A Tennessee Higher Education Commission Accomplished Center of Excellence
Annual Report 2004

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Left Image - PSAP-Induced Apoptosis is Specific. Xu, et al. In:
The Journal of Biological Chemistry 277:48913-48922. 2003.
Right Image - Tetracycline-Regulated Ectopic Expression of
H-Ras Protein and Cellular Transformation. Wang, et al. In:
Electronic Journal of Biotechnology 7(2): 195-198. 2004.

Message from the Center of Excellence

Dr. Michael J. Blackwell and Dr. Robert N. Moore

This year marks the 20th anniversary of the Center of Excellence in Livestock Diseases and Human Health. Since 1984 the Center has continually sought to improve animal agriculture and human health through the study of livestock diseases and the development of animal models of important human diseases. During the last 20 years, Center faculty have made numerous prominent advancements in cancer biology, molecular pathophysiology, reproduction, host defense, and disease transmission. Center faculty have also impacted agricultural productivity through advancements in the prevention and treatment of infectious and other non-infectious livestock diseases.

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.

We are pleased to present the 2004 annual report for the Center of Excellence in Livestock Diseases and Human Health. The Center faculty again had a stellar year in all measures of productivity. Support from the Center has been instrumental in building total external funding for its faculty in excess of $18.2 million with a 6.8:1 return on the State's investment. We are pleased with the progress made by Center faculty, and we hope you enjoy this summary presentation of Center activities and accomplishments.

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

	Fiscal Year 2004 (17 Faculty in Center)	Fiscal Year 2003 (20 Faculty in Center)
Publications		
-Refereed Articles	106	116
-Books or Book Chapters	4	11
-Proceedings	35	17
Abstracts	60	70
Presentations		
-National	35	24
-International	31	26
External Funding	$18,249,519	*$16,165,523
Research Expenditures	$3,392,244	$3,156,469
Return on Investment	6.8:1	6.1:1

*External Funding in fiscal year 2003 was reported as $16,753,650; however this figure was overstated by $588,127 due to a database error. The figure reported above reflects the correction.

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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 and Comparative Medicine
2) Mechanisms of Disease, Pathogenesis, and Immunity

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 Research and Graduate Programs 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. Center faculty consist of senior members who have research interests in line with Center objectives and have a strong history of securing external funding using Center funds. Junior members are those who have received seed money or bridge funding, or new faculty who have received start-up funds. Junior members are expected to secure external funding within two years; members who fail to secure such funding will be placed on probation for one year. If at the end of the probationary period external funding has not been secured, the member will be dismissed from the Center. During fiscal year 2004 the Center awarded $421,140 in support of 17 projects.

Support for faculty researchers totaled $421,140

Equipment

Equipment grants totaled $40,000

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 Research and Graduate Programs 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 2004 the Committee approved 2 pieces of equipment totaling $40,000. Investigators benefiting from these equipment grants were Dr. Darryl Millis, Dr. Hwa-Chain Wang, Dr. Hildegard Schuller, Dr. Howard Plummer, Dr. Joe Bartges, and Dr. Al Legendre.

Student Research

COE funded 16 student researchers; COE faculty participation increased 67% in FY04

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. In order to maximize student participation, the program is open to both COE and non-COE faculty. During fiscal year 2004, COE faculty participation in the program increased 67%, and included Drs. Baek, Frank, Schultz, Sommardahl, and Mendis-Handagama; the Center will continue to encourage participation of COE faculty. This year, the Center supported 16 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 six years approximately 43 manuscripts, several with students from this program as senior authors, were published in refereed journals.

At the end of fiscal year 2003, Dr. Claudia Kirk was asked to coordinate the summer program. In addition to laboratory research this year, Dr. Kirk provided weekly seminars at which CVM faculty and administrators spoke to the students regarding a variety of topics, including career opportunities in research, research study design, ethics in research, compliance issues in lab animal care, guidelines for professional writing - grant proposals and journal articles, and an overview of the grant and contract process.

To further enhance the program, Dr. Kirk has applied for additional funding from the Merck-Merial Veterinary Scholars Program.

Culture for Discovery

In conjunction with the CVM graduate program in Comparative and Experimental Medicine, the Graduate School of Medicine, and the departments of Animal Science and Microbiology, the Center sponsored several invited speakers through two seminar series: Mechanisms of Disease and Microbial Pathogenesis. These seminars were well-attended and fostered a culture for discovery by stimulating discussion and interaction among students and faculty. In addition, the seminars provided the potential for establishing productive external collaborations for faculty. The Center will continue efforts to secure quality speakers for this series on contemporary research topics.

Infrastructure

In support of the CVM's research enterprise, the Center provides the following:

- Skilled cell sorter technician for flow cytometry lab
- Maintenance contract on flow cytometer
- Supplies for cell sorter
- Training, as required, for cell sorter
- Secure BSL2 facility

In addition, the Center is currently developing a tissue culture core facility.

Personnel

As previously mentioned, Dr. Claudia Kirk was asked to coordinate and expand the COE Summer Research Program. Dr. Robert N. Moore, Professor and Associate Dean for Research and Graduate Studies continues as Director of the Center.

Dissemination of Research

In order to keep the public informed of research accomplishments, CVM distributes a newsletter, *Veterinary News*, and a magazine, *Veterinary Vision*. These publications, which carry features concerning on-going research activities and the results of concluded research studies, are written for the general public. Research Activities, a link on the CVM 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 CVM, 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.

Accomplishments

Center faculty 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 2003-2004 were excellent in terms of benchmarks and extramural funding base. The 17 Center faculty averaged approximately 6 refereed publications (106 total), and 4 invited presentations (67 total) at prestigious national and international meetings. The return on the State's investment in the Center as the ratio of expenditures from extramural funding to Center appropriation was 6.8:1. Extramural funding totaled $18,249,519 increasing more than $2 million this year. The total funding includes new multi-year awards for Drs. Baek, Cui, Frank, Oliver, Plummer, Schultz, and Wang totaling $1,960,873.

Extramural funding totaled $18,249,519; new grants totaled $1,960,873; return on investment 6.8:1

See Publications and Presentations for a complete listing of faculty benchmarks; see Research Expenditures and Research Funded Externally for data summary.

Seung Baek

Federal		$108,626
Industry		0
Foundation/Private		0
	Total	*$108,626*

David Brian

Federal		$249,310
Industry		0
Foundation/Private		0
	Total	*$249,310*

Mei-Zhen Cui

Federal		0
Industry		$43,726
Foundation/Private		$67,709
	Total	*$111,435*

Nicholas Frank

Federal		0
Industry		$22,094
Foundation/Private		0
	Total	*$22,094*

Darryl Millis

Federal		0
Industry		$42,508
Foundation/Private		0
	Total	*$42,508*

Stephen Oliver

Federal		0
Industry		$108,932
Foundation/Private		$47,142
	Total	*$156,074*

Gina Pighetti

Federal		$16,698
Industry		0
Foundation/Private		0
	Total	*$16,698*

Barry Rouse

Federal		$1,026,781
Industry		0
Foundation/Private		0
	Total	*$1,026,781*

Hildegard Schuller

Federal		$768,899
Industry		0
Foundation/Private		0
	Total	*$768,899*

Terry Schultz

Federal		$5,387
Industry		0
Foundation/private		0
	Total	*$5,387*

Pamela L.C. Small

Federal		$266,247
Industry		0
Foundation/private		0
	Total	*$266,247*

Patricia Tithof

Federal		0
Industry		$157,616
Foundation/Private		0
	Total	*$157,616*

Hwa-Chain Wang

Federal		$173,560
Industry		0
Foundation/Private		0
	Total	*$173,560*

Xuemin Xu

Federal		$287,008
Industry		0
Foundation/Private		0
	Total	*$287,008*

Total Research Expenditures
$3,392,469

State Appropriation
$495,600

The return on the State's investment in the COE as the ratio of expenditures from external funding to COE appropriation is **6.8:1**

Seung Baek

Federal		$324,000
Industry		0
Foundation/Private		0
	Total	*$324,000*

David Brian

Federal		$1,131,121
Industry		0
Foundation/Private		0
	Total	*$1,131,121*

Mei-Zhen Cui

Federal		$1,002,400
Industry		$647,397
Foundation/Private		$154,000
	Total	*$1,803,797*

Nicholas Frank

Federal		0
Industry		$112,353
Foundation/Private		0
	Total	*$112,353*

Charmi Mendis-Handagama

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

Darryl Millis

Federal		0
Industry		$460,233
Foundation/Private		0
	Total	*$460,233*

Stephen Oliver

Federal		$341,879
Industry		$240,052
Foundation/Private		$131,677
	Total	*$713,608*

Gina Pighetti

Federal		$65,011
Industry		0
Foundation/Private		0
	Total	*$65,011*

Howard Plummer, III

Federal		0
Industry		$752,989
Foundation/Private		0
	Total	*$752,989*

Barry Rouse

Federal		$4,832,296
Industry		0
Foundation/Private		0
	Total	*$4,832,296*

Hildegard Schuller

Federal		$3,169,401
Industry		0
Foundation/Private		0
	Total	*$3,169,401*

Terry Schultz

Federal		$378,864
Industry		0
Foundation/private		0
	Total	*$378,864*

Pamela L.C. Small

Federal		$1,480,750
Industry		0
Foundation/Private		0
	Total	*$1,480,750*

Patricia Tithof

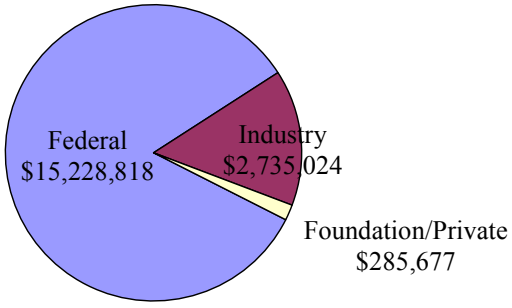
Federal		0
Industry		$522,000
Foundation/Private		0
	Total	*$522,000*

Hwa-Chain Wang

Federal		$1,150,846
Industry		0
Foundation/Private		0
	Total	$1,150,846

Xuemin Xu

Federal		$1,282,500
Industry		0
Foundation/Private		0
	Total	*$1,282,500*



External Funding

Total External Funding
$18,249,519

Total COE-related external funding increased by 12.9% in FY 04 due to significant new grants and contracts awarded to COE faculty.

The Center will continue to concentrate on developing newly recruited investigators while promoting initiatives to enhance its research capacity and direction. This year (FY04) the Center received 26 funding requests, and will expend $420,000 to fund 18 projects in the College of Veterinary Medicine and the College of Agricultural Sciences and Natural Resources. In addition, $100,000 has been committed for purchasing essential research equipment. The projects funded represent 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. 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:

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 continue to support public health oriented projects designed to support surveillance, intervention, and resolution of potential attacks directed against humans and food animals. In conjunction with the Knox County Health Department, the Center will sponsor three one day conferences designed to train responders to an agricultural incident. Theses conferences will be offered in Knox, Roane, and Hamblen counties and are aimed primarily at veterinarians and extension agents. The Center will also sponsor a one week conference on foreign animal and emerging diseases. This conference will feature speakers from various State and Federal agencies, and experts from South Africa, the Netherlands, and the United Kingdom.

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 addition, this year the Center is cooperating substantially in the offering of "invited speaker" courses in Microbial Pathogenesis and Mechanisms of Disease. These courses will increase national and international exposure of the Center's faculty, students, and programs; and, at the same time, enhance the potential for developing external collaborations for our faculty and postdoctoral opportunities for our students. This initiative has been so well supported by Center faculty that plans are to continue and to even expand this Center sponsored program.

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

Preclinical Model for Prevention of NSCLC in Former Smokers

Non-small cell lung cancer (NSCLC) accounts for 80% of lung cancers; smoking is the most significant risk factor for the development of all types of lung cancer. Smoking cessation decreases the risk of lung cancer; however, smokers who quit usually do so after years of smoking, at which time gene mutations caused by tobacco carcinogens are already evident.

Of the three types of NSCLC, peripheral pulmonary adenocarcinoma (PAC) is the most common. There are two phenotypically different types of PAC: PAC with features of bronchiolar Clara cells (PACC) and PAC with features of alveolar type II cells (PAC-type II). In previous studies, Dr. Schuller found that NNK, a potent tobacco carcinogen, causes PACC to develop in hamsters, but NNK causes PAC-type II to develop in mice.

Dr. Schuller's recent data, along with published evidence, suggest that the growth of human and murine (mouse and rat) PAC-type II cells is controlled by the epidermal growth factor receptor (EGF-r) pathway, and agents that increase intracellular cyclic AMP (cAMP) can inhibit this pathway. The data further indicate that human and hamster PACC is controlled by beta-adrenergic receptors, which are stimulated by beta-adrenergic agonists or agents that increase cAMP. Cyclic AMP is an important molecule that controls many biological processes, including cell proliferation.

These data indicate that because adenocarcinomas of either lineage can develop in humans, it is possible that agents with strong chemopreventive effects via stimulation of cAMP in murine models may, in humans, selectively promote adenocarcinomas derived from PACC cells.

In preclinical studies, murine models are widely used to test the efficacy of novel chemopreventive agents. Dr. Schuller's study documents the need for the re-evaluation of published extrapolations of rodent chemoprevention data to human lung cancer, considering similarities in tumor phenotype, cell lineage, and expression of regulatory pathways between the human disease and the animal models.

Hildegard Schuller
D.V.M., Justus Liebig University, Giessen, Germany
Distinguished Professor and Head
Pathobiology

Recent Progress
One grant funded during FY 03-04

DOE
Co-PI with Dr. George Kabalka, Chemistry
$179,135
New Radiotracers for Targeting Mutated Raf Protein for the Early Detection of Cancer

Note: COE funds were used to collect preliminary data vital to the success of this recently funded project.

In conjunction with published evidence, Dr. Schuller's data also suggest that some widely-advertised cancer preventive agents may be unsafe for smokers and former smokers due to these agents' selective promoting effects on initiated cells of PACC lineage.

Potency and Molecular Signatures of Tobacco Carcinogens in the Early Development of Human Breast Cancer

After lung cancer, breast cancer ranks second among cancer deaths in women. In the United States, one out of eight women will develop breast cancer during her lifetime – a new case is diagnosed every three minutes. Researchers have identified several factors, including age, family history, and obesity, that increase the risk of developing breast cancer.

Researchers know that cigarette smoke contains many potent cancer-causing chemicals; however, numerous investigations into the potential link between smoking and breast cancer have produced conflicting results. Epidemiological studies have suggested that exposure to tobacco substances increases the risk of developing breast cancer, but more research is required to precisely identify the tobacco carcinogens involved and the exact roles they might play in the development of breast cancer.

NNK, a tobacco-specific nitrosamine, is one of the most potent carcinogens found in cigarette smoke. Studies have shown that NNK induces lung tumors in rodents. Most studies involving tobacco carcinogens use high doses of the carcinogen to induce tumors in animals; however, such studies have not been successful in elucidating the role tobacco carcinogens play in the induction of mammary tumors in animals.

Hwa-Chain Robert Wang
B.V.M., National Chung-Hsing University, Taiwan
Associate Professor
Pathobiology

Recent Progress
One grant funded during FY 03-04

Philip Morris, Inc.
$633,326
Potency and Molecular Signatures of Tobacco Carcinogens in the Early Development of Human Breast Cancers

Note: COE funds were used to collect preliminary data vital to the success of this recently funded project.

In a recent study, Dr. Wang's group treated human breast epithelial cells with the same concentrations of NNK commonly detected in smokers. The results of their study showed, for the first time, that NNK can induce noncancerous cells to acquire cancerous properties. Dr. Wang's group is currently working to identify the molecular signatures of NNK-induced breast cancer cells.

Based on the molecular signature of cancerous cells, researchers will be able to determine the stage of cancers, and identify molecular targets for choosing agents that prevent cancer by interfering with the biological processes underlying cancer development.

The Role of GIRK in Breast Cancer and its Functional Association with Beta-Adrenergic Mediated Signal Transduction

Breast cancer is the leading cancer in women. Despite significant advances in early detection and treatment of breast cancer, a large proportion of cases demonstrate extensive metastatic spread, high relapse rate, and failure to respond to therapy. In particular, estrogen non-responsive breast cancers have a poor prognosis.

Most breast cancers develop in the glandular tissue; these cancers are classified as adenocarcinoma, a term applied to cancers of glandular tissue anywhere in the body. Dr. Plummer's group, as well as other researchers, has shown that adenocarcinoma in lung, colon, and pancreas express beta-adrenergic receptors, which mediate a variety of cellular events, and that stimulation of these receptors leads to DNA synthesis. DNA synthesis is necessary for cells to replicate, and replication enables a cancerous tumor to continue growing.

The expression of beta-adrenergic receptors has been correlated with the overexpression of arachidonic acid-metabolizing enzymes, cyclooxygenase-2 (COX-2) and lipoxygenase in adenocarcinomas of lungs, colon, prostrate, pancreas, and breast. Recent studies in Dr. Plummer's laboratory demonstrated that three estrogen-responsive and three estrogen non-responsive cell lines derived from human breast cancers exhibit a significant reduction in DNA synthesis when exposed to beta-blockers and inhibitors of COX-2 and lipoxygenase. Inhibiting DNA synthesis would prevent cells from replicating.

Dr. Plummer's group has also found a functional link between the beta-adrenergic receptor pathway and the G-protein inwardly rectifying potassium channel (GIRK1) in breast cancer cell lines, and the two pathways are involved in regulating the growth of these cancer cells. Current studies in Dr. Plummer's laboratory are underway to determine the growth regulatory mechanisms stimulated by these pathways. Modulation of GIRK channels may be an important tool in diagnosis or treatment of breast cancers.

Results from Dr. Plummer's studies will open avenues for the development of preventative approaches and treatments of breast cancer, particularly the estrogen non-responsive type of breast cancer.

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

Recent Progress
One grant funded during FY 03-04

Philip Morris, Inc.
$752,989
GIRK Channels, Beta-Adrenergic Signaling and Breast Cancer

Note: COE funds were used to collect preliminary data vital to the success of this recently funded project.

Polycyclic Aromatic Hydrocarbons (PAHs), Arachidonic Acid, and Emphysema

Cigarette smoking is the most significant risk factor in the development of emphysema, an advanced form of chronic obstructive pulmonary disease (COPD) that affects an estimated 16 million people in the United States each year. Emphysema is characterized by loss of lung function following the destruction of alveolar architecture, which greatly reduces the effective surface area required for gas exchange.

Recent studies demonstrate that cigarette smoke-induced apoptosis, or programmed cell death, plays an important role in the loss of alveolar architecture, the hallmark of emphysema. However, little is known about the components of cigarette smoke responsible or the signaling pathways involved in this effect.

Dr. Tithof's group has demonstrated that specific compounds present in cigarette smoke in high concentrations induce apoptosis in epithelial cells. These compounds include three polycyclic aromatic hydrocarbons (PAHs) and the nitrosated derivative of nicotine, NNK. Moreover, they have identified the signal transduction pathways involved in this effect.

Dr. Tithof's group found that PAHs and NNK induce endothelial apoptosis by activating the phospholipase A_2 (PLA_2)/arachidonic acid cascade, an important pathway that produces more than 100 biologically active lipid mediators that have important roles in a number of diseases, including coronary artery disease and emphysema. Dr. Tithof's study was the first to link the exposure of endothelial cells to cigarette smoke with PLA_2 activation, fatty acid release, and apoptosis.

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

Recent Progress

Found that specific components of cigarette smoke induce apoptosis in epithelial cells, and identified the signaling pathway involved in this effect.

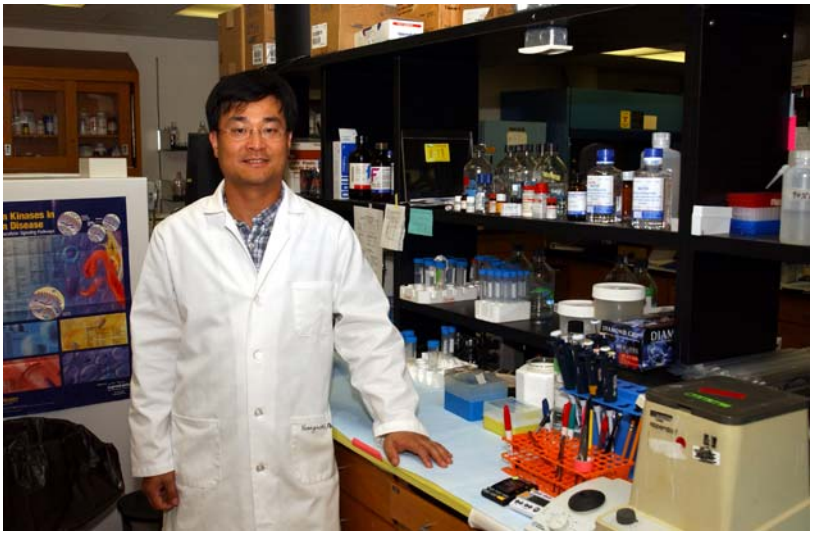
Identified three PLA_2 isoforms activated by specific PAHs, and is making progress towards determining the roles of specific PLA_2s in PAH-induced apoptosis of pulmonary epithelial cells.

Submitted three proposals based on preliminary data generated with COE support; two proposals are currently pending, one of which is in collaboration with Dr. Gary Sayler, Center for Environmental Biotechnology.

Using eight PAHs that have been implicated in the pathogenesis of emphysema, Dr. Tithof's group is working to determine the role of arachidonic acid in PAH-induced apoptosis of human pulmonary microvascular endothelial cells, and to identify the specific PLA_2 isoforms and downstream metabolizing enzymes responsible for this effect.

Results of Dr. Tithof's study will provide valuable insight into the smoking-induced mechanisms of emphysema.

Molecular Carcinogenesis – NSAIDS, Dietary Compounds, and Tumorigenesis



Non-steroidal anti-inflammatory drugs (NSAIDS) and certain dietary compounds are effective chemopreventive and anti-tumorigenic agents for several cancers, presumably via the induction of apoptosis; however, the mechanisms responsible for these properties remain largely unknown.

Dr. Baek's research is directed towards elucidating the molecular mechanisms by which NSAIDS and certain dietary compounds exert their chemopreventive and anti-tumorigenic effects. In order to determine their modes of action, Dr. Baek's group is focused on ascertaining the effects that NSAIDS and certain anti-cancer compounds and drugs have on gene expression.

Dr. Baek's group recently identified a novel protein that appears to play a pivotal role in mediating the chemopreventive effects of many anti-cancer compounds, including NSAIDS and dietary compounds. This newly identified protein, non- steroidal anti-inflammatory activated gene-1 (NAG-1), is a member of the transforming growth factor-beta (TGF-β) superfamily.

Seung Joon Baek
Ph.D., University of Maryland
Assistant Professor
Pathobiology

Recent Progress
One grant funded during FY 03-04

National Institutes of Health
$324,000
Regulation and Function of NAG-1

Submitted three proposals based on preliminary data generated with COE support; two proposals are currently pending.

Dr. Baek has found that NAG-1 is induced by NSAIDS, has anti-tumorigenic properties, and stimulates apoptosis in colon cancer cell lines and in other cancer cell lines as well. Dr. Baek's data indicate that the pro-apoptotic activity of NSAIDS may be linked to the expression of NAG-1.

Dr. Baek's group is currently studying the transcriptional regulation of NAG-1, and they are working to determine the biological and pathophysiological roles of NAG-1 protein.

Information from Dr. Baek's studies could lead to the development of new chemotherapeutic drugs.

Lysophosphatidic Acid and Tissue Factor in Atherosclerosis

Atherosclerosis accounts for nearly 75% of deaths from cardiovascular disease. The buildup of plaque (fatty deposits and other cellular debris) on the arterial walls can erode the wall of the artery, reduce elasticity, and impede blood flow. Plaques that rupture cause thrombosis (the formation of a clot inside a blood vessel) which can obstruct blood flow and lead to myocardial infarction, stroke, and sudden death.

Tissue factor (TF), a transmembrane glycoprotein found on nonvascular cells, is the principal initiator of the coagulation cascade, a complex chain reaction that converts prothrombin to thrombin, which catalyzes the eventual formation of a clot. Thrombin induces the proliferation of smooth muscle cells; TF induces smooth muscle cell migration. Migration of smooth muscle cells from the medial to the intimal layer of the arterial wall and the subsequent proliferation of these cells plays a critical role in the pathogenesis of atherosclerosis.

TF expressed on the vascular smooth muscle cell surface is pathologically significant as a contributor to plaque growth, thrombus formation, and acute coronary syndrome following plaque rupture. However, the mechanisms that regulate TF gene expression and the regulatory signaling pathways in smooth muscle cells are largely unknown.

Oxidized low-density lipoprotein (oxLDL) has many atherogenic properties, but the mechanisms involved are not well understood. Research indicates that oxidized low-density lipoprotein may contribute to the pathogenesis of atherosclerosis by up-regulating TF expression.

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

Recent Progress
Two grants funded during FY 03-04

National Institutes of Health
$1,002,400
Lysophosphatidic Acid and Tissue Factor in Atherosclerosis

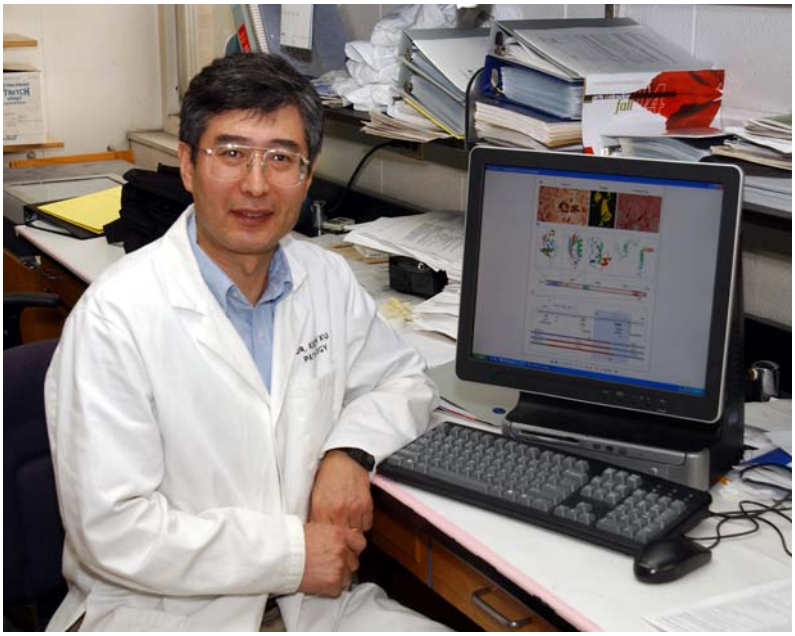
Philip Morris, Inc.
$547,400
Role of Lysophosphatidic Acid and Other Lipid Peroxidation Products in Smoking-Induced Atherosclerosis

Note: COE funds were used to collect preliminary data vital to the success of these recently funded projects.

Dr. Cui has made remarkable progress towards understanding the regulatory effects of oxLDL on TF expression. Recently, Dr. Cui's group has reported that lysophosphatidic acid (LPA), a component of oxLDL, induces TF in mRNA, TF protein, and TF activity in vascular smooth muscle cells. Dr. Cui's data also demonstrate that LPA-induced TF expression is controlled at the transcriptional level. Studies ongoing in Dr. Cui's laboratory are directed towards understanding the cellular signaling pathways that mediate the biological effects of LPA, specifically the effects on gene expression.

Results from Dr. Cui's studies could lead to the identification of new therapeutic targets for the prevention and treatment of atherosclerosis.

Role of a Novel Protein, PSAP, in Neurodegeneration



More than 15 million people worldwide suffer from the devastating effects of Alzheimer's disease, which is characterized by plaques and tangled bundles of fibers in and around the brain cells. These plaques are made up of beta amyloid, a toxic protein fragment cleaved from a larger protein called amyloid precursor protein, or APP. The tangled fibers form following changes in tau, a protein involved in intracellular transport.

Genetic analysis of the familial form of Alzheimer's disease has resulted in the identification of three causative genes: APP, presenilin 1, and presenilin 2. Among these causative genes, mutations in presenilin 1 account for the majority of known cases of familial Alzheimer's disease. APP, a protein found in brain cells, is necessary for normal brain function. Although its exact function is unknown, research indicates that APP protects brain cells from injury.

Researchers know that presenilins, proteins found in brain cells, interact with many signaling pathways; however, the exact function of these proteins is largely unknown. Researchers suspect that presenilin 1 plays a role in apoptosis, or programmed cell death, one of the mechanisms of neuronal cell death observed in Alzheimer's disease.

Dr. Xu's group has identified a novel protein, presenilin-associated protein (PSAP) that interacts with the C-terminal of presenilin 1 and causes cell death when over expressed. Dr. Xu's finding establishes, for the first time, a molecular link between presenilin 1 and an apoptotic cascade.

Xuemin Xu
Ph.D., Institute of Technology, Japan
Associate Professor
Pathobiology

Recent Progress

Identification of a novel protein, presenilin-associated protein (PSAP), establishing, for the first time, a molecular link between presenilin and apoptosis.

Great strides towards elucidating the mechanisms by which APP produces the pathogenic beta amyloid protein.

Submitted two proposals based on preliminary data generated with COE support; both proposals are currently pending.

Cleavage of APP is crucial in the pathogenesis of Alzheimer's disease; researchers suspect that presenilin 1 has an important role in regulating the enzyme that cleaves APP into beta amyloid pieces. Currently, Dr. Xu is making significant progress elucidating the molecular roles of presenilin 1 and PSAP in the formation of beta amyloid, and the mechanisms by which gamma-secretase processes APP to produce the pathogenic beta amyloid peptide.

Results from Dr. Xu's studies may provide new therapeutic targets for the design of treatments for Alzheimer's disease.

EDS Hamster Model to Understand the Effects of Light and Thyroid Hormone on Stem Cell Differentiation into Leydig Cells in Testes of Seasonal Breeders

Leydig cells in the testis are the primary source of androgens (male hormones) in the mammalian male. There are two populations of Leydig cells – fetal and adult. The fetal Leydig cell population is present at birth, and Dr. Mendis-Handagama has recently shown that in rats, fetal Leydig cells still exist up to sexual maturity. However, the adult Leydig cell population emerges during the pre-pubertal life and become the primary source of androgens in the adult mammal.

Because androgens are necessary for the overall health of many tissues and organs, as well as for the reproductive functions of the adult male mammal, establishing the adult population of Leydig cells is vital to all males. Leydig stem cells are known to differentiate from mesenchymal cells, but the trigger for differentiation is poorly understood. However, recent studies in Dr. Mendis-Handagama's laboratory revealed thyroid hormone plays a critical role in triggering the onset of Leydig stem cell differentiation in the postnatal testis.

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

Recent Progress
Studies revealed that thyroid hormone has a critical role in triggering Leydig stem cell differentiation.

Has submitted two proposals based on preliminary data generated with COE support; both proposals are currently pending.

Dr. Mendis-Handagama is currently investigating the role of light on the process of postnatal Leydig stem cell differentiation using Syrian Golden hamsters who are seasonal breeders and ethane dimethane sulphonate (EDS), a unique toxin to Leydig cells. EDS kills Leydig cells within 48 hours of administration, but the testis is re-populated with Leydig cells within 21 days. Therefore, an EDS-treated model could be used to investigate the Leydig stem cell differentiation during the re-population process.

Dr. Mendis-Handagama's group is also investigating other regulatory factors of Leydig stem cell differentiation in the postnatal testis using several rodent models, including transgenic mice. Information regarding Leydig cell differentiation is important in pediatrics, especially in treating delayed and precocious pubertal cases.

It is anticipated that results from Dr. Mendis-Handagama's studies will add new insight to the unexplained problems associated with male puberty and infertility.

Osteoarthritis and Physical Rehabilitation

Osteoarthritis is one of the most common diseases of the elderly and significantly impacts their quality of life. Osteoarthritis is not exclusive to humans. In fact, this painful and debilitating disease is even more prevalent in dogs than it is in humans, affecting one out of every five dogs as compared to one out of every six people in the United States.

There are several approaches to the management of osteoarthritis, some of which include medications and physical modalities. A number of modalities are used for veterinary purposes before being evaluated for human therapy. Recently, Dr. Millis has been investigating the use of extracorporeal shock wave treatment and neuromuscular electrical stimulation, in the form of transcutaneous electrical nerve stimulation (TENS), for the management of osteoarthritic pain.

Darryl Millis
D.V.M., Cornell University
Associate Professor
Small Animal Clinical Sciences

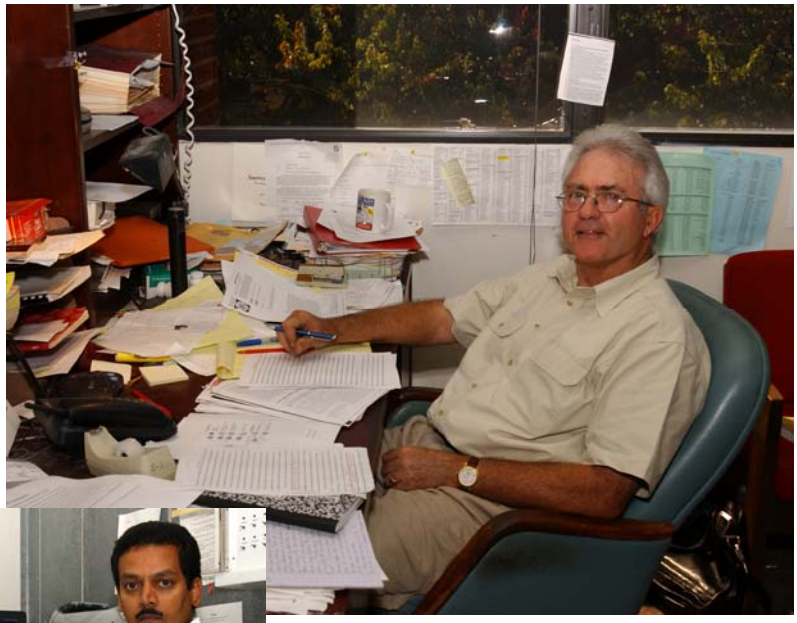
Recent Progress
Submitted one grant proposal with preliminary data generated with COE support; proposal is currently pending.

A TENS unit is a portable device that delivers a mild electrical impulse through electrodes placed on the skin to alleviate pain. TENS is believed to work either by overriding transmission of pain signals to the brain through electrical stimulation, or through the brain's release of natural painkillers called endorphins in response to electrical stimulation.

Although TENS therapy is currently considered an alternative treatment for osteoarthritis in humans, there is conflicting evidence about the benefits of this modality. TENS therapy is a particularly attractive alternative for the elderly osteoarthritis patient due to the difficulties in medicating senior patients. Information from Dr. Millis' studies could impact rehabilitation strategies for the elderly.

Physical rehabilitation is a rapidly growing area of small animal practice, but little attention has been paid to the rehabilitation of chronic conditions, like osteoarthritis, or the postoperative rehabilitation of various musculoskeletal and neurological conditions. Dr. Millis' studies on the therapeutic effects of ultrasound on muscles and tendons have provided practitioners with valuable information on the use of this modality. In particular, information on the heating characteristics of tendons will be especially useful to physical therapists of human patients.

Herpes Simplex Virus Immunity



Herpes simplex virus (HSV) infects up to 80% of the human population. HSV persists indefinitely in infected individuals, with some suffering painful periodic lesions.

Dr. Rouse's group is working to understand how HSV interacts with the immune system. Their 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. Uday Kumaraguru

Barry Rouse
BVSc., University of Bristol, England
Ph.D., University of Guelph
DSc., University of Bristol, England
Distinguished Professor
Pathobilogy

Recent Progress
Identified a method of improving CD8 memory response.

Submitted one grant proposal with preliminary data generated with COE support; proposal is currently pending.

Recently, the discovery of heat shock proteins (hsp) as an adjuvant and a delivery agent has renewed interest in peptide vaccines. Dr. Rouse's group and other researchers have shown that hsp70 coupled to a peptide acts as a potent immunogen by inducing a protective, peptide specific CD8 response -- CD8 cells are a type of T cells that look for infected cells, then attack and kill them. However, this protection had poor memory response and lasted only a few days. Dr. Rouse and Dr. Uday Kumaraguru, Research Assistant Professor, have been investigating the factors that contribute to poor memory CD8 response.

In a recent study, Drs. Kumaraguru and Rouse showed, for the first time, that the hsp70-peptide system can be used to induce helper T cell and antibody responses. More importantly, the co-administration of hsp70 linked to a CD8 peptide along with the hsp70 linked to helper peptides resulted in 3-fold improvement in CD8+ T cell memory.

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. Results from their studies could have a major impact in the prevention of viral diseases in people and animals.

Investigations into the Virulence of Mycobacterium liflandii

Mycobacterium liflandii is a newly identified pathogen that has been associated with a severe systemic disease decimating *Xenopus tropicalis* frogs in research laboratories throughout the United States, compromising the use of this frog as a new model for developmental biology. Further, *M. liflandii* is closely related to two other aquatic mycobacterial species, *M. ulcerans* and *M. marinum*, both of which cause disease in humans, raising concerns that *M. liflandii* could also infect humans.

In a previous study, Dr. Small's group discovered that *M. ulcerans* produces a polyketide-derived macrolide toxin, mycolactone. Notably, mycolactone is the first macrolide to be identified in a pathogenic bacterium. Recently, Dr. Small's laboratory found that *M. liflandii* also produces mycolactone, and they have identified the genes that encode this macrolide toxin.

The fact that *M. liflandii*, like *M. ulcerans*, produces mycolactone lends credence to the concerns regarding the virulence of *M. liflandii* towards humans. Using a guinea pig model, Dr. Small's group is determining the ability of *M. liflandii* to infect and cause disease in a vertebrate animal species.

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

Recent Progress
Identification of the genes that encode mycolactone, and the discovery that the genes are encoded on a plasmid in *M. ulcerans*, which is the first example of plasmid-mediated virulence in a mycobacterial pathogen.

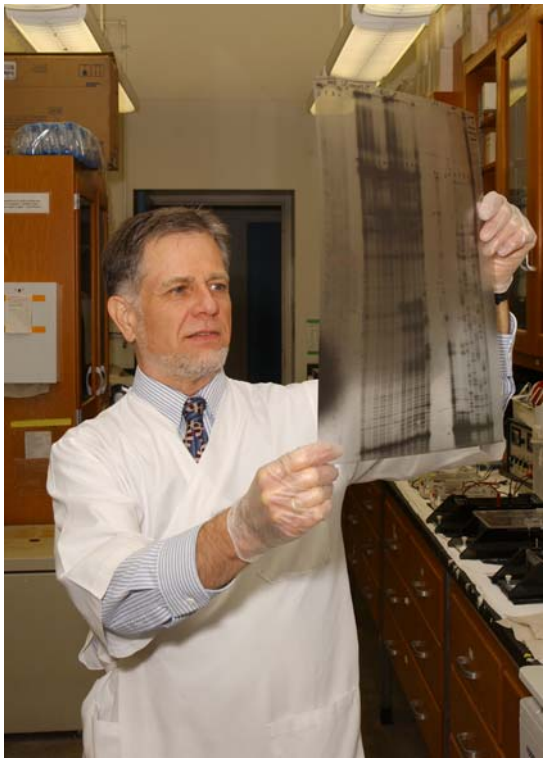
Dr. Small's group continues to make significant progress in understanding the genetic basis of mycolactone production and regulation in mycobacterial pathogens. A major advance during the past year was the identification of the genes that encode mycolactone, and the discovery that the mycolactone genes are encoded on a 175 kb plasmid in *M. ulcerans*, making this the first example of plasmid-mediated virulence in a mycobacterial pathogen. The location of these genes on a plasmid has two major implications:

1) Evolution in *M. ulcerans* has evolved through horizontal transfer of genes onto a *M. marinum* background and

2) There would likely be examples of plasmid transfer among other mycobacterial species.

In collaboration with scientists at the Pasteur Institute, this work was published in the 2004 Proceedings of the National Academy of Sciences.

Molecular Pathogenesis of Coronavirus



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

Efforts to control coronavirus infections have been frustrated by an incomplete understanding of how coronaviruses replicate, the ability of coronaviruses to rapidly mutate into new pathogenic variants, and animals' generally weak immune response to coronavirus vaccination.

The primary research focus in Dr. Brian's laboratory concerns the molecular events that occur during coronavirus replication, particularly the cis- and trans-acting factors involved in the regulation of RNA regulation and gene transcription.

Cis-acting RNA elements required for the replication of a virus with an RNA genome are unique for any given virus family, and function by interacting with viral and cellular proteins in specific ways. These specific protein-genome interactions are potential sites of engineered drug design.

Dr. Brian continues to be at the forefront of the international scientific community's effort to understand severe acute respiratory syndrome, or SARS, a member of the coronavirus family. The SARS coronavirus is in many respects closely related to the bovine coronavirus.

Dr. Brian's group has been studying the cis-acting elements of RNA replication of the SARS virus in the context of bovine coronavirus molecules. They have recently identified three cis-acting replication elements of the bovine coronavirus, and are currently working to identify the specific proteins that interact with these elements, and to characterize the interactions.

Dr. Brian's laboratory has received national and international recognition for discoveries of a fundamental nature regarding the molecular biology of viruses. Dr. Brian continues to make significant progress toward understanding how specific genetic elements in the coronavirus function to regulate the production of viral proteins and progeny.

Results from Dr. Brian's studies could significantly impact the design of new therapeutic drugs.

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

Recent Progress

Identification of three cis-acting elements of the bovine corona virus.

Continues to be at the forefront of the effort to understand SARS.

Submitted one grant proposal based on preliminary data generated with COE support. This proposal, which is in collaboration with Dr. Chris Dealwis, Biochemistry, Cellular & Molecular Biology, is currently pending.

Detection and Quantification of Antibiotic Resistance Genes and Mobile Genetic Elements in Mastitis Pathogens and Foodborne Pathogens

Antimicrobials are used extensively in food-producing animals to treat and prevent disease, and to promote growth. However, there is increased scientific interest regarding therapeutic and subtherapeutic use of antimicrobials in food-producing animals due to the potential for emergence and dissemination of multiple-drug-resistant zoonotic bacterial pathogens.

A major concern is that the significant increase in both multi-drug resistance and the range of bacterial pathogens displaying antibiotic resistance to a growing number of clinically important drugs could threaten the success of medical therapies. Antimicrobial drug-resistant bacterial pathogens pose a risk not only to animal health, but also to humans via transmission of foodborne pathogens.

Dairy farms are a major source of foodborne pathogens that could be transmitted to humans. During extensive, on-going farm-based studies, Dr. Oliver's group established the prevalence of foodborne pathogens (*E. coli* O157:H7 and *Salmonella* spp) in bulk tank milk (BTM) and feces from cull dairy cows, and confirmed that theses were potential sources of *E. coli* O157H7 and *Salmonella* spp. Their findings also indicated a source of *Listeria monocytogenes* and *Campylobacter jejuni* environmental contamination where animal waste may have drained into water adjacent to farms.

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

Recent Progress
One grant funded during FY 03-04

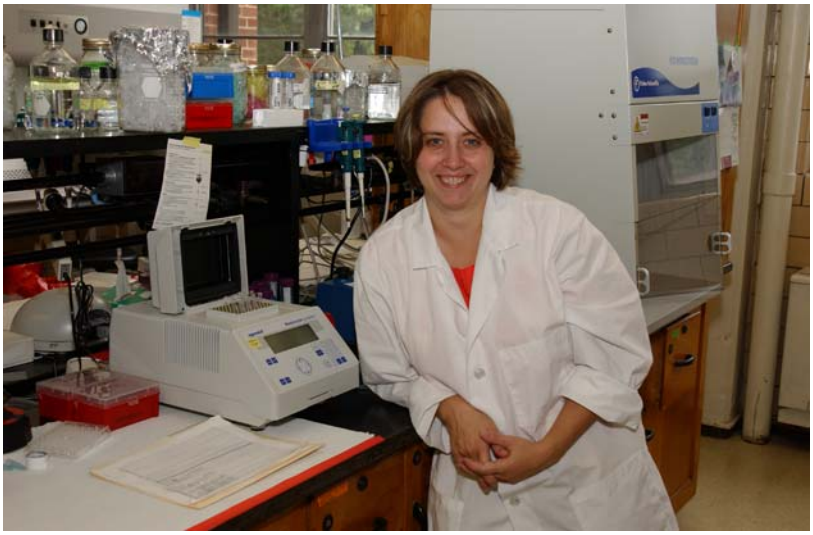
USDA
$340,000
Role of *Streptococcus uberis* in the Pathogenesis of Bovine Mastitis

Note: COE funds were used to collect preliminary data vital to the success of this recently funded project.

Dr. Oliver's group is currently conducting molecular and antibiotic resistance characterization of *L. monocytogenes* and *C. jejuni* isolated from farms in the study. Such data will be used to define pathogen distribution within and among production areas, and to identify the environmental sources of specific pathogen subtypes in different production areas. Antibiotic susceptibility profiles and prevalence of antimicrobial resistance genes from isolates will provide information on the emergence, persistence, and dissemination of antibiotic resistance.

Results from Dr. Oliver's research will facilitate the development of strategies to control and eradicate foodborne pathogens in farm environments.

Host Mechanisms that Contribute to the Pathogenesis of *Streptococcus uberis*



The susceptibility of animals to certain diseases varies widely across and within species. This basic concept also holds true for the development of mastitis in dairy cattle, which costs the dairy industry billions of dollars each year.

The overall goal of Dr. Pighetti's research is to better understand why certain animals become sicker than other animals, so that more effective targeted preventive and therapeutic strategies can be used in the future to combat disease.

One of Dr. Pighetti's current objectives is to identify the mechanisms that contribute to increased susceptibility to infection. Dr. Pighetti's laboratory has recently identified a polymorphism or a variation in an immune-related gene that identifies cows that tend to have mammary gland infections more often than do other cows.

Dr. Pighetti's most recent work has demonstrated that neutrophils, a type of immune cell that fights off infections, have an impaired ability to migrate and thus may have difficulty getting to the site of infection. In cows more susceptible to infection, neutrophils also have a tendency to produce fewer reactive oxygen species, which could also contribute to the increase in infections. An interesting observation was that these cells also tended to survive longer even though they were not as functional.

Future studies in Dr. Pighetti's laboratory will focus on identifying why these changes occur at a cellular and subcellular/molecular level, in an effort to identify possible means of therapeutically boosting the immune response. Not only could such studies offer clues in how to boost the immune response, it may also offer novel strategies to switch the inflammatory response off in cases where extensive inflammatory tissue damage can occur, such as pneumonia.

Gina Pighetti
Ph.D., Pennsylvania State University
Assistant Professor
Animal Science

Recent Progress

Recently found a polymorphism in an immune-related gene that identifies cows with increased susceptibility to mammary gland infections.

Submitted two proposals based on preliminary data generated with COE support; both proposals are currently pending.

Effect of Obesity on Physiological Parameters of Energy Metabolism in Horses

Obesity in horses is a serious health concern due in large part to its association with laminitis, a poorly understood condition that causes varying degrees of foot pain, from mild to severe life-threatening lameness.

Laminitis results from the disruption of blood flow to the laminae of the hoof, which are structures within the hoof that secure the coffin bone – the primary bone in the horse's hoof – to the hoof wall. Inflammation often permanently weakens the laminae and in severe cases, the bone and the hoof wall can separate, allowing the coffin bone to rotate and/or sink and eventually penetrate the sole. More often than not, penetration of the sole necessitates euthanasia of the animal.

Obese horses and ponies are more susceptible to laminitis, and the disorder is more commonly detected in horses that have distinct distributions of body fat in the neck and tail head regions and remain obese even when their caloric intake is reduced.

Obesity-associated laminitis is a chronic form of laminitis in which affected animals are barely able to walk in the early stages of the disease and show chronic pain for weeks to months as inflammation gradually increases or decreases despite treatments. Researchers know little about obesity-associated laminitis; consequently, there is no *specific* treatment for affected animals.

Dr. Frank is currently working to identify specific physiological risk factors for obesity associated-laminitis. In addition, Dr. Frank is developing a scoring system to define obesity in horses by correlating physical measurements and depth of subcutaneous fat with a measurement of total body fat.

Dr. Frank is making tremendous progress in his investigations into hormonal disorders, metabolism, and obesity. Dr. Frank submitted six proposals with preliminary data generated with COE support. To date three proposals have been funded and two are currently pending.

Information from Dr. Frank's study could lead to the identification of prevention and treatment strategies for at-risk animals.

Nick Frank
D.V.M., Purdue University
Ph.D., Purdue University
Assistant Professor
Large Animal Clinical Sciences

Recent Progress
Three grants funded during FY 03-04

Lloyd, Inc.
$27,340
Effects of Levothyroxine Sodium on Percentage Body Fat Mass and Insulin Sensitivity in Horses with Dietary Obesity

Lloyd, Inc.
$20,580
Effects of Long-Term Levothyroxine Sodium Administration on Glucose Dynamics and Health of Mares

Lloyd, Inc.
$10,010
Effect of Oral Levothyroxine on Thyroid Hormone Status and Energy Metabolism in Horses

Note: COE funds were used to collect preliminary data vital to the success of these recently funded projects.

Effects of Oral Levothyroxine on Thyroid Hormone Measures, Cortisol, Lymphocyte Subsets, and Energy Metabolism in Horses

Hypothyroidism in horses is not understood completely, which is due in large part to the difficulty in diagnosing the condition. Poor performance, lethargy, muscle soreness, infertility, obesity, and laminitis are all clinical signs of hypothyroidism, but accurate diagnosis can not be made based solely on clinical signs.

However, measurements of thyroid hormones may not be accurate – basal serum triiodothyronine (T_3) and thyroxine (T_4) concentrations are affected by numerous variables, which may lower values into the hypothyroid range. Also, normal horses have a wide range of values for T_3 and T_4 concentrations; therefore, use of base line values may be misleading and result in misdiagnosis.

A more accurate test for hypothyroidism is to measure the thyroid's ability to release T_3 and T_4 in response to thyroid stimulating hormone (TSH), but this method is expensive and is not widely available.

Because many so-called hypothyroid horses have been inadequately assessed, the actual frequency of this disorder is unknown; however, levothyroxine (synthetic thyroid hormone) is prescribed to hundreds of horses each year to treat the clinical signs commonly attributed to hypothyroidism.

Horse owners and veterinarians report that levothyroxine eliminates lethargy, improves performance, facilitates weight loss, increases fertility, and reduces the severity of laminitic episodes. However, levothyroxine therapy could be detrimental to healthy horses.

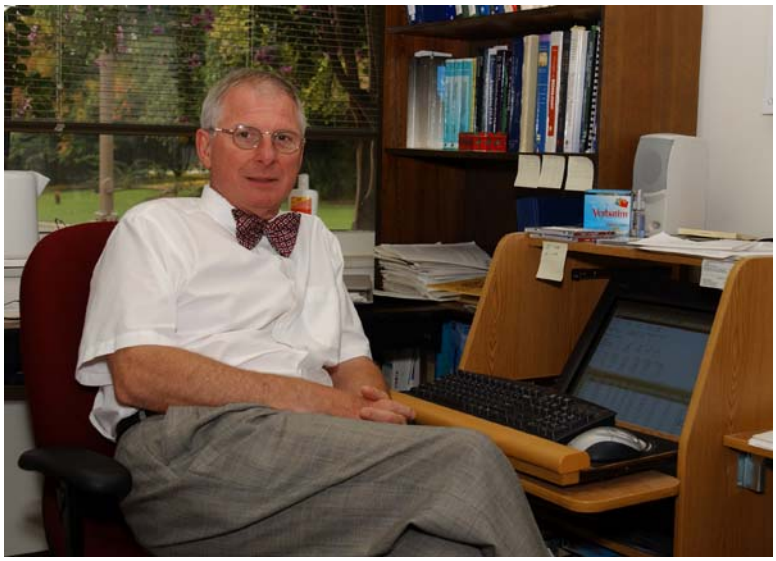
Carla Sommardahl
D.V.M., Louisiana State University
Ph.D., The University of Tennessee
Assistant Professor
Large Animal Clinical Sciences

Recent Progress
Submitted one grant proposal with preliminary data generated with COE support; proposal is currently pending.

Dr. Sommardahl is currently working to improve the methods of testing for hypothyroidism. Dr. Sommardahl is also conducting studies to determine the effects of levothyroxine therapy on energy metabolism, and on the hypothalamic-pituitary-adrenal axis and immune system in horses.

In collaborations with ORNL and also with Dr. Madhu Dhar, Department of Nutrition, Dr. Sommardahl has been investigating genetic causes of obesity for several years. Dr. Sommardahl has recently linked with her expertise with that of Dr. Nick Frank in studies in the areas of hormonal disorders, energy metabolism, and obesity. While there is an abundance of information regarding the health risks of obesity in humans, there is very little information regarding the risks associated with obesity in animals.

Development and Use of Nucleophilic Reactivity Indices as a Means of Evaluating Chemicals with Potential to be Used in Local Acts of Terrorism



A significant challenge in environmental toxicology today is determining how chemical reactivity interplays with hazard for the prediction of toxic potency. This challenge has assumed a new urgency as the substances with potential need of registration and special handling are also the same substances most likely to be used as weapons in acts of terrorism.

Most of the 100,000 chemicals currently listed in the European Inventory of Existing Commercial Chemical Substances are used as intermediates in industrial processing, and the majority of these chemicals are organic in nature. While more than 70% of these industrial organic chemicals act as non-reactive toxicants, more than 25% are reactive electro(nucleo)philes that could be used as vesicant agents in localized acts of terrorism.

Electrophiles with the structural potential for exhibiting multiple chemical reactive mechanisms may exhibit greater toxic potency, and therefore pose an even greater threat as a weapon of terrorism. However, the ability to predict the toxicity of electrophiles is currently limited by the ability to quantify chemical reactivity independent of biological activity.

In an effort to overcome this limitation, Dr. Schultz has developed an assay to evaluate the chemical reactivity and toxicity of selected electrophiles, and determine the reactivity of selected carbonyl compounds. Dr. Schultz continues to make significant contributions to the development and validation of structure-activity models that predict the toxic/biological activity of chemical compounds from molecular structure.

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

Recent Progress
Two grants funded during FY 03-04

Department of Defense
$333,000
Biosurvelliance, Agricultural and Environmental Security: A Coordinated, Innovative Effort

EPA
$45,351
Co-PI with Dr. Gary Sayler, CEB
Bioluminescent Yeast-Reporter System for Screening Chemicals for Estrogenic and Androgenic Effects

Note: COE funds were used to collect preliminary data vital to the success of these recently funded projects.

In addition, Dr. Schultz is collaborating with Dr. Neal Stewart, Tennessee Agriculture Experiment Station, and Dr. Gary Sayler, Center for Environmental Biotechnology, on a project recently funded by the Department of Defense. *Biosurvelliance, Agricultural and Environmental Security: A Coordinated, Innovative Initiative* is a $1 million effort towards the development of advanced bio-based sensors and toxicology to sense and predict epidemiological patterns in the field.

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Project Director	Title of Grant	Funding Agency	Total Award	Expenditures 04
Seung Joon Baek	Regulation and Biological Function of NAG-1	National Institutes of Health	$324,000 9/1/03 – 6/30/06	$108,627
David Brian	Mechanisms of Coronavirus RNA Amplification	National Institutes of Health	$1,131,121 7/1/02 - 8/31/07	$249,310
Mei-Zhen Cui	Lysophosphatidic Acid & Tissue Factor in Atherosclerosis	National Institutes of Health	$1,002,400 6/1/04 - 4/30/08	$0
	Role of Lysophosphatidic Acid and Other Lipid Peroxidation Products in Smoking-Induced Atherothrombosis	Philip Morris, Inc.	$547,397 6/1/04 - 6/30/07	$0
	Lysophosphatidic Acid Induction of Tissue Factor Gene Expression in Vascular Smooth Muscle Cells	American Heart Association	$154,000 6/1/03 - 630/05	$67,709
	Lysophosphatidic Acid Regulation of Transcription Factor EGR-1 in Vascular Smooth Muscle	Pfizer	$100,000 7/1/02 - 6/30/05	$43,726
Nick Frank	Effect of Oral Levothyroxine on Thyroid Hormone Status and Energy Metabolism in Horses	Lloyd, Inc.	$10,010 5/13/03 - 5/12/04	$7,754
	Effects of Long-Term Levothyroxine on Glucose Dynamics and Health in Mares	Lloyd, Inc.	$20,580 6/1/04 - 6/30/05	$0

Project Director	Title of Grant	Funding Agency	Total Award	Expenditures 04
Nick Frank	Effects of Levothyroxine Sodium on Percentage Body Fat Mass, Insulin Sensitivity, and Glucose Transporter 4 Expression in Horses with Dietary Obesity	Lloyd, Inc.	$27,340 6/1/04 - 5/31/05	$6,765
	Effects of Dietary Rice Bran Oil on Gastric and Blood Lipids and the Development of Gastric Ulcers in Horses	McCauley Bros.	$54,423 12/1/02 - 12/1/03	$7,575
Charmi Mendis-Handagama	Anti-Spermatogenic Effects of Thyroid Hormones in Three Month Old Sprague Dawley Rats	World Health Organization	$69,750 12/1/01 -12/1/03	$5,150
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 - 3/30/05	$0
	Injectable Deracoxib Study	Novartis	$100,000 11/1/03 - 11/1/04	$40,356
	The Effect of Diet on Muscle Atrophy Following Surgery for Cranial Cruciate ligament Rupture	Iams	$92,444 1/15/03 - 1/15/04	$0
	Shockwave Clin. Pilot Study	HealthTronics	$18,000 5/15/02 -2/31/04	$2,152

Project Director	Title of Grant	Funding Agency	Total Award	Expenditures 04
Stephen Oliver	Evaluation of Safety 7 Efficacy of *Streptococcus uberis* Vaccines in Dairy Cows	Pfizer	$240,052 4/1/04 - 12/31/04	$108,932
	Recurrent Coliform mastitis in New York Dairy Cows	Cornell University	$99,922 7/1/03 - 12/5/04	$47,142
	Cefquinome Milk Residue Study	East TN Clinical Research Initiative	$16,705 1/1/04 -12/31/04	$0
	Role of *Streptococcus uberis* Adhesion (SUAM) Molecule in the Pathogenesis of Bovine mastitis	USDA	$341,879 6/1/04 - 9/30/07	$0
	SUAM: *Streptococcus uberis* Adhesion Molecule	Private	$15,050 1/1/04 - 12/15/05	$0
Gina Pighetti	Leptin Regulation of Mammary Cell Growth	U.S. Army	$65,011 12/5/01 - 12/5/04	$0
H. Plummer, III	GIRK Channels, Beta-Adrenergic Signaling and Breast Cancer	Philip Morris, Inc.	$752,989 6/1/04 -6/30/07	$0
Barry Rouse	Vaccination Against Herpes Simples Virus	National Institutes of Health	$1,396,346 3/1/00 -2/28/05	$258,887
	Immunity Mechanisms in Herpes Virus Infections	National Institutes of Health	$1,656,250 1/1/01 -12/31/05	$374,594

Project Director	Title of Grant	Funding Agency	Total Award	Expenditures 04
Barry Rouse	Mechanisms of Herpetic Keratitis	National Institutes of Health	$1,779,700 9/1/02 - 9/29/07	$393,300
Hildegard Schuller	Transplacental pancreatic Carcinogenesis by NNK	National Institutes of Health	$1,158,400 4/1/03 - 3/31/07	$279,526
	Preclinical Model for Chemoprevention of NSCLC in Former Smokers	National Institutes of Health	$868,800 5/1/03/ - 4/30/06	$265,284
	NNK, Beta-Adrenergic AA Releases, and Lung Cancer	National Institutes of Health	$1,142,201 4/1/02 - 3/31/06	$224,089
Terry Schultz	Biosurvelliance, Agricultural and Environmental Security: A Coordinated, Innovative Approach	Department of Defense	$333,333 6/1/04 - 6/30/05	$0
	Bioluminescent Yeast-Reporter System for Screening Chemicals for Estrogenic and Androgenic Effects	EPA	$45,531 10/1/03 - 9/30/06	$5,387
Pamela L.C. Small	Mycolactone-Mediated Virulence in *M. ulcerans*	National Institutes of Health	$1,480,750 1/1/01 - 2/28/06	$266,247
Patricia Tithof	Role of Arachidonic Acid in Endothelial Cell Apoptosis Induced by Tobacco Components	Philip Morris, Inc.	$522,000 6/1/01 - 6/30/04	$157,616

Project Director	Title of Grant	Funding Agency	Total Award	Expenditures 04
Hwa-Chain Robert Wang	Potency and Molecular Signatures of Tobacco Carcinogens in the Early Development of Human Breast Cancer	Philip Morris, Inc.	$633,326 7/1/03 - 6/30/06	$137,917
	Pathway Leads to Apoptosis in SRC Transformed Cells	National Institutes of Health	$517,520 4/1/97 - 12/31/03	$35,643
Xuemin Xu	Role of a Novel protein (PSAP) in Neurodegeneration	National Institutes of Health	$1,282,500 9/1/01 - 8/31/05	$287,008
		Total	**$18,249,519**	**3,392,244**

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

Institution: College of Veterinary Medicine **Center:** COE in Livestock Disease & Human Health

	FY 2003-04 Actual			FY 2004-05 Proposed			FY 2005-06 Requested		
	Matching	Appropr.	Total	Matching	Appropr.	Total	Matching	Appropr.	Total
Expenditures	247,800	495,600	**743,400**	247,800	495,600	**743,400**	260,190	520,380	**780,570**
Salaries									
Faculty	13,387	26,775	**40,162**	8,652	17,304	**25,956**	9,085	18,169	**27,254**
Other Professional	69,191	138,382	**207,572**	93,980	187,960	**281,940**	98,679	197,358	**296,037**
Clerical/ Supporting	35,915	71,830	**107,745**	48,302	96,604	**144,906**	14,581	29,163	**43,744**
Assistantships	26,242	52,484	**78,726**	29,588	59,177	**88,765**	31,068	62,136	**93,203**
Total Salaries	**144,735**	**289,470**	**434,206**	**180,522**	**361,045**	**541,567**	**153,413**	**306,826**	**460,238**
Longevity	819	1,639	**2,458**	844	1,688	**2,532**	886	1,772	**2,658**
Fringe Benefits	21,498	42,996	**64,493**	25,704	51,407	**77,111**	20,732	41,464	**62,196**
Total Personnel	**166,233**	**332,466**	**501,157**	**207,070**	**414,140**	**621,210**	**174,145**	**348,290**	**525,092**
Non-Personnel									
Travel	1,036	2,072	**3,108**	7,833	15,667	**23,500**	8,225	16,450	**24,675**
Software	213	426	**639**			**0**			**0**
Books & Journals			**0**			**0**			**0**
Other Supplies	58,560	117,120	**175,681**	66,957	133,914	**200,870**	34,309	68,618	**102,927**
Equipment	34,037	68,073	**102,110**	11,331	22,661	**33,992**	11,897	23,795	**35,692**
Maintenance	11,339	22,679	**34,019**	15,027	30,053	**45,080**	15,778	31,556	**47,334**
Scholarships	4,870	9,740	**14,609**	9,127	18,255	**27,382**	9,584	19,167	**28,751**
Consultants			**0**			**0**			**0**
Renovation			**0**			**0**			**0**
Other (Specify)			**0**			**0**			**0**
Print/Pub/Postage/Frght/ Publicity/Comp Svc/Rental/ Ins/Grp Food & Lodging/ Conference Registration	1,451	2,903	**4,354**	67	133	**200**	70	140	**210**
Services	6,423	12,845	**19,268**	5,044	10,088	**15,132**	5,296	10,593	**15,889**
Total Non-Personnel	**117,929**	**278,854**	**353,787**	**115,385**	**230,771**	**346,156**	**85,159**	**170,319**	**255,478**
GRAND TOTAL	**284,162**	**611,320**	**854,944**	**322,455**	**644,911**	**967,366**	**259,304**	**518,608**	**780,570**
Revenue									
New State Appropriation		495,600	**495,600**		492,900	**495,600**		520,380	**520,380**
Carryover State Appropriation		202,631	**202,631**		149,311	**149,311**			**0**
New Matching Funds	247,800		**247,800**	246,450		**247,800**	260,190		**260,190**
Carryover from Previous Matching Funds	101,316		**101,316**	74,655		**74,655**			**0**
Total Revenue	**349,116**	**698,231**	**1,047,347**	**321,105**	**642,211**	**967,366**	**260,190**	**520,380**	**780,570**