Signaling Via GPR30, American Cancer Society
• Evaluating of GPR30, a Novel Estrogen Receptor for Assessing Responsiveness to Anti-estrogen Therapy, US Department of Defense-Army

CLINICAL RESEARCH

Paul Calabresi, M.D.
• Evaluation of Serum l-Carnitine in Cancer Patients: A Descriptive Study, Sigma-Tau Pharmaceuticals, Incorporated, An Open Label Study of the Safety and Efficacy of Taurodoline 2% Solution Administered Intravenously, Carter-Wallace Incorporated
• An Open Label Study of the Safety and Efficacy of Taurodoline 0.5% Electrolyte Solution Administered Intravenously, Carter-Wallace Incorporated