

**2000-2001
SUMMARY OF SCHOLARLY ACTIVITIES
DEPARTMENT OF PHARMACOLOGY**

I. ARTICLES PUBLISHED IN BOOKS AND JOURNALS

A. Full length published articles.

M. Azuma, K. Takahashi, T. Fukuda, Y. Ohyabu, I. Yamamoto, S. Kim, H. Iwao, S.W. Schaffer, and J. Azuma. Taurine Attenuates Hypertrophy Induced by Angiotensin II in Primary Cultured Neonatal Rat Cardiac Myocytes. *Eur. J. Pharmacol.* 403:181-188 (2000).

P. Babal, M. Ruchko, J.W. Olson, and M.N. Gillespie. Interactions Between Agmatine and Polyamine Uptake Pathways in Rat Pulmonary Artery Endothelial Cells. *Gen. Pharmacol.* 34:255-261 (2000).

P. Babal, M. Ruchko, C.C. Campbell, S.P. Gilmour, J.L. Mitchell, J.W. Olson, and M.N. Gillespie. Regulation of Ornithine Decarboxylase Activity and Polyamine Transport by Agmatine in Rat Pulmonary Artery Endothelial Cells. *J. Pharmacol. Exp. Ther.* 296:372-377 (2001).

S.W. Bailey and J.E. Ayling. Food and Vitamin Preparations Containing the Natural Isomer of Reduced Folates. US Patent 6,254,904 (2001).

S.W. Bailey and J.E. Ayling. Compositions for Human and Animal Consumption Containing Reduced Folates and Methods for Making and Using Same. US Patent 5,997,915 (2000).

G.H. Brough, S. Wu, D. Cioffi, T.M. Moore, M. Li, N. Dean, and T. Stevens. Contribution of Endogenously Expressed Trp1 to a Ca²⁺ Entry Pathway. *FASEB J.* 15:1727-1738 (2001).

R. Chen, K.S. Harrod, J.W. Olson, and M.N. Gillespie. Regulation of Gadd153 mRNA Expression by Hypoxia in Pulmonary Artery Smooth Muscle Cells. *Res. Com. Chem. Path. Pharmacol.* 108:3-14 (2000).

M. Chinkers. Protein Phosphatase 5 in Signal Transduction. *Trends Endocrinol. Metab.* 12:28-32 (2001).

W.B. Denny, D.L. Valentine, P.D. Reynolds, D.F. Smith and J.G. Scammell. Squirrel Monkey Immunophilin FKBP51 Is a Potent Inhibitor of Glucocorticoid Receptor Binding. *Endocrinology* 141:4107-4113 (2000).

V. Grishko, M. Solomon, G.L. Wilson, S.P. LeDoux, and M.N. Gillespie. Oxygen Radical-Induced Mitochondrial DNA Damage and Repair in Pulmonary Vascular Endothelial Cell Phenotypes. *Am. J. Physiol.: Lung Cell Molec. Physiol.* 280:L1300-L1308 (2001).

V. Grishko, M. Solomon, J.F. Breit, D.W. Killilea, S. P. LeDoux, G.L. Wilson, and M.N. Gillespie. Hypoxia Promotes Oxidative Base Modifications in the Pulmonary Artery Endothelial Cell VEGF Gene. *FASEB J.* 15: 1267-1269 (2001).

H. Kang, S.L. Sayner, K.L. Gross, L.C. Russell and M. Chinkers. Identification of Amino Acids in the Tetratricopeptide Repeat and C-Terminal Domains of Protein Phosphatase 5 Involved in Autoinhibition and Lipid Activation. *Biochemistry* 40:10485-10490 (2001).

R. Kumar, N. Grammatikakis, and M. Chinkers. Regulation of the Atrial Natriuretic Peptide Receptor by Heat Shock Protein 90 Complexes. *J. Biol. Chem.* 276:11371-11375 (2001).

T. Moore, N. Norwood, J. Creighton, P. Babal, G. Brough, D. Shasby, and T. Stevens. Receptor-Dependent Activation of Store-operated Calcium Entry Increases Endothelial Cell Permeability. *Am. J. Physiol.* 279:L691-L699 (2000).

N. Norwood, T.M. Moore, D. Dean, R. Bhattacharjee, J. Creighton, P. Babal, and T. Stevens. Store-operated Calcium Entry and Endothelial Cell Permeability. *Am. J. Physiol.* 279:L815-L824 (2000).

J.G. Scammell, J.L. Wright, and C.M. Tuck-Muller. The Origin of Four Squirrel Monkey Cell Lines Established by Karyotype Analysis. *Cytogenet. Cell Genet.* 93:263-264 (2001).

S.W. Schaffer, K. Takahashi, and J. Azuma. Role of Osmoregulation in the Actions of Taurine. *Amino Acids* 19:527-546 (2000).

T. Stevens, J.G.N. Garcia, D.M. Shasby, J. Bhattacharya, and A.B. Malik. Mechanisms Regulating Endothelial Cell Barrier Function. *Am. J. Physiol.* 279:L419-L422 (2000).

T. Stevens. Is There a Role for Store-Operated Calcium Entry in Vasoconstriction? *Am. J. Physiol. Lung Cell Mol. Physiol.* 280:L866-L869 (2001).

K. Takahashi, Y. Ohyabu, S.W. Schaffer, and J. Azuma. Cellular Characterization of an *In-Vitro* Cell Culture Model of Seal-Induced Cardiac Ischemia. *J. Pharm. Pharmacol.* 53:379-386 (2001).

G. Urban, T. Golden, I.V. Aragon, J.G. Scammell, N.M. Dean, and R.E. Honkanen. Identification of an Estrogen-Inducible Phosphatase (PP5) That Converts MCF-7 Human Breast Carcinoma Cells into an Estrogen-Independent Phenotype When Expressed Constitutively. *J. Biol. Chem.* 276:27638-27646 (2001).

D. Weber, R. Rustandi, and D.B. Zimmer. Interaction of Dimeric S100B($\beta\beta$) With the Tumor Suppressor Protein p53: A Model for Ca^{2+} -Dependent S100 Target Protein Interactions. IN: R. Pochet (Ed.) Calcium: The Molecular Basis of Calcium Action in Biology and Medicine. Kluwer Academic Publishers, Netherlands, pp. 521-539 (2000).

B. Articles in press.

J.G. Scammell, W.B. Denny, D.L. Valentine, and D.F. Smith. Overexpression of the FK506-Binding Immunophilin FKBP51 Is the Common Cause of Glucocorticoid Resistance in Three New World Primates. *Gen. Comp. Endocrinol.* (2001).

T. Stevens. Pulmonary Vasoconstriction Induced by G_q Agonists. Is There a Role for Store Operated Calcium Entry? *Am. J. Physiol.* (2001).

T. Stevens, B. Rosenberg, W. Aird, T. Quertermous, J.G.N. Garcia, R. Hebbel, R. Tuder, and S. Garfinkel. Endothelial Cell Phenotypes in Heart, Lung and Blood Diseases. *Am. J. Physiol.* (2001).

S. Vasudevan, S.W. Bailey, and J.E. Ayling. Stereospecific Synthesis of 2-Desamino-tetrahydropterins as Probes of Hydroxylase Cofactor Recognition. IN: S. Milstien (Ed.) Proceedings of the 12th International Symposium on Chemistry and Biology of Pteridines and Folates. Kluwer Publishers, Norwell, MA (2001).

S. Wu, J. Sangerman, M.Li, G.H. Brough, S.R. Goodman, and T. Stevens. Essential Control of an Endothelial Cell I_{SOC} by the Spectrin Membrane Skeleton. *J. Cell Biol.* (2001).

II. **PUBLISHED ABSTRACTS.**

J. Creighton and T. Stevens. Calcium Inhibition of Adenylyl Cyclase 6 Is Regulated by cAMP in Lung Microvascular Endothelial Cells. *FASEB J.* 15:A161 (2001).

D. Cioffi, M. Zhu, S.R. Goodman, and T. Stevens. Association of Trp-1 and -4 Store Operated Calcium Entry Channels With the Spectrin Membrane Skeleton in Endothelium. *FASEB J.* 15:A161 (2001).

D. Cioffi, J. Creighton, K. Canales, D.M.F. Cooper, and T. Stevens. Expression of a Calcium-Stimulated Adenylyl Cyclase Prevents Thrombin-Induced Gap Formation in Microvascular Endothelium. *FASEB J.* 15:A161 (2001).

E.A. Cioffi, S. Wu, B. Wallace, and T. Stevens. Modulation of Fura-2 Luminescence by Alkaline Earth Cations Both *In Vitro* and *In Vivo* in Pulmonary Macro- and Microvascular Endothelial Cells. *FASEB J.* 15:A492 (2001).

M.N. Gillespie, V. Grishko, M. Solomon, S.P. Ledoux and G.L. Wilson. Mitochondrial DNA Repair May Govern Lung Vascular Endothelial Cell Survival After Xanthine Oxidase-Induced Injury. *Am. J. Resp. Crit. Care Med.* 163:A760 (2001).

V. Grishko, M. Solomon, J.F. Breit, D.W. Killilea, S.P. LeDoux, G.L. Wilson, and M.N. Gillespie. Hypoxia Promotes Oxidative Base Modifications in the Pulmonary Artery Endothelial Cell VEGF Gene. *FASEB J.* 15:1267-1269 (2001).

J. King, T. Weathington, J. Creighton, F. McDonald, M.N. Gillespie, J. Olson, J. Parker, and T. Stevens. Characterization of Phenotypically Distinct Endothelial Cell Populations From Rat Lung. *FASEB J.* 15:A492 (2001).

N. Norwood, S. Wu, S. Dudek, J.G.N. Garcia, and T. Stevens. Endothelial Cell Myosin Light Chain Kinase-1 and Activation of Store Operated Calcium Entry. *FASEB J.* 15:A492 (2001).

M. Ruchko, M.N. Gillespie, and J.W. Olson. Suppression of Ornithine Decarboxylase Activity Prevents Monocrotaline-Induced Rat Lung Fibronectin IIIA Splicing. *FASEB J.* 15:A858 (2001).

M. Ruchko, M.N. Gillespie, and J.W. Olson. Evidence That Monocrotaline-Induced Apoptosis in Rat Lungs Is Dependent Upon Elevated-Ornithine Decarboxylase Activity. *FASEB J.* 15:A858 (2001).

S.W. Schaffer and M. Mozaffari. Regulation of Myocardial Phospholipid N-Methylation by Insulin and Diabetes. *IN: A. Angel and N.S. Dhalla (Eds.) Diabetes and Cardiovascular Disease.* Kluwer Academic/Plenum Publishers, NY (2001).

S. Schaffer and V. Solodushko. Effect of Hyperglycemia on Myocyte Apoptosis. *J. Mol. Cell. Cardiol.* 33:A152 (2001).

J. Taylor, S. Wu, G.H. Brough, M. Li, and T. Stevens. Selective Endothelial Expression of T-type Voltage Gated Calcium Channels in Lung Microvascular Cells. FASEB J. 15:A492 (2001).

S. Vasudevan, S.W. Bailey, and J.E. Ayling. Stereospecific Synthesis of 2-Desamino-tetrahydropterins as Probes of Hydroxylase Cofactor Recognition. Pteridines 12:91 (2001).

S. Wu, G.H. Brough, N. Dean, and T. Stevens. Contribution of Endogenously Expressed Trp-1 to a Calcium Selective Store Operated Calcium Entry Pathway in Endothelium. FASEB J. 15:A161 (2001).

S. Wu, E. Cioffi, and T. Stevens. Distinct Store Operated Calcium Entry Pathways in Pulmonary Macro- and Microvascular Endothelial Cells. FASEB J. 15:A161 (2001).

K.A. Ziel, M.J. Solomon, and M.N. Gillespie. Hypoxia Regulates Tissue-Type Plasminogen Activator in Rat Main Pulmonary Artery Endothelial Cells. Am. J. Resp. Crit. Care Med. 163:A609 (2001).

K.A. Ziel, J.F. Breit, M.J. Solomon, and M.N. Gillespie. Oxidant Stress in Rat Main Pulmonary Artery Endothelial Cells. FASEB J. 15:A452 (2001).

III. BOOKS PUBLISHED

None.

IV. PRESENTATIONS

J.E. Ayling. The Uniquely Human Inefficient Conversion of Folic Acid to Tetrahydrofolates. Third Homocysteinemia and Atherosclerosis RFA Grantee's Meeting, NIH, Bethesda, MD (2001).

J.E. Ayling. Stereospecific Synthesis of 2-Desamino-tetrahydropterins as Probes of Hydroxylase Cofactor Recognition. 12th Int. Symp. on Chemistry and Biology of Pteridines and Folates, Washington, DC (2001).

M.N. Gillespie. (1) Nuclear DNA Is a Target of Oxidants Generated During Hypoxic Signaling: Implications for Gene Expression; and (2) Mitochondrial DNA Integrity May Govern Lung Vascular Endothelial Cell Survival After Xanthine Oxidase-Induced Injury. Am. Thorac. Soc., San Francisco, CA (2001).

S. Schaffer. (1) Effect of Hyperglycemia on Myocyte Apoptosis; and (2) Regulation of Apoptosis by Osmotic Stress. Int. Symp., Heart Res., Banff, Alberta, Canada (2001).

S. Schaffer. (1) Osmotic Preconditioning through Taurine Depletion and Treatment; (2) Protein Kinase C Distribution: Mechanism Underlying the Interaction Between Taurine and Angiotensin II; and (3) Adverse Effects of Taurine Depletion. 7th Int. Cong., Amino Acids, Vienna, Austria (2001).

S. Schaffer. Mechanisms Underlying Taurine-Dependent Heart Failure. 8th World Cong., Clinical Nutrition, Phitsanulok, Thailand (2000).

T. Stevens. Regulation of Endothelial Cell Function by the Coordination Between Calcium and cAMP Signals. Physiol. Soc., King's College, London, England (2000).

T. Stevens. Calcium, cAMP and Endothelial Barrier Regulation. Symp., Molecular Regulation of Vascular Permeability, Johns Hopkins University, Baltimore, MD (2001).

T. Stevens. Regulation of Endothelial Cell Adhesion by Calcium and cAMP Signal Transduction. Institute for Environmental Medicine, University of Pennsylvania, Philadelphia, PA (2001).

V. NATIONAL PROFESSIONAL RECOGNITION

The Department of Pharmacology had five faculty members serving on editorial boards of major journals. Dr. Mark Gillespie and Dr. Troy Stevens served on the Editorial Board of the *American J. of Physiology: Lung Cell and Molecular Physiology*; Dr. Stephen Schaffer on *Molecular and Cellular Biochemistry*, Section Editor for *Amino Acids*; Dr. Samuel Strada on *CNS Drug Reviews*; and Dr. Jonathan Scammell on the Editorial Advisory Board of *Journal of Pharmacology and Experimental Therapeutics*.

Dr. Mark Gillespie served as Chair of the Nominating Committee and served on the Leadership Committee for the Pulmonary Circulation Assembly of the American Thoracic Society, served on four NIH Study Sections including Lung Biology and Pathology, NRSA Fellowship Awards, STTR/SBIR, and the Program Project Grant Review Committee; Dr. Jack Olson served as Merit Reviewer for the Department of Veteran Affairs. Dr. Jonathan Scammell is a member of the Biochemical Endocrinology Study Section, NIH. Dr. Stephen Schaffer served on the Review Board of the Southern Consortium, American Heart Association, International Advisory Committee for the 8th World Congress on Clinical Nutrition, Scientific Advisory Committee for ISHR World Congress, President of the 7th International Congress on Amino Acids and Proteins and Ad-Hoc member of NSBRI Study Section. Dr. Troy Stevens served as an Ad Hoc Member for Lung Biology and Pathology Study Section, NHLBI, Respiratory and Applied Physiology Study Section, Experimental Cardiovascular Sciences, Program Project Grants, NHLBI; and served on the Pulmonary Circulation Planning and Program Committees for the American Thoracic Society. Dr. Samuel Strada served as Representative for the Association for Medical School Pharmacology to the AAMC Council of Academic Societies.

The Department received additional funding through a number of research grant awards. Dr. June Ayling received a Grant-in-Aid from the American Heart Association, Southern Consortium for research on "Accumulation of Folic Acid Polyglutamates." Dr. Stephen Schaffer received a research grant from NIH on "Effect of Diabetes and Hypertension on Ischemic Injury."

VI. BRIEF SUMMARY OF DEPARTMENTAL ACTIVITIES AND PROGRESS

The Transgenic Animal/ES Cell Core Facility was established with Dr. Danna Zimmer serving as Co-Director. This facility provides assistance in the production of transgenic mouse models by either DNA microinjection or gene targeting in embryonic stem (ES) cells. In relation to the core facility, an intensive literature-driven course on the development and utilization of mouse models in biomedical research was developed and the department hosts a monthly seminar series.

The Department hosted visits by several distinguished scientists: Drs. Edward Block (Univ. of Florida), Jim Nelson (Univ. of Texas, San Antonio), Paul Schumaker (Univ. of Chicago), Linda Van Eldik (Northwestern Univ.), Steven Vogel (Med. Col. of Georgia)

The Department accepted four students for the Summer Undergraduate Research Fellowship (SURF) program. Ms. Lauren Cronenberg and Ms. Ashley Weimorts, from USA; Mr. Jan Kemnade, from Rice University; and Mr. John May, from Duke University, who was also awarded an Individual Fellowship by ASPET. Dr. Danna Zimmer sponsored his project which focused on the identification of target protein binding motifs on S100 proteins. The Department also hosted several undergraduate students participating in the University Committee for Undergraduate Research (UCUR) through the Department of Biomedical Sciences.

Dr. Troy Stevens sponsored Ms. Priya Bhat, Sophomore Medical Student, in the Medical Student Summer Research program. Ms. Bhat presented a poster entitled "Proliferation Rates Discriminate Between Lung Macro- and Microvascular Endothelial Cells: Relevance of Embryological Origin and Sensitivity to Disease."