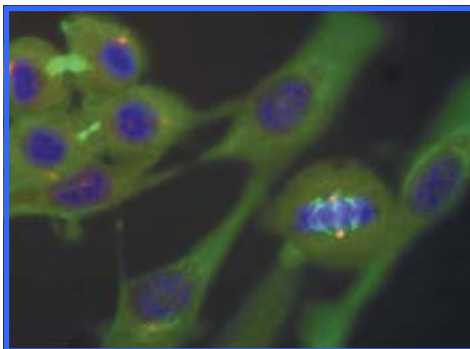




Vascular Biology Initiates a Program in the Cell and Molecular Biology of Cancer

The Vascular Biology Center of Excellence has begun a new initiative in the cell and molecular biology of cancer that is aimed toward understanding signal transduction processes and aberrant gene expression in cancer cells. Results of these studies will aid in the development of tumor models which will infinitely advance research in this area. A principal emphasis relates broadly to an understanding of molecular and cellular processes that control normal cell adhesion and cell growth that are altered in tumor cell processes. More specifically, the Center is focused on what regulates the control of cell adhesion and motility as well as cell cycle and cell death.



The goal of this program is to discover prognostic tumor markers that may translate into novel therapeutic strategies that are less toxic and yet more effective. Model systems of breast and prostate cancer cell lines are in use, as well as mouse models that gauge metastatic potential of implanted primary tumors. Vascular Biology Collaborators to date include: Drs. Xin Zhang, Yi Lu, Celia Longhurst, Jeffrey Gingrich, Lisa K. Jennings, Lawrence Pfeffer, Lee Schwartzberg (The West Clinic) and Bruce Webber (Trumbull Laboratories). It is anticipated that many of the initiatives will serve as a cornerstone of the newly established University of Tennessee Boston Baskin Cancer Institute.

The tetraspanin superfamily of proteins provides a primary target for the regulation of cancer metastasis. The tetraspanin CD9 is expressed on several cell types including developing B cells and endothelial cells and platelets. Expression of CD9 has an inverse relationship to the metastatic potential of several cancers. Dr. Celia Longhurst is using the B cell Raji line as a human model system to study the mechanisms of CD9-promoted cell growth and motility. CD9 plays a role in the adhesion of pre-B cells to the bone marrow stroma during development. CD9 is expressed on pre-B cell leukemias and may modulate the growth, survival and dissemination of leukemia cells.

Dr. Jennings in collaboration with Drs. Schwartzberg and Webber, will examine cell lines and fresh tumor samples from patients with breast cancer will be examined. They seek to better characterize factors necessary for breast cancer differentiation, progression and metastasis. Understanding the role of CD9 in regulating metastases could lead to the development of novel therapeutic strategies specifically targeted at this protein. Recent success in this area has been encouraging and supports the concept of less toxic therapies that are rationally designed to inhibit or promote specific critical cellular pathways responsible for malignant behavior.

Dr. Yi Lu is focusing on tumor angiogene-

(Continued on page 2)

In This Issue:

Cancer Initiative	1
Honors	2
Leonard Share Award	3
Research Grants	3
Collaboration Dinner	3
Journal Club	4
Manuscripts	4
TAM Consortium	4

Program Advisory Board:

Timothy Fabian, M.D.
Marshall B. Elam, M.D., Ph.D.
Gadiparthi Rao, Ph.D.
KU Malik, Ph.D., D. Sc.
Charles W. Leffler, Ph.D.
Alan Mast, M.D., Ph.D.
Tarun B. Patel, Ph.D.
Chunxiang Zhang, M.D., Ph.D.
Lawrence Pfeffer, Ph.D.
Rajendra Raghov, Ph.D.
Lee Schwartzberg, M.D.
Xin Zhang, M.D., Ph.D.

Associate Directors:

Aviv Hassid, Ph.D.
William Pulsinelli, M.D., Ph.D.

Vascular Biology
Center of
Excellence
Key Collaborative
Initiatives

Graduate Education

Training Programs

Recruitment of Faculty

Incentives for
Existing Faculty

TAM Cardiovascular
Research Consortium

Symposia and
Specialized Programs

Shared Research
Facilities

The Vascular Biology
Center of Excellence

956 Court Ave

Coleman, H300

Memphis, TN 38163

FAX (901)448-7181

Phone (901)448-5067

Center Director

Lisa K. Jennings, Ph.D.

Assistant to the Director

Cori Grant, M.S.

TAM Associate Director

Mary Jacoski, M.S.

Center Coordinator

Peggy McKnight, M.S.

Sr. Admin. Assistant

Charlett Golden

(Continued from page 1)

sis. Vascular endothelial growth factor (VEGF) plays a pivotal role in tumor angiogenesis. Tumor suppressor gene p16 is a cyclin-dependent kinase inhibitor and a negative cell cycle regulator. Dr. Lu is studying the effect of p16 overexpression in human breast cancer cells and the relationship of p16 to downregulation of VEGF expression and suppression of tumor cell angiogenesis. Studies underway in Dr. Lu's lab have shown that adenoviral-mediated overexpression of p16 decreased VEGF levels in human breast cancer MDA-MB-231 cells. Other recent studies using nude mice have suggested that p16 downregulates VEGF gene expression, suppresses angiogenesis and metastasis in breast cancer cells. Dr. Lu is collaborating with St. Jude Children's Research Hospital faculty member, Dr. Andy Davidoff.

Other studies in the Center initiative have been proposed or are underway which hypothesize different mechanisms for prostate tumor metastasis. For example, Xin Zhang, M.D., Ph.D. is studying KAI1/

CD82, a member of the tetraspanin superfamily that has been identified as a metastasis suppressor in many cancers. Similar to other tetraspanins, KAI1/CD82 has been reported to regulate cell migration and cancer cell invasiveness. To date, Dr. Zhang's studies show that restoration of the KAI1/CD82 expression in prostate cancer cells inhibits cell motility. Additionally he has found that the signaling molecules p130^{CAS} and paxillin are required for KAI1/CD82-mediated suppression of prostate cancer cell motility, KAI1/CD82 disrupts the formation of focal adhesion (a motility-related subcellular structure) and KASP (a novel Ig superfamily protein) associates with KAI1/CD82, and the association is likely functionally meaningful. Thus, Dr. Zhang hypothesizes that the KAI1/CD82-mediated suppression of cancer metastasis depends on its inhibition of cell motility through regulating the intracellular signaling pathways that control cell movement.

Vascular Biology Honors

Yi Lu, Ph.D. — AAPS Meritorious Manuscript Award, American Association of Pharmaceutical Scientists. "Creation of Polarized Cells Coexpressing CYP3A4, NADPH Cytochrome P450 Reductase and MDR1/P-Glycoprotein." 2002.

Yi Lu, Ph.D. — Invited speaker, Jenapharm Pharmaceutical Company, Schering GmbH&Co. "Prostate Cancer Gene Therapy Using Recombinant Adenovirus Expressing a Novel Apoptosis-Inducing Gene." Berlin, Germany. April, 2002.

K.U. Malik, Ph.D. — Invited Speaker, University of Medicine and Dentistry of New Jersey. "Signaling mechanisms involved in eicosanoid synthesis: Implications in vascular smooth muscle cell growth and hypertension." Stratford, New Jersey.

K.U. Malik, Ph.D. — Invited Speaker, College of Medicine, Louisiana State University. "Contribution of eicosanoids to vascular smooth muscle cell signaling, hyperplasia and hypertrophy and hypertension." New Orleans, LA.

Hiroko Nishimura, Ph.D. — Invited Speaker, Angiotensin Gordon Research Conference. "Maturation-dependent modulation of angiotensin receptors: a unique avian model." Barga, Italy.

Svetozar Grgurevich, Ph.D. — Poster Presentation. "The effects of in vitro cholesterol-lowering on collagen induced platelet secretion." 9th Midwest Platelet and Vascular Biology Conference. St Louis, MO. October, 2002

Lisa K. Jennings, Ph.D. — Member, Oak Ridge National Laboratory Science and Technology Review Committee, 2002.

Rao Gadiparthi, Ph.D. — Ad-hoc member, Experimental Cardiovascular Sciences Study Section, NIH.

Lisa K. Jennings, Ph.D. — Ad-hoc member, Program Project Grant Study Section, NIH/NHLBI.

2002 Leonard Share Young Investigator Award

Jean-Hugues Parmentier, Ph.D. a collaborator with the Vascular Biology Center is this year's recipient of the 2002 Leonard Share Young Investigator Award. The award, presented in conjunction with the E. Eric Muirhead Hypertension Research Day, recognizes outstanding research in the area of cardiovascular-renal disease by professional students and trainees at UTHSC and affiliated institutions. Dr. Parmentier received a plaque and a \$2000 stipend to be used as a travel award or for professional advancement. He won the award for his research project entitled "Functional Significance of Protein Kinase C zeta and Phospholipase D in Vascular Smooth Muscle Cells: Implica-

tions for Vascular Wall Growth and Remodeling Induced by Norepinephrine and Angiotensin II."

Dr. Parmentier joined Dr. K.U. Malik's laboratory as a postdoctoral research trainee in 1996 after receiving his Ph.D. from the University of Henri Poincare, Nancy, France and the University of Liege, Belgium. His research focus is the signaling pathway which regulates PKC zeta and PLD activation in aortic VSMC. Specifically, he is using pharmacological inhibitors, oligonucleotide antisense and ectopic expression of dominant negative mutants in response to angiotensin II and norepinephrine.

Findings from this research, may lead to a greater understanding of the biology of restinosis.



Drs. Share and Parmentier during the award presentation

Research Grants Awarded to VBCE

Rao Gadiparthi, Ph.D. National Institutes of Health. NFATs and Vascular Injury. 04/01/02 - 02/28/06. 1,179,750.

Marshall Elam, M.D., Ph.D. American Heart Association. Regulation of the SREBP-1c Promoter by Insulin and cAMP. 07/01/02 - 06/30/04. 77,000.

Fang Li, Ph.D. American Heart Association. Contribution of Phospholipase D to Angiotensin II-induced protein Kinase B activation and Vascular Smooth Muscle Cell. 07/01/02 - 06/30/04. 36,000.

Hiroko Nishimura, Ph.D. American Heart Association. Urine concentration and aquaporin water channels: unique avian models. 07/01/02-06/30/03. 154,000.

Vascular Biology Center Annual Collaboration Dinner

The Vascular Biology Center held its Annual Collaborating Faculty Dinner and Board Meeting at The Racquet Club of Memphis on September 17, 2002. The annual dinner is designed to bring the advisory board and collaborating faculty together for an informal evening to discuss current and future shared areas of research. This year's dinner was attended by more than 30 board members, faculty and staff of the Center of Excellence.

The Vascular Biology Center board is composed of a wide variety of campus and communal professionals including MDs and PhDs with varied research interests in the area of Vascular Biology. During the meeting, the fourteen members of the board received and critiqued information regarding current Center activities and

provided valuable guidance for development of new initiatives.

"Because vascular biology is such a broad area of research it is extremely important to bring investigators from departments across the campus together to discuss possible collaborations. These collaborations will someday advance medical science in critical areas not often thought to be related to vascular biology such as cancer and infertility" remarked Dr. Celia Longhurst, an Assistant Professor in the Department of Medicine.

Center affiliated faculty currently conduct research in the areas of cell adhesion, spreading and motility; blood lipids and their role in atherogenesis; bone proteins and growth factors; and coagulation factor (regulatory and counter regulatory)

signaling pathways in cell migration.

This year's dinner was extremely successful with discussions leading to the proposal of several new initiatives. When carried through, these initiatives will expand the scope of research in the Center. They include new initiatives in vascular injury, signaling pathways of vascular cells and breast cancer which includes angiogenesis and metastasis.

Additionally, Dr. Jennings and Dr. William Pulsinelli, Chairman of Neurology and Vascular Biology Assistant Director, discussed organizing a Stroke Working Group which has since been established. This group will coordinate basic and clinical research in the area of acute stroke and secondary prevention.

Vascular Biology Data Club—Every Thursday 8:30 a.m.
Vascular Biology Journal Club — 2nd and 4th Monday of the Month 12:00
Coleman F306—for more information contact Dr. Xin Zhang (448-3448)

Select Peer-Reviewed Manuscripts by VBCE Collaborating Faculty

Structural and functional characterization of tissue factor pathway inhibitor following degradation by matrix metalloproteinase-8. Cunningham AC, Hasty KA, Enghild JJ and Mast AE. *Biochem J* 367:451-458. 2002.

Characterization of the association of tissue factor pathway inhibitor with human placenta. Mast AE, Acharya N, Malecha MJ, Hall CL and Dietzen DJ. *Arter Thromb and Vasc Biol.* In Press. 2002.

Nitric oxide-induced motility in aortic smooth muscle cells: role of protein tyrosine phosphatase SHP-2 and GTP-binding protein Rho. Chang Y, Ceacareanu B, Dixit M, Sreejayan N and Hassid A. *Circ Res* 91:390-397, 2002.

Comparison of shear-stress-induced platelet microparticle formation phosphatidylserine expression in the presence of aIIb3 antagonists. Haga JH, Slack SM and Jennings LK. *J Cardiovas Pharm.* In press. 2002.

The Second Extracellular Loop of CD9 Influences adhesion and pericellular fibronectin matrix assembly of transfected CHO cells. Cook GA, Grgurevich S and Jennings LK. *Blood.* In press. 2002.

Downregulation of a unique photoreceptor protein correlates with improper outer segment assembly. Wohabrebbi A, Umstot ES, Iannaccone A, Desiderio DM and Jablonski MM. *J Neurosci Res* 67(3): 401-15. 2002.

Both constitutive and inducible prostaglandin H synthase affect dermal wound healing in mice. Laulederkins SJ, Thompson-Jaeger S, Goorha S, Chen Q, Fu A, Rho JY, Ballou LR and Raghov R. *Lab Invest* 82(7):919-27. 2002.

The tissue-specific, compensatory expression of cyclooxygenase-1 and -2 in transgenic mice. Zhang J, Goorha S, Raghov R and Ballou LR. *Prostaglandins Other Lipid Mediat* 67(2):121-35. 2002.

Paradoxical regulation of Sp 1 transcription factor by glucagon. Keembiyehetty CN, Candelaria RP, Majumdar G, Raghov R, Martinez-Hernandez A and Solomon SS. *Endocrinology* 143(4):1512-20. 2002.

A Potential Role for Nuclear Factor of Activated T Cells in Receptor Tyrosine Kinase and G Protein-coupled Receptor Agonist-induced Cell. Yellaturu CR, Ghosh SK, Rao RK, Jennings LK, Hassid A and Rao GN. *Biochemical Journal.* In Press. 2002.

Regulation of the rat SREBP-1c promoter in primary rat hepatocytes. Deng X, Cagen Lm, Wilcox HG, Park EA, Raghov R and Elam MB. *Biochem Biophys Res Comm* 290:256-262. 2002.

Role of in-vitro cholesterol depletion in mediating human platelet aggregation. Grgurevich S and Jennings LK. *Thrombosis and Haemostasis.* In Press. 2002.

TAM Notes . . .



The TAM Network relies on its investigator database in order to determine whom to contact regarding participation in clinical trials. If you would like to update your information in the database or if you would like information on joining the TAM Network, please contact Mary V. Jacoski at 901-448-1597 or email at mjacoski@utmem.edu.



The University of Tennessee Health Science Center is an EEO/AA/Title VI/Title IX/Section 504/ADA/ADEA employer. R07-3380-001-002-03.

**For more information
 about the Vascular Biology
 Center of Excellence call
 (901) 448-4350 or visit
 us on the Web at
www.utmem.edu/vascular**