CENTER OF EXCELLENCE *in livestock diseases and human health*

ANNUAL REPORT 2003

The University of Tennessee College of Veterinary Medicine

Center of Excellence in Livestock Diseases and Human Health

A Tennessee Higher Education Commission Accomplished Center of Excellence

Annual Report 2003

Michael J. Blackwell, Dean
Robert N. Moore, Director

The University of Tennessee College of Veterinary Medicine

Message from the Center of Excellence


Dr. Michael J. Blackwell

We are pleased to present the 2003 annual report for the Center of Excellence in Livestock Diseases and Human Health. We hope you enjoy this summary presentation of Center activities and accomplishments.

The Center's faculty had a stellar year in all measures of productivity. Through the use of animal models, Center faculty have made prominent advancements in cancer biology, molecular pathophysiology, reproduction, host defense, and disease transmission. Center faculty have also made important advances in understanding infectious and other non-infectious livestock diseases.

We are pleased with the progress made by the Center's faculty, and we are proud of the Center's accomplishments. We are especially proud that one of the Center's charter faculty members, David Brian, has been at the forefront of the effort to understand SARS.

The Center has expanded to include faculty in important areas of investigation relevant to the Center's mission. Working cooperatively with the Food Safety Center of Excellence, the Center for Environmental Biotechnology, and the Departments of Microbiology, Nutrition, and Mechanical, Aerospace and Biomedical Engineering, the Center has contributed significantly to the research enterprise of the College of Veterinary Medicine, the Institute of Agriculture, and the University.

Support from the Center has been instrumental in building total external funding for its faculty in excess of $16.5 million with a 6:1 return on the State's investment.

The Center and its investigators are always interested in establishing new projects and collaborations. Please contact us or any of the Center faculty if you have questions or interests.

Michael J. Blackwell, Dean
Robert N. Moore, Director


Jada Huskey and Dr. Robert N. Moore

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Program Report

Introduction

The Center was created in 1984 to promote interdisciplinary activities designed to

- Improve the quality of human life through better animal health
- Expand livestock disease research capabilities in the College of Veterinary Medicine and the Institute of Agriculture
- Identify and characterize animal diseases that are similar to human disease
- Develop new strategies for the diagnosis, treatment, and prevention of disease

Background

Since 1984, the Center has developed successful programs that impact the understanding, treatment, and prevention of livestock and human diseases. These programs predominately focus on molecular and cellular approaches to research in

- Infectious Diseases/Population Medicine
- Toxicology
- Reproduction
- Host Defense
- Molecular Genetics
- Carcinogenesis

The Center has developed investigative strengths along innovative, sophisticated, and contemporary lines in two general areas:

1. Animal Models/Comparative Medicine
2. Livestock Diseases/Toxicology

These areas are each highly interrelated, and the Center plays a critical role in developing these focused areas of strength in both the College of Veterinary Medicine and Agricultural Sciences and Natural Resources.

Research Funding

The Center of Excellence in Livestock Diseases and Human Health supports investigators and promotes research through a variety of mechanisms. Although it is not a primary source of research funding, the Center facilitates established investigator's efforts to maintain and expand their research programs and promotes new investigator's potential to develop competitive research programs. The COE Advisory Committee reviews funding requests based on three main criteria: scientific merit, potential to lead to extramural funding, and relevance to the Center's objectives. During fiscal year 2003 the Center awarded $431,090 in support of 19 projects.

Support for faculty researchers totaled $431,090

Equipment

The Center promotes the research infrastructure of both the CVM and the Institute of Agriculture through the purchase and maintenance of essential research equipment. The COE Advisory Committee reviews equipment requests based on three criteria: justification of need, current availability of equipment, and number of investigators who may benefit. During fiscal year 2003 the Committee approved 3 pieces of equipment totaling $72,882. Investigators benefiting from these equipment grants were Drs. Mendis-Handagama, Frank, and Millis. In addition, the Center and CVM jointly obligated $50,000 for the purchase of

Equipment grants totaled $72,882

micro-array instrumentation to be housed in the Department of Nutrition.

Research Training

The College of Veterinary Medicine funds at least 10 Ph.D. trainees with a professional medical degree. Some of these trainees are based in the Department of Pathology as part of their residency/PhD program while others are awarded without restriction. Many of these trainees eventually link with Center of Excellence faculty. These young investigators significantly bolster the achievements of the Center. Faculty benefiting from these trainees includes Drs. Brian, Rouse, Tithof, and Schuller.

CVM funded 10 Ph.D. trainees that benefit the Center faculty

Student Research

In an effort to promote biomedical research, the Center provides summer opportunities for veterinary students to perform research in laboratories within the College of Veterinary Medicine. During fiscal year 2003, The Center supported 15 first - and second-year students. This program has been quite successful. Several students have presented their work at national scientific meetings, and numerous manuscripts detailing the student's work have been submitted for publication in refereed journals. Over the past five years approximately 40 manuscripts, several with students from this program as senior authors, were published in refereed journals.

The Center funded 15 student researchers

The students involved in the summer research program and a brief description of their activities follow:

Julie Albright

From Brentwood, Tennessee, Julie Albright is a third year student in the professional curriculum. Prior to entering the CVM, Julie earned a Bachelor of Science degree in Psychology, with a concentration in neuroscience, from Vanderbilt University.

Julie conducted behavioral observations and used a computer program to record types and frequencies of behaviors while working with Dr. Ed Ramsay on a study of wolf-dog hybrids.

Julie is interested in a career as a behavior specialist.

Chris Bass

A second year student in the professional curriculum, Chris Bass is from Knoxville, Tennessee. Chris attended undergraduate school at Ouachita Baptist University in Arkadelphia, Arkansas, where he majored in Biology and minored in Chemistry.

Chris isolated messenger RNA and set up micro arrays while working with Dr. Legendre on a pilot study designed to better understand canine lymphomas.

Cary Bosworth

Cary Bosworth is a third year student in the professional curriculum. A native of Newport News, Virginia, she attended undergraduate school at Vanderbilt University, where she majored in Math.

While working with Drs. Rebecca Seaman and David Edwards, Cary obtained fine needle aspirates from mast cell tumors and stained and evaluated slides for a study on agyrophilic nucleolar organizing regions and mast cell tumors.

Laura Brandt

Laura Brandt, from Jonesborough, Tennessee, is a second year student in the professional curriculum. Laura attended undergraduate school at East Tennessee State University where she majored in English and Spanish.

Under the direction of Dr. Nicholas Frank, Laura isolated messenger RNA from samples and conducted Northern blot analyses to determine gene expression for studies of obesity-associated laminitis in horses. Laura also assisted with data analysis during this project.

Stefanie Gagliardi

Stefanie Gagliardi is a second year veterinary student from Gaffney, South Carolina. Stefanie attended undergraduate school at Clemson University, where she majored in Animal and Veterinary Sciences.

Under the direction of Dr. Frank Andrews, Stefanie dissected stomach tissues from horses and prepared stomach tissues for histological evaluation while working on a study of the role of volatile fatty acids and calcium in equine gastric ulcers.

Chad Lothamer

From Brentwood, Tennessee, Chad Lothamer is a second year student in the professional curriculum. Chad completed his undergraduate education at The University of Tennessee with a major in Animal Science.

While working with Dr. Melissa Kennedy, Chad used established techniques to amplify coronavirus genetic material from cheetah biologic samples and evaluated serologic assays during a study of feline coronavirus.

Heather Robertson

A second year student in the professional curriculum, Heather Robertson grew up in Madison, Tennessee and earned her undergraduate degree in Animal Science from Middle Tennessee State University.

Heather performed diagnostic tests and assisted with data analysis while working with Dr. Sharon Patton on a study of the development of parasite risk assessment and control strategies for captive breeding of Island Fox and Channel Island national Park

Matt Rosenbaum

Matt Rosenbaum grew up in Germantown, Tennessee. Prior to entering the CVM, he attended undergraduate school at The University of Tennessee, Chattanooga.

Working with Dr. Mendis-Handagama, Matt isolated Leydig stem cells from neonatal-prepubertal rats for an on-going project concerning male contraception.

Once he has earned his DVM degree, Matt would like to do a residency in lab animal medicine or pathology.

Olya Smrkovski

Olya Smrkovski is a third year student in the professional curriculum. Originally from Moscow, Russia, Olya earned a degree in Geology from The University of Tennessee, Knoxville.

Based on her work with Dr. Stephen Kania, an abstract was submitted to and accepted by the 2003 Veterinary Cancer Society. Olya will present at an upcoming meeting in Wisconsin. After graduation, Olya would like to complete an internship and residency in Oncology.

Julie Soppe

Originally from Youngstown, Ohio, Julie Soppe attended undergraduate school at The University of Tennessee, Knoxville, where she majored in Animal Science and Science and Technology. Julie is a second year student in the professional curriculum.

Julie worked on a lipoprotein study with Dr. Nicholas Frank. Julie is currently evaluating data collected during the study in order to prepare a journal article.

Ginger Takle

A native of Cincinnati, Ohio, Ginger Takle is a third year student in the professional curriculum. Prior to entering the CVM, Ginger attended undergraduate school at Bowling Green State University where she majored in Biology.

Ginger worked with Dr. Cheryl Greenacre on a comparison response to cutaneous electrostimuli in iguanas administered various analgesics.

After completing a zoo internship and residency, Ginger aspires to become the Head Veterinarian at the San Diego Zoo.

David Toplon

David Toplon, a second year student in the professional curriculum, is originally from Nashville, Tennessee. He completed his undergraduate degree at Emory University in Atlanta, Georgia, majoring in Biology, Math, and Environmental Science.

During his work with Dr. Sharon Patton's Channel Island Fox project, David identified and quantified parasites found in fecal samples, and he conducted an extensive literature review.

Melissa Vannatta

A native of Shelbyville, Tennessee, Melissa Vannatta is a third year student in the professional curriculum. Melissa completed her undergraduate work at The University of Tennessee, Knoxville, with a major in Agriculture and an emphasis in animal science.

Melissa worked with Dr. Darryl Millis to characterize differences in joint kinematics among animals walking on the ground, on a treadmill, and the underwater treadmill. Melissa is currently preparing a journal article based on her work during the summer.

Rebecca Wagner

Rebecca Wagner is a second year student from Cortland, New York. Rebecca attended Wells College in Aurora, New York, and majored in biological and chemical sciences with a concentration in biology.

Working with Dr. Karen Tobias, Rebecca conducted a retrospective study of dogs treated with acepromazine for seizures during the last five years. Rebecca is currently preparing a journal article based on her work with Dr. Tobias.

Latisha Webb

Originally from Louisville, Kentucky, Latisha Webb is a second year student in the professional curriculum. Latisha attended undergraduate school at Milligan College in Johnson City, Tennessee, where she majored in Biology and minored in Chemistry.

Under the direction of Drs. Nicholas Frank and Carla Sommardahl, Latisha performed endocrine testing procedures and analyzed samples for a study on the effect of synthetic hormone on thyroid hormone measures and energy metabolism in horses.

Culture for Discovery

In conjunction with the CVM graduate program in Comparative and Experimental Medicine, the Graduate School of Medicine, and the Departments of Microbiology and Animal Science, the Center sponsored a number of speakers through two biomedical seminar series: Mechanisms of Disease and Microbial Pathogenesis. These well-attended seminars, which presented contemporary research topics, were intended to foster a culture for discovery by stimulating discussion and interaction among students and faculty. The following is a list of guest speakers and seminar topics:

Marc Peters-Golden, MD
Lipoxygenases and Lung Disease
University of Michigan
School of Public Health
Assistant Professor, Environmental Sciences

Peter Mancuso, Ph.D.
Leptin Receptors and Macrophage Function
University of Michigan
School of Public health
Assistant Professor, Environmental Sciences

Bruce D. Levy, MD
Resolvins
Harvard Medical School
Associate Professor, Department of Pulmonary and Critical Care Medicine

Gopal Thinakaran, Ph.D.
Alzheimers Disease
University of Chicago
Associate Professor, Department of Neurobiology, Pharmacology

Pierre Borgeat, Ph.D.
Leukotriene B4
Director
Rheumatology & Immunology Research Center
Laval University, Quebec

Robert Langenbach, Ph.D.
Cox-1 and Cox-2 Knockout Mice
NIEHS
Laboratory of Environmental Carcinogenesis and Mutagenesis

Christina C. Leslie, Ph.D.
Phospholipase A2
National Jewish Center for Immunology and Respiratory Medicine
Professor, Department of Pediatrics

Matthew W. Breyer, MD
Prostaglandin Receptors
Vanderbilt University
Professor, Department of Physiology and Biophysics

Chris Minion, Ph.D.
Mycoplasma Get No Respect
Iowa State University
Associate Professor, Department of Veterinary
Microbiology & Preventive Medicine

John Bannantine, Ph.D.
Genome Sequence of Mycobacterium avium subsp. Paratuberculosis
USDA-ARS
National Animal Disease Center

Jeannie Burton, Ph.D.
Host Immune Response to E. coli Mastitis
Michigan State University
Associate Professor, Department of Animal Science

Daniel Portnoy, Ph.D.
Cell Biology of Listeria Monocytogenes
University of California, Berkeley
Professor, Department of Molecular And Cell Biology

Michael Starnbach, Ph.D.
Cytotoxic T Cells and the Immune Response
Harvard University
Assistant Professor, Department of Microbiology and Molecular Genetics

Tom Schwan, Ph.D.
Borrelia burdorferi and Tick Vectors
Rocky Mountain Laboratories
National Institute of Allergy and Infectious Diseases, NIH

Michael Doyle, Ph.D.
Epidemiology of E. coli 0157:H7 on Dairy Farms
University of Georgia
Professor and Director, Center for Food Safety

Personnel

Dr. Robert N. Moore, Professor and Associate Dean for Research and Graduate Studies, continues as Director of the Center.

The College of Veterinary Medicine has added a Director of Development, Dr. Claire Eldrige, to elevate the profile of the College and to increase support for programs throughout the College. Prior to joining the College, Dr. Eldrige served as vice chancellor for development and college relations at the University of Virginia's College at Wise.

In order to keep the general public informed of accomplishments and on-going research, Ms. Sandra Harbison has been appointed media relations coordinator.

Dissemination of Research

In order to keep the general public informed of research accomplishments, CVM distributes a newsletter, *Veterinary News,* and a magazine, *Veterinary Vision.* Both of these publications carry features concerning on-going research activities and the results of concluded research studies. Research Activities, a link on the College website, gives an overview of the types of research conducted by CVM and COE faculty.

CVM also issues press releases to state, regional, and national media resulting in numerous television and print features on the College, many of which relate directly to research conducted through the Center. In addition, faculty are encouraged to share their research by speaking to professional groups, community groups, and civic groups.

In past years, the Center has highlighted accomplishments of individual investigators; however, beginning with fiscal year 2003 more aggressive advertisement of Center accomplishments was undertaken. This included a dramatic increase in visitors invited to the Center through cooperative presentation of 'invited speaker' courses in Microbial Pathogenesis and Mechanisms of Disease.

In addition, extensive mailing of this report is intended to increase public awareness of the Center and the accomplishments of its faculty.
Lastly, in fiscal year 2005 the Center will participate substantially in the thirty year anniversary of the CVM which coincides with the twentieth anniversary of the Center.

Accomplishments

Core faculty within the Center continue to make excellent progress in on-going projects, gaining national and international recognition for their expertise and accomplishments. Details of faculty research are provided in Faculty Reports.

Center accomplishments for the year 2002-2003 were excellent in terms of benchmarks and extramural funding base.

The 20 Center faculty averaged approximately 6 scientific and scholarly publications (116 total), and 3 invited presentations (50 total) at prestigious national and international meetings (Table 2). See Publications and Presentations for a complete listing of faculty benchmarks.

The return on the State's investment in the Center as the ratio of expenditures from extramural funding to Center appropriation was 6:1 (Table 1).

Extramural funding totaled $16,753,650; new grants totaled $3,051,422; return on investment 6:1

Extramural funding totaled $16,753,650 increasing $5.36 million this year. The total funding includes new multi-year awards to Drs. Rouse, Schuller, Brian, Cui, and S. Oliver totaling $3,051,422. See Research Expenditures and Research Funded Externally for data summary; details are provided in Table 1.

Research Expenditures

Joseph Bartges		
Federal		0
Industry		$59,684
Foundation/Private		0
	Total	$59,684
David Brian		
Federal		$202,590
Industry		0
Foundation/Private		0
	Total	*$202,590*
Mei-Zhen Cui		
Federal		0
Industry		$32,262
Foundation/Private		$6,388
	Total	*$38,650*
Nicholas Frank		
Federal		0
Industry		$24,600
Foundation/Private		0
	Total	*$24,600*
Charmi Mendis-Handagama		
Federal		$55,164
Industry		0
Foundation/Private		0
	Total	*$55,164*
Darryl Millis		
Federal		0
Industry		$154,258
Foundation/Private		0
	Total	*$154,258*
Jack Oliver		
Federal		$21,109
Industry		0
Foundation/Private		0
	Total	*$21,109*
Stephen Oliver		
Federal		0
Industry		$68,417
Foundation/Private		0
	Total	*$68,417*
Barry Rouse		
Federal		$966,276
Industry		0
Foundation/Private		0
	Total	*$966,276*
Hildegard Schuller		
Federal		$362,817
Industry		0
Foundation/Private		0
	Total	*$362,817*
Pamela L.C. Small		
Federal		$462,494
Industry		0
Foundation/private		0
	Total	*$462,494*
Patricia Tithof		
Federal		0
Industry		$170,349
Foundation/Private		$60,828
	Total	*$231,177*
Hwa-Chain Wang		
Federal		$72,755
Industry		0
Foundation/Private		0
	Total	$72,755
Xuemin Xu		
Federal		$462,602
Industry		0
Foundation/Private		0
	Total	*$462,602*

Total Research Expenditures
$3,156,469

State Appropriation
$516,000

The return on the State's investment in the COE as the ratio of expenditures from external funding to COE appropriation is 6:1

Research Funded Externally

Joseph Bartges

Federal		0
Industry		$270,639
Foundation/Private		$59,684
	Total	*$330,323*

David Brian

Federal		$1,539,400
Industry		0
Foundation/Private		0
	Total	*$1,539,400*

Mei-Zhen Cui

Federal		0
Industry		$100,000
Foundation/Private		$240,000
	Total	*$340,000*

Nicholas Frank

Federal		0
Industry		$10,010
Foundation/Private		0
	Total	*$10,010*

Alan Mathew

Federal		0
Industry		$72,434
Foundation/Private		$48,560
	Total	*$120,994*

Charmi Mendis-Handagama

Federal		$69,750
Industry		0
Foundation/Private		0
	Total	*$69,750*

Darryl Millis

Federal		0
Industry		$397,416
Foundation/Private		0
	Total	*$397,416*

Jack Oliver

Federal		$264,003
Industry		0
Foundation/Private		0
	Total	*$264,003*

Stephen Oliver

Federal		0
Industry		$241,740
Foundation/Private		$99,922
	Total	*$341,662*

Barry Rouse

Federal		$4,832,296
Industry		$165,500
Foundation/Private		0
	Total	*$4,997,796*

Hildegard Schuller

Federal		$3,204,681
Industry		0
Foundation/Private		0
	Total	*$3,204,681*

Pamela L.C. Small

Federal		$2,018,127
Industry		0
Foundation/private		0
	Total	*$2,018,127*

C.A. Speer

Federal		$20,000
Industry		0
Foundation/Private		0
	Total	*$20,000*

Patricia Tithof

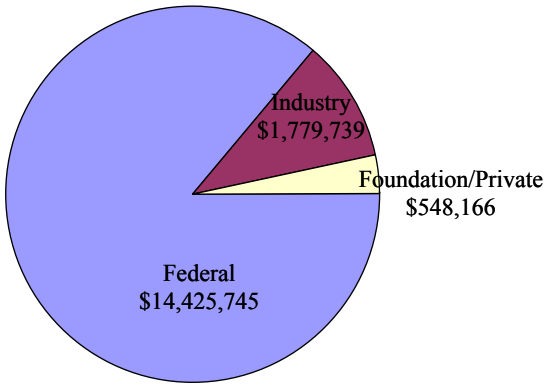
Federal		0
Industry		$522,000
Foundation/Private		$100,000
	Total	*$622,000*

Hwa-Chain Wang

Federal		$517,020
Industry		0
Foundation/Private		0
	Total	*$517,020*

Xuemin Xu

Federal		$1,960,468
Industry		0
Foundation/Private		0
	Total	*$1,960,468*



External Funding

Total External Funding
$16,753,650

Total COE-related external funding increased by 32% in FY 03 due to significant new grants and contracts awarded to COE faculty.

Of particular note are new multi-year awards to Drs. Rouse, Schuller, Brian, Cui, and S. Oliver which total $3,051,422.

Future Plans

The Center will continue to concentrate on developing newly recruited investigators while promoting initiatives to enhance its research capacity and direction.

In fiscal year 2004 the Center will expend $544,140 to fund 20 projects, including equipment, in the College of Veterinary Medicine and the College of Agricultural Sciences and Natural Resources (Table 3). This represents an increase of approximately $113,000 over the preceding year. The increased number of projects funded over the last two years represents a broadening interest in promoting food animal research and investing in companion animal research projects that relate directly to developing technologies applicable to human health. From fiscal year 2002 to fiscal year 2003, the investment in the increased number of projects has resulted in a 32% increase in extramural funding for Center related grants and contracts.

Further, the Center has entered into cooperative interactions with other units to enhance research that supports its objectives. These include a collaborative project between orthopedic surgeons in the Center and faculty in biomedical engineering and the joint hiring, with the Center for Environmental Biotechnology, of a research assistant professor to develop projects in environmental toxicology and pathophysiology. Initiatives to be developed are listed and explained as follows:

Homeland Security

Awareness of the vulnerability of the state and nation to bioterrorist and agroterrorist attacks has increased dramatically since the events of September 11, 2001. The Center in cooperation with the College of Veterinary Medicine will support public health oriented projects designed to support surveillance, intervention, and resolution of potential attacks directed against humans and food animals. In planned proposals to promote homeland defense, the Center will provide the infrastructure for agroterrorism research for the College of Veterinary Medicine.

Research Training/Opportunities for Collaboration

The Center will continue to increase its involvement in research training of veterinary students and graduate students by continuing to provide increased opportunities for summer internships, matching travel grants, and stipend upgrades to help recruit and retain top quality graduate students.

In fiscal year 2003 the Center cooperated substantially in the offering of "invited speaker" courses in Microbial Pathogenesis and Mechanisms of Disease. These courses increased national and international exposure of the Center's faculty, students, and programs; and, at the same time, enhanced the potential for developing external collaborations for our faculty and postdoctoral opportunities for our students. This initiative was so well-supported by Center faculty that plans are to continue and to even expand Center participation in the offering of advanced graduate courses in 2004.

The Center will continue to participate conceptually and materially in strategic planning to develop areas of investigative strength in the College of Veterinary Medicine and the Institute of Agriculture.

Faculty Reports

Animal Models and Comparative Medicine

Cancer Biology
Dr. Hildegard Schuller
Dr. Hwa-Chain Robert Wang
Dr. Howard K. Plummer, III

Molecular Physiology
Dr. Mei-Zhen Cui
Dr. Patricia K. Tithof
Dr. Xuemin Xu

Infection, Immunity, Transmission
Dr. Barry T. Rouse
Dr. Pamela L.C. Small
Dr. Joseph W. Bartges

Reproduction
Dr. Hugo Eiler
Dr. S.M. Lilitha Charmindrani Mendis-Handagama

Autoimmunity
Diane V.H. Hendrix

Livestock Diseases and Toxicology

Coronaviruses
Dr. David A. Brian
Dr. Barton W. Rohrbach

Virulence, Antibiotic Resistance, Diagnostics
Dr. Stephen P. Oliver
Dr. Alan G. Mathew
Dr. C.A. Speer

Equine Gastric Ulcers
Dr. Nicholas Frank

Tall Fescue Toxicosis
Dr. Jack W. Oliver

Environmental Toxicology
Terry W. Schultz

Hildegard M. Schuller
D.V.M., Justus Liebig University, Giessen, Germany
Ph.D., College of Veterinary Medicine, Hannover, Germany
Distinguished Professor and Acting Head
Department of Pathobiology

Dr. Hildegard Schuller (seated) and staff

Recent Publications

Harris, R.E., Beebe-Donk, J, Schuller, H.M. Chemoprevention of lung cancer by nonsteroidal anti-inflammatory drugs among cigarette smokers. *Oncol Rep* 9: 693-695, 2002.

Schuller, H.M., Zhang, L., Weddle, D.L., Castonguay, A., Walker, K., Miller, M.S. The cyclooxygenase inhibitor ibuprofen and the FLAP inhibitor MK886 inhibit Pancreatic carcinogenesis induced in hamsters by transplacental exposure to ethanol and the tobacco carcinogen NNK. *J Cancer Res Clin Oncol* 128: 525-532, 2002.

Schuller, H.M., Plummer III., H.K., Jull, B.A. (Invited Review) receptor-mediated effects of tobacco toxicants on pulmonary neuroendocrine cells. *Anat Rec* Part A 270A: 51-58, 2003.

Regulatory Mechanisms in Lung Cancer

For over 20 years Dr. Schuller's research has been dedicated to the study of lung cancer; her achievements have been recognized nationally and internationally. Dr. Schuller's studies are designed to provide an in-depth understanding of the regulatory mechanism governing the growth of normal lung cells and the cancers arising from such cells.

Dr. Schuller has hypothesized that different lung cell types and different types of lung cancer may not be governed by the same regulatory mechanisms. Known risk factors may, in turn affect these regulatory mechanisms differently.

Dr. Schuller's group has previously determined that nicotinic acetylcholine, a specific cell receptor with an important biological function, regulates growth of small cell lung carcinoma and the cell of origin for this cancer type, the pulmonary neuroendocrine cell. Dr. Schuller also found that NNK, a tobacco-specific carcinogenic product, activates this receptor with high affinity. This important finding links, for the first time, the stimulation of a specific receptor by a tobacco-specific toxicant with the activation of a series of cell-specific events that may result in uncontrolled growth. Dr. Schuller's group is testing the hypothesis that substances that inhibit the re-uptake of serotonin will protect against the development and spread of small cell lung cancer.

The Center of Excellence and three grants from the National Institutes of Health support Dr. Schuller's research.

Hwa-Chain Robert Wang
BVM, National Chung-Hsing University, Taiwan, R.O.C
Ph.D., University of Virginia
Associate Professor
Department of Pathobiology

Dr. Hwa-Chain Robert Wang

Recent Publications

Fecteau, KA., Mei, J., and Wang, H-C.R. 2002. Differential modulation of signaling pathways and apoptosis of ras-transformed 10T1/2 cells by the depsipeptide FR901228. *Journal of Pharmacology and Experimental Therapeutics*, 300:890-899.

Mei, J., Hu, H., McEntee, M., Plummer III, H., Song, P., and Wang, H-C.R. 2003 Transformation of noncancerous human breast epithelial cell MCF10A induced by the tobacco-specific carcinogen NNK. *Breast Cancer Research and Treatment* , 79:95-105.

Signatures of Tobacco Specific Carcinogen NNK in the Induction of Human Breast Cancer Cells

Breast cancer is one of the most prevalent human cancers among women in the United States with almost 180,000 women diagnosed with breast cancer each year. Epidemiological studies have suggested that exposure to tobacco substances increase the risk of developing human breast cancers. However, it is still unclear as to whether tobacco carcinogens are able to initiate the development of breast cancer or act with other environmental carcinogens to promote tumor formation.

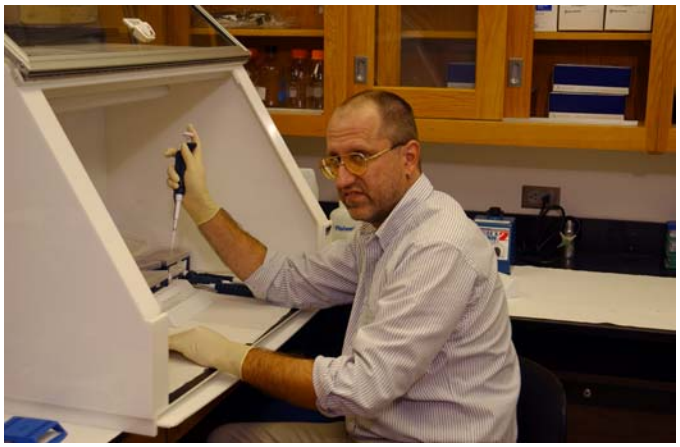
Previous studies by Dr. Wang's group have empirically verified, for the first time, that NNK, a tobacco specific carcinogen, is competent to play a role in initiating non-cancerous human breast epithelial cells into acquiring cancerous properties.

Dr. Wang's group is currently engaged in an innovative study designed to understand the potential synergistic or additive effect of NNK with benzopyrene, another carcinogen, on the induction of the cellular transformation of non-cancerous breast cells. This study is innovative in that the signatures of NNK at its potential synergism with benzopyrene in breast carcinogenesis have not been addressed to date.

Understanding how carcinogens play a role in the induction of human breast cancer will allow researchers to develop strategies for cancer prevention.

The Center of Excellence, the National Cancer Institute, and a new grant from Phillip Morris support Dr. Wang's research.

Howard K. Plummer, III
Ph.D., Bowling Green State University
Assistant Professor
Department of Pathobiology



Dr. Howard Plummer

Recent Publications

Cakir, Y., Plummer III, H.K., Tithof, P.K., and Schuller, H.M. 2002. Beta-adrenergic and arachidonic acid-mediated growth regulation of human breast cancer cell lines. *International Journal of Oncology* 21:153-157.

Schuller, H.M., Plummer III, H.K. and Jull, B.A. 2003. Receptor mediated effects of nicotine and its nitrosated derivative NNK on pulmonary neuroendocrine cells. *Anatomical Record* 270: 51-58.

Mei, J., Hu, H., McEntee, M., Plummer III, H., Song, P. and Wang, H.C.R. 2003. Transformation of Non-Cancerous Human Breast Epithelial Cell Line MCF10A by the Tobacco-Specific Carcinogen NNK. *Breast Cancer Research and Treatment* 79:95-105.

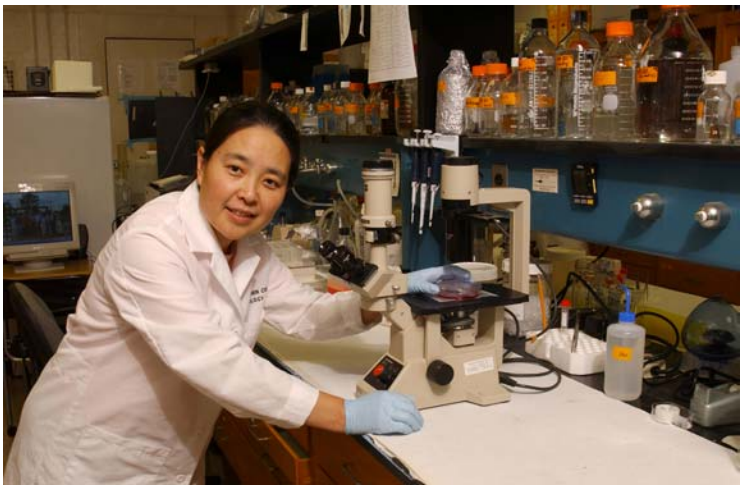
Molecular Characterization of Beta-adrenergic Receptors and Potassium Channels in Breast Cancer

Breast cancer is the leading cancer in women. Studies in human cancer cell lines or in animal models have shown that the growth of a type of cancer called adenocarcinoma in the lungs, pancreas, and colon are under control of a cell surface receptor in the beta-adrenergic system.

Data from Dr. Plummer's laboratory have indicated that similar to these cancers in other organs, growth of a subset of human breast cancers is under control of this same beta-adrenergic cell surface receptor-cellular signaling system. Dr. Plummer's group has identified a functional link between the beta-adrenergic receptor pathway and the GIRK1 potassium channel in human breast cancer cell lines. Data from Dr. Plummer's laboratory indicate that a carcinogen found in tobacco smoke, NNK, stimulates this system in breast cancer cells.

Dr. Plummer's group is also investigating the functional association of GIRK1 with beta-adrenergic, arachidonic acid-mediated signal transduction. A high proportion of breast cancer cases demonstrate extensive metastatic spread, cancer relapse, and failure of existing therapies. In particular, estrogen non-responsive breast cancers have a poor prognosis. The expression of beta-adrenergic receptors has been correlated with the over expression of certain arachidonic acid-metabolizing enzymes in adenocarcinomas of lungs, colon, prostate, pancreas, and breast. Recent studies in Dr. Plummer's laboratory indicate that three estrogen-responsive and three non-estrogen specific cell lines derived from human breast cancers demonstrate a significant reduction in DNA synthesis beta-adrenergic blockers and inhibitors of COX-2 and lipoxygenase.

Mei-Zhen Cui
Ph.D., Tokyo Institute of Technology, Japan
Assistant Professor
Department of Pathobiology



Dr. Mei-Zhen Cui

Recent Publications

Xu, X., Shi Y., Wei, G., Mao, G., Zhao, G., Agrawal, S., Chisolm, G., and Cui, M.-Z., The novel presenilin-1-associated protein (PSAP) is a pro-apoptotic mitochondrial protein. *J. Bio. Chem.* 2002. 277 (50):48913-48922. 2003

Tan, M., Xu, X., Ohba, M., Ogawa W. and Cui, M.-Z., Thrombin rapidly induces protein kinase D phosphorylation and protein kinase C delta mediates the activation. *J. Biol. Chem.* 2003, 278(5): 2824-2828. 2003

Cui, M.-Z., Zhao, G., Winokur, A., Laag, E. Bydash J. R., Penn, M. S., Chisolm, G. M., and Xu, X., Lysophosphatidic Acid Induction of Tissue Factor Expression in Aortic Smooth Muscle Cells. *Atheroscler, Thromb and Vasc. Biol.* 2003; 23: 224-230. 2003

Tissue Factor Involvement in Vascular Disease

Studies in Dr. Cui's laboratory are directed towards understanding the molecular mechanism underlying vascular diseases, specifically atherosclerosis and thrombosis.

Dr. Cui's group has found that thrombin activates protein kinase D (PKD) in vascular smooth muscle cells. These results reveal a novel function of PKCδ in mediating thrombin-induced PKD activation and identified PKD as a new component in thrombin-induced intracellular signaling pathway in smooth muscle cells.

Tissue factor, the initiator of the coagulation cascade, is expressed by cells in atherosclerotic lesions. Dr. Cui's data have shown, for the first time, that lysophosphatidic acid (LPA), a component of oxidized lipoproteins and an agent released by activated platelets, markedly induces tissue factor messenger RNA, tissue factor protein, and tissue factor activity in vascular smooth muscle cells. Activation of MEKs and ERKs mediates LPA-induced TF expression. Dr. Cui's results suggest that elevated LPA could be a thrombogenic risk factor.

Dr. Cui's group is studying the regulation of tissue factor expression by components of oxidized low density lipoproteins and attempting to define the role of oxidized lipids in atherosclerosis and thrombosis.

The Center of Excellence, the American Heart Association, and a new grant from Pfizer support Dr. Cui's Research.

Patricia K. Tithof
D.V.M., Michigan State University
Ph.D., Michigan State University
Associate Professor
Department of Pathobiology

Dr. Patricia Tithof

Recent Publications

Weddle DL, Tithof P, Williams M, Schuller HM. Beta-adrenergic growth regulation of human cancer cell lines derived from pancreatic ductal carcinomas. *Carcinogenesis* 22(3): 473-479. 2003.

Tithof PK, Elgayyar M, Barnhill M, Schuller HM, Andrews R. 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, a nicotine derivative, induces apoptosis of endothelial cells. *Am. J. Physiol.* 281:H1946-H1954. 2003.

Schoieb AM, Dudrick PS, Bell JD, Tithof PK. In vitro inhibition of growth and induction of apoptosis in cancer cell lines by thymoquinone. *Int. J. Oncol*. 22: 107-113. 2003.

Molecular Mechanisms in Cardiovascular Disease

In the United States, cardiovascular disease kills almost as many people as all other causes of death combined, and the toll on the national economy exceeds $150 billion annually.

Dr. Tithof's research in cardiovascular physiology concerns the effects of specific components of cigarette smoke on the biology of endothelial cells and the metabolism of arachidonic acid, a potent physiological messenger. Arachidonic acid is a fatty acid present in high quantities in the membranes of all cells and is a substrate for the production of eicosanoids, a family of biologically active lipid mediators that have an important role in atherosclerosis. The protective effects that these fatty acids and aspirin provide against smoking-induced atherosclerosis suggest that components of cigarette smoke stimulate the arachidonic pathway. However, previous studies have not focused on the specific components of cigarette smoke responsible for this effect.

Dr. Tithof's group has demonstrated that compounds present in cigarette smoke in high concentrations induce endothelial cell apoptosis, a form of cell death. These compounds include polycyclic aromatic hydrocarbons (PAHs) and the nitrosated derivative of nicotine, NNK. Moreover, they have identified the signal transduction pathways involved in this effect. PAHs and NNK induce endothelial apoptosis by activating the arachidonic cascade, an important pathway that produces more than 100 biologically active mediators, many of which are involved in coronary artery disease. Though PAH compounds are known carcinogens, researchers do not yet clearly understand their role in the atherosclerotic process.

The Center of Excellence, Phillip Morris, and the American Heart Association support Dr. Tithof's research.

Xuemin Xu
Ph.D., Institute of Technology,
Nagatsuta, Yokohama 227 (Japan)
Associate Professor
Department of Pathobiology

Dr. Xuemin Xu

Recent Publications

Xuemin Xu, Yong-chang Shi, Wei Gao, Guozhang Mao, Guojun Zhao, Sudesh Agrawal, Guy Chisolm, and Mei-Zhen Cui. (2002). The novel presenilin-1-associated protein (PSAP) is a pro-apoptotic mitochondrial protein. *J Biol Chem* 277:48913-48922.

Yaping Gu, Susamma Verghese, Ravi Mishra, Xeumin Xu, Yongchang Shi, and Neena Singh. (2002). Mutant prion protein (PrP) mediated aggregation of normal PrP in the endoplasmic reticulum: Implications for prion propagation and neurotoxicity. *J of Neurochemistry* 83: 1-13.

Tan, M., Xu, X., Ohba, M., Ogawa W. and Cui, M.-Z. (2002), Thrombin rapidly induces protein kinase D phosphorylation and protein kinase C delta mediates the activation *J. Biol. Chem* 278: 2824-2828.

Molecular and Cellular Mechanisms of Alzheimer's Disease

Following heart disease, cancer, and stroke, Alzheimer's disease is the fourth major cause of death in the United States. The majority of the familial forms of Alzheimer's disease (FAD) cases have been associated with mutations in presenilin-1 (PS1) and presenilin-2 (PS2). Accumulating evidence supports a role for presenilin in apoptosis, or programmed cell death, one of the mechanisms of neuronal cell death observed in Alzheimer's disease.

Dr. Xu's group identified a novel protein, presenilin-associated protein (PSAP), capable of inducing programmed cell death. Dr. Xu's recent studies have revealed that PSAP is a mitochondrial molecule. Mitochondria play a central role in apoptosis. Because PSAP is a pro-apoptotic molecule and is localized in mitochondria, PSAP is well-positioned in regulating neuronal cell death in the brain.

Dr. Xu's group is currently working to generate a null mice model in which the PSAP gene is knocked out; they will use this animal model to determine the normal biological function and the possible pathological function of PSAP in brain development and in neurodegenerative disease.

These on-going studies may lead to the identification of new therapeutic strategies for Alzheimer's disease.

The Center of Excellence and the National Institutes of Health support Dr. Xu's research.

Barry T. Rouse
BVSc., University of Bristol, England
Ph.D., University of Guelph
DSc., University of Bristol, England
Distinguished Professor
Department of Pathobiology

Dr. Barry Rouse

Recent Publications

Schmid, D. S., and Rouse, B. T. 2003. *Respiratory virus vaccines in Mucosal Immunology*, third edition. Ed. By J. R. McGhee and J. Meskecky. Academic Press. NY. In press.

Rouse, B. T. 2003. *Immunopathology of herpetic stromal keratitis.* Immunology of the lacrimal gland of the Tear Film. Ed. By M Zierhut, D. Sullivan, M. Stern. Swets and Zeitlinger Publishers, Sassenheim. The Netherlands. In press.

Pack, C. and Rouse, B. T. 2003. *DNA vaccines against herpes viruses in DNA Vaccines*. Edited by H. C. Ertl. Kluwer Academics/Plenam NY. Pp. 126-140.

Herpes Simplex Virus

Herpes simplex virus (HSV) infects up to 80% of the human population. HSV persists indefinitely in infected individuals, with some suffering painful periodic lesions. Such lesions occurring in the eye can cause a chronic inflammatory reaction, herpetic stromal keratitis (HSK), and often result in blindness. HSK is one of the leading infectious causes of vision impairment in the United States. On-going studies in Dr. Rouse's laboratory are directed towards understanding the mechanisms by which herpes simplex infection causes blindness.

Dr. Rouse is working to understand how HSV interacts with the immune system. His aim is to understand how cells and molecular events set into play by HSV lead to chronic inflammatory lesions or resolution of the disease. Ultimately, it may be possible to manipulate host defenses to allow for protection by vaccine or lead to resolution of injury via substances introduced by gene transfer technology and capable of influencing the immune system.

Dr. Rouse is conducting studies to determine the mechanisms by which HSV infection results in angiogenesis and the role of a neurovascularization in HSV pathogenesis. Dr. Rouse is also working to define optimal means of inducing immunity against HSV.

Dr. Rouse's group has generated national and international interest, and his laboratory is recognized as one of the premier viral immunology programs in the country.

The Center of Excellence and three grants from the National Institutes of Health support Dr. Rouse's research.

Pamela L.C. Small
Ph.D., Stanford University
Associate Professor
Department of Pathobiology

Dr. Pam Small

Recent Publications

Small, P.L.C. and J. Hayman. "Pathogenesis of Mycobacterium ulcerans, the role of mycolactone, a unique macrolide toxin" in The Buruli Ulcer, Kluwer Academic Publishers, Netherlands 2001 In Press

Snyder, D. Scott and P.L.C. Small. Uptake and cellular actions of mycolactone on L929 fibroblasts. *Microbial Pathogenesis*.34:91-101, 2002.

Cope, R.B., W. M. Haschek, and P.L.C. Small. Ultraviolet-B radiation enhances both the nodular and ulcerative forms of Mycobacterium ulcerans infection in a CrI:IAF (HA)-hrBR hairless guinea pig model of Buruli ulcer disease. *Photodermatology, Photoimmunology and Photomedicine*. 18:271-279. 2002.

Molecular Pathogenesis of Mycobacterial Infections

Mycobacterium ulcerans is the causative agent of Buruli ulcer, a severe, persistent necrotizing skin disease. Dr. Small's group has identified a macrolide toxin, mycolactone, which is responsible for the immunosuppression and cell death in Buruli ulcer. In animal studies Dr. Small's group has also shown that mycolactone can block the acute inflammatory response to other bacteria injected into the animal. Although mycolactone shares the anti-inflammatory and immunosuppressive properties of many macrolides, it is the first identified in a pathogenic organism.

Dr. Small's group has constructed fluorescently labeled derivatives of mycolactone and has shown that mycolactone enters the cell by diffusion and accumulates in the cytosol. However, they have not yet identified a cellular target. Identifying a cellular target for mycolactone will be important in developing the pharmaceutical potential of the molecule.

Researchers know nothing about the genetics or gene expression of macrolides in mycobacteria. Dr. Small's group is working to identify genes required for mycolactone production. Once Dr. Small's group has identified genes for mycolactone, they will give high priority towards constructing a defined mutant that will be used as a basis for a vaccine against Buruli ulcer.

In addition, Dr. Small is collaborating with Drs. Stephen Oliver and C.A. Speer on *Mycobacterium paratuberculosis*. These studies are aimed at developing better diagnostic tools for *M. paratuberculosis* in cattle. The goal of this research is to determine the level of infection of *M. paratuberculosis* in Tennessee cattle, as well as ascertaining whether an epidemiological link exists between *M. paratuberculosis* and Crohn's diseases in humans.

The Center of Excellence and the National Institutes of Health support Dr. Small's research.

Joseph W. Bartges
D.V.M., University of Georgia
Ph.D., University of Minnesota
Professor
Department of Small Animal Clinical Sciences

Dr. Joe Bartges

Recent Publications

Bartges JW, Lane IF. Medical management of urolithiasis. In: Slater DH, ed. *Textbook of Veterinary Surgery* Philadelphia:WB Saunders. 2003. 1661-1672.

Seim H, Bartges JW. Enteral and parenteral nutrition. In: Tams TR, ed. *Handbook of Small Animal Gastroenterology*. 2nd edition. Philadelphia:WB Saunders. 2003. 416-462.

Bartges JW. Discolored urine. In: Ettinger SJ, Feldman EC, eds. *Textbook of Small Animal Internal Medicine* Philadelphia: WB Saunders. 2003. In press.

Zoonotic Enteric Bacteria Transmission

Dr. Bartges' research focuses on urinary tract diseases, the effects of nutrition and health on disease, and zoonotic intestinal diseases. The Center of Excellence is currently supporting studies to determine whether or not dogs and cats with acute and chronic diarrhea serve as reservoirs for potentially pathogenic enteric bacteria.

Dogs and cats are an important component of human health; however, they may also serve as a source for zoonotic organisms. Physicians often recommend that immunocompromised people abandon their pets because of the potential for transmitting zoonotic diseases, especially enteric bacterial pathogens.

While there are several studies evaluating the prevalence of zoonotic bacteria in food production and wild animals, there are few such studies concerning dogs and cats. There are reports of dogs and cats transmitting zoonotic enteric bacteria to people with HIV infection, young children, the elderly, and cancer patients undergoing chemotherapy and/or radiation therapy.

Dr. Bartges hypothesizes that there exists a relationship between infected animals and human beings that share a common environment. This project is part of a larger funded research program examining zoonotic pathogens. Research in this area focuses on developing rapid screening tests used by health professionals; treatment protocols to eliminate the carrier state for these organisms; educational modules on pet ownership for children in grades K-12, lay organizations, and health professional organizations; and perhaps the study of companion animals as potential vectors for bio-terrorism.

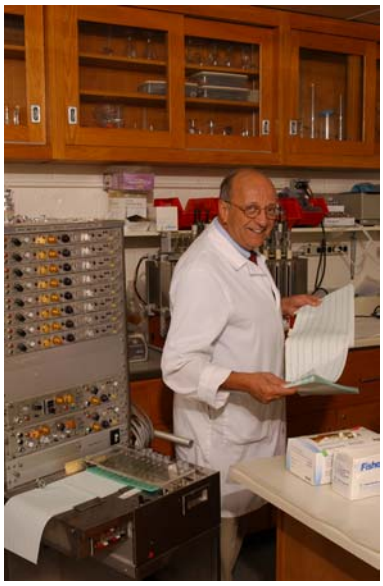
Dr. Bartges currently holds the Acree Endowed Chair of Small Animal Research.

Hugo Eiler
D.V.M., University of Chile, Santiago, Chile
Ph.D., University of Illinois, Urbana
Professor
Department of Comparative Medicine

Recent Publications

Haffner, J., K Fecteau, and H. Eiler. 2003. Inhibition of collagenase breakdown of equine corneas by tetanus antitoxin, equine serum, and acetylcysteine. *Vet. Ophthalmology* 6 (1):67-72.

Eiler, H. 2003. Endocrinology. In, *Dukes' Physiology of Domestic Animals*. W. Reece (Ed.), Cornell University Press, Comstock. In Press.



Dr. Hugo Eiler

Effect of Serotonin

Dr. Eiler's research is focused in two areas: reproduction and veterinary endocrinology. In terms of reproduction, Dr. Eiler's group is investigating how the fetus signals the mother that it is time for delivery. This involves the identification of endocrine signals, where they originate, and the way they function.

The core of Dr. Eiler's working hypothesis is that the fetal intestine produces a hormone-like substance (serotonin) capable of regulating pregnancy. Serotonin is secreted into fetal blood from the fetal intestine. During pregnancy, fetal serotonin promotes the growth of the placenta. However, at the end of gestation, there is a withdrawal of serotonin from fetal blood which causes the arrest of placental growth and detachment of the placenta. A partial failure of this mechanism may cause retention of the placenta in the postpartum female. Identification of the site of failure may allow us to develop a new treatment for retained placenta not only in cows and mares, but also in women.

Dr. Eiler's group is currently using the rabbit and the rat to develop a more conventional laboratory model that will facilitate the evaluation of the narcotic effect of serotonin. Serotonin reuptake inhibitors are widely used in the treatment of mood disorders, sleep disorders, and an increasing variety of psychotic conditions in both humans and animals.

The current hypothesis is that a sustained high concentration of serotonin in the synaptic cleft leads to remission of symptoms. This may be obtained by administration of serotonin uptake inhibitors such as fluoxetine. Dr. Eiler's hypothesis is that administration of exogenous serotonin can also increase availability of serotonin to neurons. It is Dr. Eiler's view that serotonin has the possibility of being either a substitute or a synergist for uptake inhibitors.

S.M. Lilitha Charmindrani Mendis-Handagama
D.V.M., The University of Sri Lanka, Peradeniya
Ph.D., Monash University, Australia
Associate Professor
Department of Comparative Medicine

Dr. Charmi Mendis-Handagama

Recent Publications

Mendis-Handagama, S.M.L.C., Ariyaratne, H.B.S., Kim, I. 2003. Prolonged and transient neonatal hypothyroidism on postnatal Leydig cell differentiation in the rat testis. *Arch. Androl*. In Press

Kim, I., Ariyaratne, H.B.S., Mendis-Handagama, S.M.L.C. 2002. Changes in the testis interstitium of Brown Norway rats with aging and effects of luteinizing and thyroid hormones on the aged testes in enhancing the steroidogenic potential. *Biol. Reprod*. 66:1359-1366.

Male Fertility Regulation and Contraception

One aspect of Dr. Mendis-Handagama's research focuses on finding the basic scientific information necessary to develop a reversible male contraceptive that maintains the normal androgen levels. Such a method will be an attractive alternative to the limited contraceptive methods currently available for men. Andropause, or the reduced levels of circulating male hormones due to aging, is treated by testosterone/androgen therapy – the only treatment available. A limitation of hormone therapy is that androgen treatment is contraindicated in conditions such as cardiovascular and prostate disease, both common diseases in the aging male.

Recent studies in Dr. Mendis-Handagama's laboratory, using a rat model, have revealed the potential of using thyroid hormone and luteinizing hormone (LH) in treating andropause, with no risks added to either cardiovascular or prostate disease. It is clear that thyroid hormone and LH have important regulatory function on testicular hormone production and spermatogenesis. However, researchers do not know the mechanism of action on testis function of thyroid hormone alone or in synergism with LH.

Dr. Mendis-Handagama's group is currently investigating the interactions between the hypothalamo-pituitary-thyroid and hypothalamo-pituitary-testis loops associated with testicular function in the mammalian male. Results from these studies will be used to understand how luteinizing hormone (LH) and thyroid hormone could act synergistically to produce degeneration of mature male germ cells and rejuvenation of aged testes in terms of its hormone secretory function observed in rats during their previous studies.

The Center of Excellence and the World Health Organization support Dr. Mendis-Handagama's research.

Diane V.H. Hendrix
D.V.M., The University of Tennessee
Associate Professor
Department of Small Animal Clinical Sciences

Dr. Diane Hendrix

Recent Publications

Hendrix DVH, Rohrbach BW, Bochsler PN, English RV. Histologic findings and persistence of *Blastomyces dermatitidis* in the eyes of dogs treated with systemically administered itraconazole. *Journal of the American Veterinary Medical Association*. In Press.

Adkins AE, Hendrix DVH*. Cataract evaluation and treatment in the dog: a review. *Compendium of Continuing Education for the Practicing Veterinarian*. In Press.

Skorobohach BJ, Ward DA, Hendrix DVH. Effects of oral administration of methazolamide on intraocular pressure and aqueous humor flow rate in clinically normal dogs. *American Journal of Veterinary Research,* 2003;64(2):183-7.

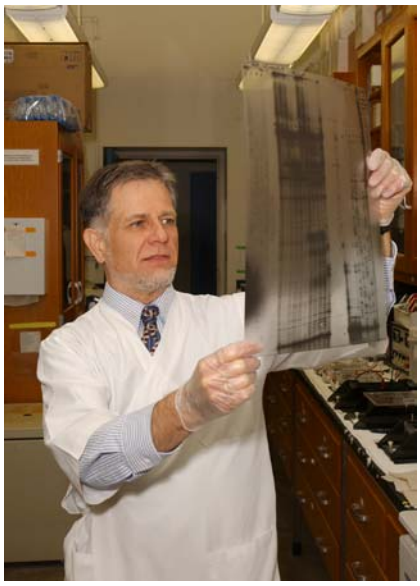
Efficacy of Topical Ocular Application of Tacrolimus

Both dogs and humans can develop a disease of decreased tear production, caused by an immune-mediated attack of the lacrimal gland. In humans, the disease is often part of a more systemic autoimmune disease, Sjögren's syndrome. In dogs, Keratoconjunctivitis sicca (KCS) is a devastating and potentially blinding disease that can cause corneal ulceration and rupture as well as pigmentation and vascularization of the cornea.

The currently accepted therapy for KCS in dogs is cyclosporine (CSA) ointment. Problems associated with the use of CSA for KCS in dogs include a lack of response to CSA in up to 30% of dogs with KCS; a maximum duration of twelve hours action requiring twice daily topical therapy; and facial hair loss in some dogs treated with CSA. The most common treatment of dry eye in humans is symptomatic therapy consisting of applying ocular lubricants and surgically removing the lacrimal punctae.

Tacrolimus (TACRO) is an immunosuppressive agent similar to CSA but more potent. Dr. Hendrix has previously determined that TACRO is safe for dogs. Dr. Hendrix's current hypothesis is that topical ophthalmic TACRO is an effective treatment of KCS in dogs, and may also be an effective treatment of Sjögren's syndrome in humans.

David A. Brian
D.V.M., Michigan State University
Ph.D., Michigan State University
Professor
Department of Pathobiology



Dr. David Brian

Recent Publications

Raman, Sharmila, Peter Bouma, Gwyn D. Williams, and David A. Brian. 2003. Stem-loop III in the 5' UTR is a *cis*-acting element in bovine coronavirus DI RNA replication. *J. Virol.* 77:6720-6730.

Brian, David A. and Ralph Baric. Structure and replication of the coronavirus genome. 2003 In: (Luis Enjuanes, ed). "Coroanviruses" in Current Topics in Microbiology and Immunology, Springer-Verlag. In press.

Wu, Hung-Yi, James S. Guy, Dongwon Yoo, Reinhard Vlasak, and David A. Brian. 2003. Common RNA replication signals among group 2 coronaviruses: evidence for in vivo recombination between animal and human coronavirus molecules. *Virology* .

Molecular Pathogenesis of Coronavirus

Corona virus infections cause costly respiratory and gastroenteric diseases in livestock and fowl, and chronic, disabling diseases in humans.

The primary research focus in Dr. Brian's laboratory is the molecular biology of coronavirus replication. Dr. Brian's group is making an intense effort to understand how 5 separate genetic elements in the coronavirus function to regulate production of viral proteins and progeny virus. In an effort to understand the determinants of this process, Dr. Brian's group is researching a sixth genetic region – a hot spot for variability. These studies could significantly impact the design of new therapeutic strategies.

Dr. Brian's group has discovered a small genetic variant (a viral minigenome) of the bovine coronavirus that replicates in the presence of normal virus. They are experimentally engineering this minigenome to carry many kinds of potential antiviral molecules into cells. One molecule is an enzyme, a ribozyme, designed to destroy the polymerase gene – the gene on which the virus depends for replication. This novel therapeutic approach would, in theory, cure a virus-infected cell without killing it.

Dr. Brian's laboratory has received national and international recognition for fundamental discoveries regarding the basic molecular biology of viruses. Dr. Brian's expertise recently placed him at the forefront of the efforts to understand severe acute respiratory syndrome or SARS, a member of the coronavirus family. Dr. Brian recently received supplemental funding from the National Institutes of Health for further SARS studies.

The Center of Excellence and the National Institutes of Health support Dr. Brian's research.

Barton W. Rohrbach
V.M.D, University of Pennsylvania
M.P.H., The Johns Hopkins University
Associate Professor
Department of Large Animal Clinical Sciences

Dr. Bart Rohrbach

Recent Publications

Rohrbach BW. Q-Fever. In: Fraser CM, ed. *The Merck Veterinary Manual*. 9th ed. Rahway, New Jersey: Merck and Co., Inc., 2003.

Rohrbach BW. Tularemia. In: Fraser CM, ed. *The Merck Veterinary Manual*. 9th ed. Rahway, New Jersey: Merck and Co., Inc., 2003.

Frank LA, Rohrbach BW, Bailey EM, West JR, Oliver JW. Steroid hormone concentration profiles in healthy intact and neutered dogs before and after cosyntropin administration. *Domest Anim Endocrinol* 2003 Jan;24(1):43-57

Effect of Intranasal Administration of Modified Live, Oral Vaccine against Bovine Coronavirus

Morbidity due to undifferentiated bovine respiratory disease (UBRD) in recently weaned calves in commercial backgrounding operations ranges from 30-80% and mortality from 1-2%. There is speculation that BCV may have a causative role in UBRD. The majority of cases of UBRD occur during the first 28 days in backgrounded calves.

A modified live attenuated coronavirus vaccine is currently licensed for oral use to prevent enteric disease in newborn calves. Dr. Rohrbach and his collaborators are conducting a randomized clinical trial to determine whether intranasal use of this vaccine will cause a reduction of UBRD in recently weaned calves.

The vaccine under study contains attenuated strains of bovine rotavirus and bovine coronavirus. It is given orally to newborn calves to stimulate rapid mucosal immunity. Isolates of bovine coronavirus from the respiratory and intestinal tracts of cattle are indistinguishable. It is reasonable to assume that this same type of rapid mucosal immunity would be simulated in the respiratory tract of naïve calves.

Results of this study may provide evidence for use of a vaccine to reduce morbidity from UBRD and help clarify the relationship between bovine coronavirus and UBRD.

Stephen P. Oliver
Ph.D., The Ohio State University
Professor
Department of Animal Science


Dr. Stephen Oliver (right) and staff

Recent Publications

Oliver, S. P., R. N. Gonzalez, J. S. Hogan, B. M. Jayarao, and W. E. Owens. 2003. *Microbiological procedures for the diagnosis of bovine udder infection.* 4th Edition, The National Mastitis Council, Inc., Madison, WI. In Press.

Oliver, S. P., R. A. Almeida, B. E. Gillespie, S. J. Ivey, H. Moorehead, P. Lunn, H. H. Dowlen, D. L. Johnson, and K. C. Lamar. 2003. Efficacy of extended pirlimycin therapy for treatment of experimentally-induced *Streptococcus uberis* intramammary infections in lactating dairy cattle. *Veterinary Therapeutics* 4(3):299-308.

Pangloli, Philipus, Yobouet Dje, S. P. Oliver, A. G. Mathew, D. A. Golden, W. J. Taylor, and F. A. Draughon. 2003. Evaluation of methods for recovery of *Salmonella* from dairy cattle, poultry and swine farms. *J. Food Prot.* In Press.

Pathogens in Bovine Mastitis

Mastitis costs dairy producers in the United States over $2 billion annually. Losses attributable to mastitis may cost Tennessee dairy producers more than $25 million annually. Mastitis in dairy cows is quite likely the most costly disease affecting dairy producers in Tennessee, the United States, and countries throughout the world.

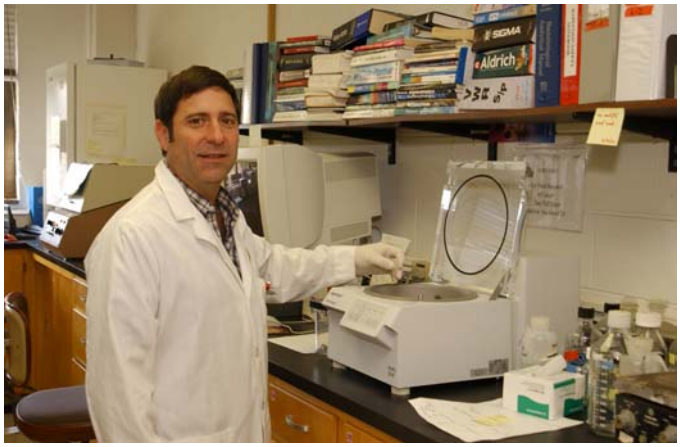
Dr. Oliver's group has been conducting studies designed to identify virulence factors produced by certain mastitis organisms (*Streptococcus* species) and implications of immunity to them. Dr. Oliver's group has been working to develop more accurate and better-defined strategies for controlling these mastitis pathogens.

Other studies by Dr. Oliver's group have determined that *Streptococcus uberis* and *Streptococcus dysgalactiae* readily adhere to and invade cells lining the bovine udder. When cultured in the laboratory and in the presence of epithelial cells, mastitis pathogens synthesize proteins not detected when bacteria are cultured alone. It is likely that these unique proteins are involved in virulence of bacteria, including their capacity to adhere to and invade mammary epithelial cells. Culturing mastitis pathogens in the laboratory and in the presence of epithelial cells may result in expression of bacterial virulence factors similar to that which occurs in the animal. This important discovery will be exploited to develop vaccines and manage mastitis.

Dr. Oliver's expertise in mastitis and milk quality has led to a new research initiative in food safety. In addition, Dr. Oliver has increased awareness regarding the importance of environmental pathogens in bovine mastitis. Further, Dr. Oliver has discovered fundamentally important information critical to controlling the heterogeneous organisms that cause mastitis.

The Center of Excellence and several contracts support Dr. Oliver's research.

Alan G. Mathew
Ph.D., Purdue University
Professor and Head
Department of Animal Science



Dr. Alan Mathew

Recent Publications

Mathew, A. G., F. Jackson, and A. M. Saxton. 2002. Effects of antibiotic regimens on resistance of Escherichia coli and Salmonella serovar Typhimurium in swine. *J. Swine. Health and Prod*. 20:7-13.

Franklin, M. A., A. G. Mathew, J. R. Vickers, and R. A. Clift. 2002. Characterization of microbial populations and volatile fatty acid concentrations in the jejunum, ileum, and cecum of pigs weaned at 17 versus 24 days of age. *J. Anim. Sci.* 80:2904-2910.

Arnett, D. B., P. Cullen, P. D. Ebner, A. G. Mathew. 2003. Characterization of resistance patterns and detection of apramycin resistance genes in E. coli isolated from swine exposed to various environmental conditions. *International Journal of Food Microbiology.* 89:11-20.

Bacterial Antibiotic Resistance

Some evidence suggests that agricultural use of antibiotics may be partly responsible for drug-resistant bacteria, which in turn may decrease the efficacy of similar antibiotics used in human medicine.

In their efforts to characterize genetic factors that lead to antibiotic resistance in animal and human pathogens in order to formulate effective control strategies, Dr. Mathew's group has generated much interest nationally and internationally.

Dr. Mathew's group is also investigating how different uses of antibiotics in livestock and pets affect antibiotic resistance patterns, concentrations, and shedding of food borne pathogens. Dr. Mathew's findings include the determination that the penta-resistance gene and integron sequence normally associated with *Salmonella* Typhimurium DT104 is widespread among other isotopes of salmonella associated with livestock. This extremely important finding indicates that other subtypes of this pathogen may make control through therapeutics difficult in the future.

Dr. Mathew's group has also determined that Class I integrons are common in non-pathogenic enteric bacteria, suggesting that these genes, which are important in the development, persistence, and spread of multi-resistant strains of bacteria, may ultimately spread to important pathogens. In further studies, Dr. Mathew's group has characterized management factors and antibiotic dosing regimens that reduce the prevalence of resistant bacteria, thus allowing the development of effective control strategies.

The Center of Excellence, Iams, and the National Pork Board support Dr. Mathew's research.

C.A. Speer
Ph.D., Utah State University
Distinguished Professor, Cellular and Molecular Immunology
Department of Forestry, Wildlife and Fisheries

Dr. C.A. Speer

Recent Publications

Leid, J.G., C.A. Speer and M.A. Jutila. 2002. Ultrastructural examination of cytoskeletal linkage of L-selectin and comparison of L-selectin cytoskeletal association to that of other human and bovine lymphocyte surface antigens. *Cellular Immunology* 215:219-231.

Leid, J.G., D. Hunter and C.A. Speer. 2002. Early diagnosis of Johne's disease in the American bison by monoclonal antibodies directed against antigen 85. *Ann NY Acad Sci* 969:66-72.

Dubey, J.P., R.J. Cawthorn, C.A. Speer and G.A. Wobeser. 2003. Redescription of the sarcocysts of Sarcocystis rylei (Apicomplexa: Sarcocystidae). *J. Eukaryotic Microbiol*. 50:430-436.

Diagnosis and Vaccination of Johne's Disease

Johne's disease is one of the three most important diseases of beef and dairy cattle in the United States with economic losses of more that $250 million annually. Johne's disease, induced by *Mycobacterium avium* subsp. *Paratuberculosis* (MPTB), is manifested as a chronic wasting disease. Recent evidence implicates MPTB as the etiologic agent of Crohn's disease in humans. Researchers suspect that MPTB is transmitted to humans via certain dairy products.

Although several diagnostic assays are available for MPTB, they are time-consuming, labor intensive and unreliable. The nature of MPTB infections has made it inordinately difficult to develop a sensitive and reliable diagnostic test. However, there is hope of developing a highly sensitive and specific diagnostic test based on antigen 85, a protein which is shed early in the blood of animals acutely infected with MPTB. Antigen 85 consists of a highly conserved complex of three fibronectin-binding proteins secreted by *Mycobacterium*-infected macrophages during infection by *M. tuberculosis, M. bovis,* and MPTB.

The preliminary data from studies conducted by Dr. Speer and his collaborators indicated that monoclonal antibody technology might eventually lead to a reliable diagnostic test for the early detection of MPTB infection in ruminants. With further research, such a test might also be used for identifying contaminated diary products as well as for diagnosing Crohn's disease in humans.

The Center of Excellence and the USDA support Dr. Speer's research.

Nicholas Frank
D.V.M., Purdue University
Ph.D., Purdue University
Assistant Professor, Large Animal Clinical Medicine
Department of Large Animal Clinical Sciences

Dr. Nicholas Frank

Recent Publications

Frank N, Sojka JE, Patterson BW, Wood KV, Bonham CC, Latour MA. Effect of hypothyroidism on kinetics of metabolism of very-low-density lipoprotein in mares. *Am J Vet Res*. 2003;64:1052-1058.

Frank N, Sojka JE, Latour MA. Effects of hypothyroidism and withholding of feed on plasma lipid concentrations, concentration and composition of very-low-density lipoprotein, and plasma lipase activity in horses. *Am J Vet Res*. 2003;64:823-828.

Frank N, Sojka JE, Messer NT. Equine thyroid dysfunction. *Vet Clin N Am Equine Pract* 2002;18:1-15

Equine Gastric Ulcer Disease

In the United States, owners spend $15 billion annually to maintain over 5.2 million horses. The horse industry contributes $25.3 billion to the gross domestic product; racing accounts for $7.4 billion of this figure.

The economic impact of Equine Gastric Ulcer Syndrome (EGUS) in horses is not known; however, researchers estimate prevalence to be from 25 to 81 percent. Clinical signs of EGUS include poor performance, colic, and weight loss. Severe cases of EGUS can result in death due to hemorrhage and gastric rupture.

Racehorses fed high concentrate (grain) diets may be more likely to develop gastric ulcers due to byproducts and volatile fatty acids (VFAs) that are produced when these diets are fermented by resident bacteria. Because the concentration of stomach acid is high, these VFAs may cause damage and gastric ulcer when absorbed through the stomach wall.

Dr. Frank's group has determined that certain acids as well as a low PH are important factors in the development of gastric ulcers in horses fed high concentrate diets. Dr. Frank hypothesizes that feeding horses diets rich in rice bran oil (RBO) will reduce the severity of gastric ulcers and significantly alter gastric and circulating lipids in horses; and that adding RBO to the diet will reduce gastric VFA concentrations, lower gastric ulcer scores, and alter measured blood lipid and lipoprotein parameters.

The Center of Excellence and Lloyd, Inc. support Dr. Frank's research.

Jack W. Oliver
D.V.M., Purdue University
Ph.D., Purdue University
Professor, Veterinary Pharmacology
Department of Comparative Medicine

Dr. Jack Oliver

Recent Publications

Frank, L.A., B.W. Rohrbach, E.M. Bailey, J.R. West, and J.W. Oliver. Steroid hormone concentration profiles in healthy intact and neutered dogs before and after cosyntropin administration. *Dom. Anim. Endocrinol*., 24:43-57, 2002.

Ward, D.A., L.K. Abney and J.W. Oliver. The effects of topical ocular application of 0.25% demecarium bromide on serum acetylcholinesterase levels in normal dogs. *Vet. Ophthal*., 6:23-25, 2003.

Frank, L.A., K.A. Hnilica, B.W. Rohrbach and J.W. Oliver. Retrospective evaluation of sex hormones and steroid hormone intermediates in dogs with alopecia. *Vet. Dermatol*., 14:91-97, 2003.

Tall Fescue Toxicity

Tall fescue, a forage crop, is grown on more than 34 million acres of pastures. More than 75% of these pastures are infested with the endophyte *Neotyphodium coenophialum*. Tall fescue toxicosis is a condition that results from the consumption of tall fescue infected with *Neotyphodium coenophialum*. Tall fescue toxicosis is a costly disease to animal producers; annual losses attributable to tall fescue toxicosis exceed $1 billion in the United States and $100 million in Tennessee.

Dr. Oliver is working to prevent the health problems in herbivores that consume tall fescue while maintaining the drought and insect resistance that the fungus conveys to the plant. Dr. Oliver and his collaborators have made many advances in the field including the development of a patented anti-fescue toxicosis vaccine. Previous studies by Dr. Jack Oliver's group established that vascular change occurs when herbivores consume infected tall fescue. The abnormalities in blood flow are integrally related to the economic losses encountered by the cattle industry in the United States and in other countries.

Recent studies have focused on amino acid changes in the sera of steers that graze infected tall fescue. These studies show a tendency for arginine deficiency and a change in the nitric oxide pathway in steers that graze infected tall fescue. Dr. Oliver's group is currently studying the effect of arginine deficiency on the reproductive function of bulls, steers, and heifers.

The Center of Excellence and the USDA support Dr. Oliver's research.

Terry W. Schultz
Ph.D., The University of Tennessee
Professor
Department of Comparative Medicine


Dr. Terry Schultz

Recent Publications

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Schultz, T.W. and Sinks, G.D. 2002. Xenoestrogenic gene expression: Structural feature of active polycyclic aromatic hydrocarbons. *Environmental Toxicology and Chemistry* 21: 783-786.

Seward, J.R., Cronin, M.T.D. and Schultz, T. W. 2002. Effect of precision of molecular orbital descriptors on the modeling of toxicity of selected pyridines. *SAR QSAR in Environmental Research* 13: 325-340.

Environmental Toxicant Testing and Modeling

Under the direction of Dr. Terry Schultz, research in the Biological Activity Testing and Modeling Laboratory focuses on developing structure-activity models and computer-aided, knowledge-based systems that predict toxic potencies from molecular structure. This research is significant in that hazard assessments can be conducted while conserving time, resources, personnel, and animals.

Dr. Schultz's group has developed one of the largest single-endpoint databases for xenoestrogens in the world. From these data, Dr. Schultz and his collaborators from around the world have developed mathematical models that rapidly predict toxic potency from molecular structure. Dr. Schultz's group has also developed a strategy for formulating valid quantitative structure-activity relationships (QSARS), which at the same time minimize the number of toxicological data points required. Dr. Schultz's group continues to work towards standardizing the methods for determining the quality of a toxicity model.

Dr. Schultz's group is currently involved in studies designed to provide fundamental toxic potency and molecular descriptor knowledge for the development and use of QSARS to predict the toxicity of organic chemicals. In this study, Dr. Schultz's group is studying compounds such as acrylates and methacrylates, which are among the more prevalent industrial organic chemicals in the world. The results of this study will be valuable to industry and regulatory agencies throughout the world.

Also noteworthy is that during the last three years, 18 publications with significant student contribution (14 publications with students as first or second author) have resulted directly from the Center's support of Dr. Schultz's research.

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Department of Microbiology, College of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands (January, 2003)

Mei-Zhen Cui

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Liang, S., Cui, M.-Z., Penn, M. and Chisolm, G., Oxidized lipoprotein regulation of tissue factor in smooth muscle cells. September 28 – October 2, 2003, International Atherosclerosis Conference, Kyoto, Japan.

Hugo Eiler

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M. Lilitha Charmindrani Mendis-Handagama (Charmi)

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Diane V. H. Hendrix

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Alan G. Mathew

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Jack W. Oliver

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Presented invited paper entitled "Research and educational programs of The University of Tennessee Food Safety

Center of Excellence" at The Food Safety Summit, The University of Minnesota, October, 2002.

Presented an invited seminar entitled "Mastitis control, milk quality and udder health" at the Tennessee Cow Care Seminar, Sweetwater, TN, November, 2002.

Presented a seminar entitled "Mastitis and dairy food safety research at The University of Tennessee" at the 1st Annual Tennessee Dairy Advisory Board Meeting, Nashville, TN, November, 2002.

Presented an invited seminar entitled "Approaches for the prevention of mastitis in heifers and multiparous cows during the periparturient period" at Pharmacia Animal Health, Kalamazoo, MI, January, 2003.

Presented two invited seminars entitled "SUAM: An important virulence factor of *Streptococcus uberis*" and "Development of a *Streptococcus uberis* intramammary challenge model" at Pfizer Veterinary Medicine Biological Discovery Animal Health Group, Groton, CT, February, 2003.

Presented invited seminar entitled "Research and educational opportunities at The University of Tennessee Food Safety Center of Excellence" to the Department of Food Science, Cornell University, Ithaca, NY, March, 2003.

Invited participant on a panel discussion entitled "Creating and working with successful competitive grant teams" at The University of Tennessee Institute of Agriculture Workshop on Partnerships for Grant & Contract Funding, Knoxville, TN, May, 2003.

Presented invited talk on "Entrepreneurial activities of The University of Tennessee Food Safety Center of Excellence" at The University of Tennessee Research Foundation/Tech 2020 Center for Entrepreneurial Growth Symposium, Knoxville, TN May, 2003.

Presented two invited talks entitled "Research on mastitis prevention and control" and "On-farm food safety research conducted at the UT Food Safety Center of Excellence" at the National Ag in the Classroom Teachers Conference, Middle Tennessee Experiment Station, Spring Hill, TN, June, 2003.

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TABLE 1

RESEARCH PROJECTS FUNDED EXTERNALLY
Report Period 2002 -2 32003

Project Director	Title of Grant	Funding Agency	Total Award	Expenditures 03
Joseph Bartges	Evaluation of A Pet Anti-Aging Wellness System	eBrands	$75,700 4/15/03 – 6/30/04	$4,184
	Studies on Urate Urothithiasis in Dalmations: Prevalence of Kidney Stones, Survey of Dalmatian Owners	Dalmation Club	$59,684 3/1/03 – 6/30/04	$0
	Nutrition Technician	Nestle Purina	$107,150 3/7/03 – 3/6/08	$0
	Comparisons of 2 Dietary Approaches to Managing Canine Chronic Renal Failure	Iams	$74,289 4/1/99 – 12/31/05	$18,795
	APR Studies	Hill's pet Nutrition	$13,500 11/1/97 – 10/31/04	$10,583
David Brian	Mechanisms of Coronavirus RNA Amplification	NIH	$1,539,400 7/1/96 – 5/31/07	$202,590
Mei-Zhen Cui	Scientist Development Award	American Heart Association	$240,000 1/1/98 – 12/31/02	$6,388
	Lipid Lysophosphatidic Acid Regulation of Transcription Factor Egr-1 in Vascular Smooth Muscle Cells	Pfizer	$100,000 7/01/02 – 6/30/04	$32,262

Project Director	Title of Grant	Funding Agency	Total Award	Expenditures 03
Nicholas Frank	Effect of Oral Levothyroxine on Thyroid Hormone Status and Energy Metabolism in Horses	Llyod, Inc	$10,010 5/13/03 – 5/14/04	$24,600
Alan Mathew	Effect of Diet on Microflora of Dogs	Iams	$72,434 8/23/01 – 7/01/02	$0
	Effect of Egg Yolk Antibodies and Antibiotic Regimens on Shedding of *Salmonella Typhimurium*	National Pork Board	$48,560 5/1/03 – 5/1/04	$0
Charmi Mendis-Handagama	Antispermatogenic Effects of Luteinizing and Thyroid Hormones in Three-Month-Old Sprague Dawley Rats	World Health Organization	$69,750 12/1/01 – 11/30/03	$55,164
Darryl Millis	Multi-Center Clinical Study of the Effect of an Investigational Drug on Chronic Pain in Dogs with Osteoarthritis	Novartis	$249,789 1/30/00 – 12/1/03	$66,212
	Effect of Milk Ultrafiltration Fraction on Osteoarthritis in Dogs	Iams	$55,183 10/1/00 – 12/1/02	$88,046
Jack Oliver	Reactivity of Bovine Vasculature to Ergovaline and Erfine of Toxic Tall Fescue	USDA	$264,003 9/1/97 – 9/30/02	$0

Project Director	Title of Grant	Funding Agency	Total Award	Expenditures 03
Stephen Oliver	Recurrent Coliform Mastitis in New York Dairy Cows	Cornell University	$99,922 1/1/03 – 12/5/04	$0
	Efficacy of Extended Ceftiofur Therapy for Treatment of Naturally Occurring Subclinical Mastitis in Lactating Dairy Cows	Pharmacia & Upjohn	$200,112 5/1/01 – 12/1/02	$47,172
	Efficacy of Masticide for the Treatment and Prevention of Teat Lesions During the Winter Months	Sporicidin International	$41,628 9/1/00 – 8/31/02	$21,245
Barry Rouse	Immunity Mechanisms in Herpes Virus Infections	NIH	$1,656,250 1/1/01 – 12/31/05	$294,970
	Mechanisms of Herpetic Stromal Keratitis	NIH	$1,779,700 9/30/02 – 9/29/07	$290,285
	Vaccination Against Herpes Simplex Virus	NIH	$1,396,346 3/1/01 – 2/28/05	$381,021
	Biodelivery Sciences	Biodelivery Sciences	$12,000 Open	$0
	Herpes Zosterfication	Smith-Kline Biological	$127,746 Open	$0
	HSV Zosterform Model	Mohave Therapeutics	$25,754 1/28/02 – 1/27/03	$0

Project Director	Title of Grant	Funding Agency	Total Award	Expenditures 03
Hildegard Schuller	Transplacental Pancreatic Carcinogenesis by NNK	NIH	$1,158,400 4/1/03 – 1/27/03	$59,230
	NNK, Beta-Adrenergic AA Release and Lung Cancer	NIH	$1,142,201 4/1/02 – 3/31/06	$287,786
	Preclinical Model for Chemoprevention of NSLC in Former Smokers	NIH	$868,800 5/1/03 – 4/30/06	$14,584
	Assistance in Analysis and Characterization	UT-Battelle	$38,280 7/1/01 – 6/30/03	$1,267
Pamela L.C. Small	Mycolactone-mediated Virulence in *Mycobacterium Ulcerans*	NIH	$2,018,127 1/1/01 – 2/28/06	$462,494
C.A. Speer	Study of Johne's Disease	USDA	$20,000 10/1/02 – 9/30/03	$0
Patricia K. Tithof	Role of Arachidonic Acid in Endothelial Cell Apoptosis Induced by Tobacco Components	Philip Morris	$522,000 6/1/01 – 5/31/04	$170,349
	Role of Phospholipase-Mediated Release of Arachidonic Acid in Apoptosis of Endothelial Cells Exposed to Tobacco Products	American Heart Association	$100,000 7/1/01 – 6/30/03	$60,828

Project Director	Title of Grant	Funding Agency	Total Award	Expenditures 03
Hwa-Chain Robert Wang	Pathway Leads to Apoptosis in SRC Transformed Cells	NIH	$517,020 1/1/99 – 12/31/03	$72,755
Xuemin Xu	Role of Apolipoprotein in AD Amyloid Formation	NIH	$677,968 5/1/99 – 5/30/03	$48,272
	Role of a Novel protein (PSAP) in Neurodegeneration	NIH	$1,282,500 9/1/01 – 8/31/05	$414,300
		Total	**$16,753,650**	**$3,156,469**

TABLE 2

FACULTY BENCHMARKS
Report Period 2002 – 2003

Publications and Presentations	**2003**
Articles	116
Books or Book Chapters	11
Published Proceedings	17
Total Publications	144
Abstracts	70
Invited Presentations at:	
National Meetings	24
International Meetings	26
Faculty in Center	20

TABLE 3

COE AWARDS
Fiscal Year 2004

Investigator	Department
David Brian Molecular Pathogenesis of Corona Virus	Pathobiology
Mei-Zhen Cui The *in-vivo* Role of Lysophosphatidic Acid in the Development of Atherosclerosis	Pathobiology
Nicholas Frank Effect of Obesity on Physiological Parameters of Energy Metabolism in Horses	Large Animal Clinical Sciences
Diane Hendrix Efficacy of Topical Ocular Application of Tacrolimus	Small Animal Clinical Sciences
Charmindrani Mendis-Handagama EDS Hamster Model to Understand the Effects of Light and Thyroid Hormone on Stem Cell Differentiation into Helping Leydig Cells in Testes of Seasonal Breeders	Comparative medicine
Darryl Millis Postoperative Physical Therapy of Orthopedic Patients	Small Animal Clinical Sciences
Jack Oliver Growth and Reproductive Performance Following Arginine Supplementation of Beef Cattle Grazing in Endophyte-Infected Tall Fescue pastures	Comparative Medicine
Stephen Oliver Detection and Quantification of Antibiotic Resistance Genes and Mobile Genetic Elements in mastitis pathogens and Foodborne pathogens	Animal Science
Barry Rouse Improvement of Vaccine Using Hsp70 as Antigen Carriers	Pathobiology
Hildegard Schuller Regulatory mechanisms in Lung Cancer	Pathobiology
Terry Schultz Development and Use of Nucleophilic Reactivity Indices as a Means of Evaluating Chemicals with Potential to be Used in Local Acts of Terrorism	Comparative Medicine

Carla Sommerdahl — Large Animal Clinical Sciences
Effects of Oral Levothyroxine on Thyroid Hormone Measure, Cortisol, Lymphocyte Subsets, and Energy Metabolism in Horses

C.A. Speer — Forestry, Wildlife, and Fisheries
Diagnosis and Vaccination of Johne's Disease

Patricia Tithof — Pathobiology
Polycyclic Aromatic Hydorcarbons, Arachidonic Acid and Emphysema

Hwa-Chain Robert Wang — Pathobiology
Ras Oncogene-Induced Signaling Pathway Leading to Apoptosis

Xuemin Xu — Pathobiology
Determine the Role of TNF-Receptor-PSAP Death Signaling Pathway in the Pathogenesis of Alzheimer's Disease

Start-Up Awards

Seung J. Baek — Pathobiology
PPAR-Gamma Ligands in Colorectal Cancer

Gina Pighetti — Animal Science
Host Mechanisms that Contribute to the Pathogenesis of *Streptococcus uberis* Mastitis

Howard Plummer — Pathobiology
The Role of G1RK in Breast Cancer and its Functional Association with Beta-Adrenergic Mediated Signal Transduction

Pamela Small — Pathobiology
Molecular Pathogenesis of Mycobacterial Infections

CENTERS OF EXCELLENCE/CENTERS OF EMPHASIS
ACTUAL, PROPOSED, AND REQUESTED BUDGET

Institution College of Veterinary Medicine — Center of Excellence

	FY 2002-03 Actual			FY 2003-04 Proposed			FY 2004-05 Requested		
	Matching	Appropr.	Total	Matching	Appropr.	Total	Matching	Appropr.	Total
Expenditures	258,000	516,000	**774,000**	248,550	497,100	**745,650**	286,650	573,300	**859,950**
Salaries									
Faculty	9,588	19,176	**28,764**	8,400	16,800	**25,200**	8,820	17,640	**26,460**
Other Professional	28,080	56,161	**84,241**	66,091	132,181	**198,272**	62,835	125,669	**188,504**
Clerical/ Supporting	18,421	36,842	**55,263**	24,379	48,758	**73,137**	25,598	51,196	**76,794**
Assistantships	26,794	53,588	**80,382**	21,287	42,573	**63,860**	22,351	44,702	**67,053**
Total Salaries	**82,883**	**165,767**	**248,650**	**120,157**	**240,312**	**360,469**	**119,604**	**239,207**	**358,811**
Longevity	**1,132**	**2,265**	**3,397**	**1,466**	**2,931**	**4,397**	**1,799**	**3,598**	**5,397**
Fringe Benefits	17,660	35,320	**52,980**	24,084	48,168	**72,252**	25,028	50,057	**75,085**
Total Personnel	**101,675**	**203,352**	**305,027**	**145,707**	**291,411**	**437,118**	**146,431**	**292,862**	**439,293**
Non-Personnel									
Travel	3,198	6,396	**9,594**	7,450	14,899	**22,349**	5,110	10,220	**15,330**
Software	90	179	**269**			**0**			**0**
Books & Journals	363	727	**1,090**	567	1,133	**1,700**	595	1,190	**1,785**
Other Supplies	44,834	89,669	**134,503**	126,029	252,057	**378,086**	85,731	171,462	**257,193**
Equipment	24,294	48,588	**72,882**	39,237	78,473	**117,710**	17,500	35,000	**52,500**
Maintenance	11,757	23,515	**35,272**	14,711	29,423	**44,134**	14,308	28,616	**42,924**
Scholarships	513	1,027	**1,540**	11,333	22,667	**34,000**	11,900	23,800	**35,700**
Consultants			**0**			**0**			**0**
Renovation			**0**			**0**			**0**
Other (Specify) Cost Share	(787)	(1,573)	**(2,360)**			**0**			**0**
Print & Dup	3	7	**10**	4,666	9,334	**14,000**	4,900	9,800	**14,700**
Communications	273	547	**820**	166	334	**500**	175	350	**525**
Rental, Pub, Sp Svc,Ent	10,679	21,359	**32,038**			**0**			**0**
Total Non-Personnel	**95,217**	**190,441**	**285,658**	**204,159**	**408,320**	**612,479**	**140,219**	**280,438**	**420,657**
GRAND TOTAL	**196,892**	**393,793**	**590,685**	**349,866**	**699,731**	**1,049,597**	**286,650**	**573,300**	**859,950**
Revenue									
New State Appropriation		516,000	**516,000**		497,100	**497,100**		573,300	**573,300**
Carryover State Appropriation		80,421	**80,421**		202,631	**202,631**			**0**
New Matching Funds	258,000		**258,000**	248,550		**248,550**	286,650		**286,650**
Carryover from Previous Matching	40,211		**40,211**	101,316		**101,316**			**0**
Total Revenue	**298,211**	**596,421**	**894,632**	**349,866**	**699,731**	**1,049,597**	**286,650**	**573,300**	**859,950**

Center of Excellence in Livestock Diseases and Human Health

A Tennessee Higher Education Commission Accomplished Center of Excellence

Annual Report 2003

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