Commonwealth Health Research Board

2007 Annual Report

"To promote and protect the health of the citizens of the Commonwealth through human health research."

Commonwealth Health Research Board Members

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Message From The Chairman

The Commonwealth Health Research Board (CHRB) provides grant funding for creative and innovative research projects that have scientific merit and hold promise for maximizing human health benefits for citizens of the Commonwealth of Virginia. The CHRB supports both new research efforts and the expansion or continuation of existing research.

Since its inception, the CHRB has made 101 grant awards totaling approximately $7 million in grant funding to institutions of higher education and other not-for-profit or nonprofit organizations that conduct health, or health related research, in Virginia. When the required 33% matching funds are added to the CHRB funded amount, the total project funds amount to $10.3 million for health research in Virginia.

Grants have been awarded to 16 institutions of higher education and other organizations across the Commonwealth to include: University of Virginia, Eastern Virginia Medical School, Virginia Commonwealth University, Virginia Military Institute, The College of William and Mary, University of Richmond, Longwood University, Norfolk State University, George Mason University, Lynchburg College, James Madison University, Sweet Briar College, Shenandoah University, Virginia Polytechnic Institute and State University and the Riverside Health System. Grants have been awarded for research on a wide variety of important health conditions including: Alzheimer's disease, diabetes, cancer, asthma, Lyme disease, cardiovascular disease, renal disease, new chemotherapeutic interventions, and genetic diseases, to mention a few.

The CHRB encourages collaborative research efforts and gives priority to those research efforts where the Board's support can be leveraged to foster contributions from other entities. CHRB grant recipients, for grant awards made in 1999 through 2003, have leveraged $13.8 million in additional private and federal grant funds to further their research studies. In addition, numerous publications in peer-reviewed scientific journals and periodicals as well as presentations of the data at regional and national scientific meetings have resulted from CHRB grant funded research projects.

We are proud of the accomplishments of the CHRB and our grant recipients as we work toward a healthier future for all Virginians. As Chairman, I am pleased to present the 2007 CHRB Annual Report.

S. Lawrence Kocot, Chairman
Commonwealth Health Research Board
November 2007

Commonwealth Health Research Board Evaluation Highlights

Comments from Principal Investigators concerning their research and their success in obtaining additional grant funds from federal or private foundation organizations as a result of initial CHRB grant support.

Margaret Saha, Ph.D.
The College of William and Mary: 2000 CHRB grant recipient for a project entitled, *Imaging the aging brain: In vivo detection of key aging molecules in small animals.*

"The CHRB is an extremely valuable source of funding because it not only allows, but encourages, innovative and risky interdisciplinary projects that could not have received funding elsewhere. This allows investigators to obtain the preliminary data and be successful in future funding endeavors.

Certainly, in part, funding from the CHRB, and the preliminary data obtained from that funding, has allowed me to obtain a grant from the Department of Defense Breast Cancer Research Program (BCRP) of the Office of the Congressionally Directed Medical Research Programs, "In Vivo Molecular Imaging of Mammary Tumorigenesis in Murine Model Systems" (2005-2006), $107,015."

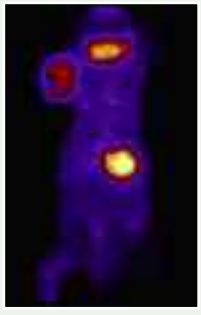


Image of a live mouse showing expected iodide accumulation in stomach and thyroid and accumulation of signal as a marker of a developing breast tumor (left side of photo).

Yuping Deng, Ph.D., Eastern Virginia Medical School: 2003 CHRB grant recipient for a project entitled, *Improving the immune response to influenza vaccination in older adults by modulating the innate immunity.*

"The CHRB grant has been critical for my career development to transition to an independent research scientist, and for my graduate student Yu Jing who successfully completed her Ph.D. study while working on this project. Data generated from this grant has helped us secure the NIH funding."

As a result of the CHRB grant award, Dr. Deng was awarded a three-year grant from the National Institute of Allergy and Infectious Diseases NIH in the amount of $487,292 (including indirect cost) for the period August 1, 2004 to August 31, 2007.

Daniel Gioeli, Ph.D., University of Virginia: 2003 CHRB grant recipient for a project entitled, *Development of a novel prostate cancer therapy.*

"I would like to thank the CHRB for the funding opportunity. The CHRB funding was instrumental to this work which would not have begun without the early support of the CHRB."

As a result of the CHRB grant award, Dr. Gioeli was awarded a three-year grant from the Department of Defense in the amount of $333,000 for the period January 1, 2004 to December 31, 2006.

CHRB Introduction

The goals of the Commonwealth Health Research Board (CHRB) are to provide grant funding for research to advance the understanding of biological systems, to improve the treatment and control of human disease, and to improve human health services and the delivery of human health care.

The CHRB provides grant funding for research efforts that have the potential of maximizing the health of Virginia's citizens. Research efforts eligible for support include traditional medical and biomedical research related to the causes and cures of human diseases, as well as research related to human health services and the delivery of human health care.

More specifically, in accordance with § 23-279 of the *Code of Virginia*, the Board encourages collaborative research efforts among two or more institutions or organizations, gives priority to those research efforts where Board support can be leveraged to foster contributions from federal agencies or other entities, and supports both new research efforts and the expansion or continuation of existing research.

Background

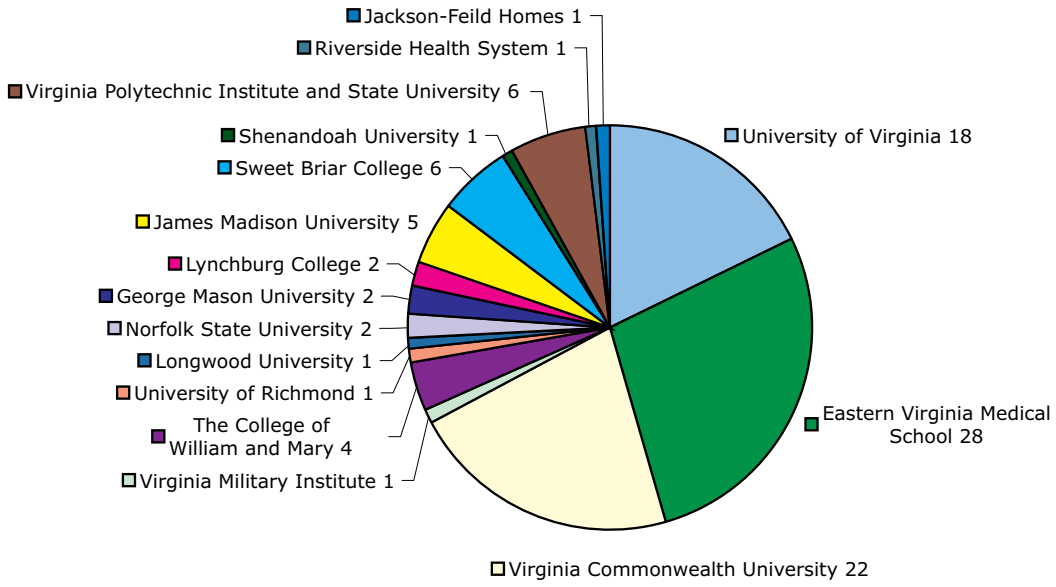
Legislation in 1997 created the Commonwealth Health Research Fund to provide financial support for research projects that have the potential of maximizing health benefits for the citizens of the Commonwealth. This initiative of the General Assembly and the Governor used the proceeds from the sale of Trigon stock to create the framework and fiscal resources for a research grant program. The funds result from the stock and cash distributed to the Commonwealth of Virginia pursuant to the conversion of Blue Cross and Blue Shield from a mutual insurance company to a stock corporation. Income from the funds is used to make grants. The estimated value of the Fund as of June 30, 2007 was $32.8 million.

The Commonwealth established the Commonwealth Health Research Board (CHRB) to develop and implement the grant program. The following chart shows the number and amount of grant funds awarded along with the amount of matching funds provided by the grantee institution.

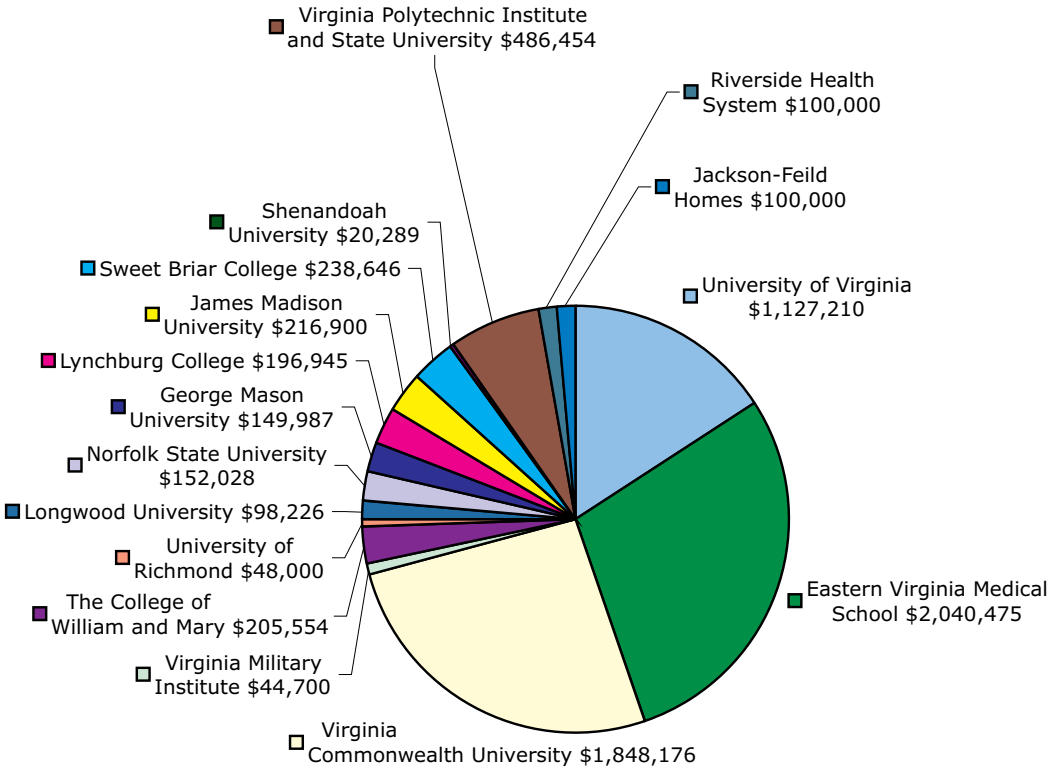
Grant Year	Number of Grant Awards	CHRB Grant Awards	Grantee Matching Funds	Total Project Funds
1999	9	$ 597,377	$ 260,151	$ 857,528
2000	11	$ 719,442	$ 429,489	$ 1,148,931
2001	13	$ 825,590	$ 341,680	$ 1,167,270
2002	12	$ 718,382	$ 344,603	$ 1,062,985
2003	8	$ 509,806	$ 199,999	$ 709,805
2004	14	$ 887,914	$ 376,735	$ 1,264,649
2005	10	$ 755,436	$ 305,909	$ 1,061,345
2006	12	$ 954,058	$ 451,983	$ 1,406,041
2007	12	$ 1,105,585	$ 512,493	$ 1,618,078
Cumulative Total	**101**	**$ 7,073,590**	**$ 3,223,042**	**$ 10,296,632**

Grant Statistics

Number of CHRB Grant Awards to Date by Institution or Organization



CHRB Grant Funding to Date by Institution or Organization

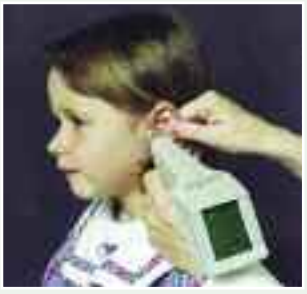


Birgit Winther, M.D.
University of Virginia: 1999 CHRB grant recipient for a project entitled, *Effects of common colds caused by viruses on middle-ear pressure in children.*

"I am so grateful for the CHRB award. It had major impact on my research career. In addition, it provided new information on the effect of cold virus on the ears in children. The new information was used as a stepping stone for a NIH award which I have now had for two years."

Dr. Winther received a 5-year grant award from the National Institutes of Health (NIH) in the amount of $980,000 as a result of the initial CHRB grant award.

Nasal mucus is obtained for laboratory testing of cold viruses by PCR.



Middle ear pressure is obtained with a digital tympanometer.

Grant Awards FY 2007/2008

Michael McVoy, Ph.D.
Virginia Commonwealth University: 2001 CHRB grant recipient for a project entitled, *Antiviral mechanisms of herpes virus DNA packaging inhibitors*.

"It takes substantial preliminary data and a proven track record in the form of publications for a new investigator to obtain federal research grants. For scientists engaged in research at institutions within the Commonwealth of Virginia, the opportunities to obtain sufficient funds with which to generate this preliminary data and a solid publication record (i.e., > $50,000) are extremely limited (I know of only two - Jeffress and CHRB). I am therefore very grateful for the CHRB grant that my lab received. It came at a critical time in my career in which I very much needed those funds to move my research to a point where I could be competitive for NIH grants. It also engendered an important and fruitful collaboration with my partner in this grant, Jay Brown at the University of Virginia. I only wish that more funds were available for small grants of this type."

As a result of the CHRB grant award, Dr. McVoy was awarded a grant from the National Institute of Allergy and Infectious Diseases (NIH/NIAID) R21 AIO53768: *Analysis of cytomegalovirus DNA cleavage/packaging genes*, in the amount of $347,500 for the period 10-01-03 to 09-30-05. Dr. McVoy also has a grant renewal pending: NIH/NIAID R01 AI46668, Human cytomegalovirus DNA cleavage and packaging in the amount of $1,489,575 for the period 07-01-06 to 06-30-11.

Commonwealth Health Research Board

Total funding for all grant awards in FY 2007/2008 including second year grant funding for five 2006/2007 grant awards

Submitting Institution/ Organization	Principal Investigator	Grant Title	CHRB Grant Award	Matching Funds	Total Project Funds
Eastern Virginia Medical School	Dianne Daniel, Ph.D.	MCM7 and MCM8 in the Control of DNA Replication in Ovarian Cancer	$100,000	$40,800	$140,800
Virginia Commonwealth University	Jason Rife, Ph.D.	Arm/Rmt ribosomal methylation and antibiotic resistance	$99,915	$32,972	$132,887
George Mason University	Geraldine Grant, Ph.D.	The Role of KLF4 and FRZB1 on the Differentiation of Normal Chondrocytes in vitro	$99,987	$38,620	$138,607
Eastern Virginia Medical School	Jorge Jacot, Ph.D.	Functional/Structural Capillary Rarefaction Associated with Pericyte Degeneration a Plausible Novel Mechanism in the Early Development of Diabetic-like Retinopathy	$100,000	$33,000	$133,000
James Madison University	Terrie Rife, Ph.D.	Understanding Transcriptional Changes of Nitric Oxide Synthase I Leading to Diabetes	$45,000	$33,240	$78,240
University of Virginia	Joanna Goldberg, Ph.D.	A novel vaccine approach to combat pathogenic bacteria: a focus on the category B biothreat agents causing meliodiosis and glanders	$100,000	$33,000	$133,000
Virginia Polytechnic Institue and State University	Dongmin Liu, Ph.D.	Phytochemical genistein and pancreatic islet function	$97,956	$32,325	$130,281
Eastern Virginia Medical School	Henri Parson, Ph.D.	Characterization of Diabetic Neuropathy and Genetic Differences in African-Americans	$96,516	$70,008	$166,524
University of Virginia	G. Paul Matherne, M.D.	Evaluation of metabolic remodeling in the prevention of left ventricular hypertrophy with A1 adenosine receptors	$75,000	$94,894	$169,894
Eastern Virginia Medical School	Diane Duffy, Ph.D.	Aspirin, Eggs and Pregnancy: A New Method of Birth Control?	$96,604	$39,414	$136,018
Virginia Commonwealth University	Shyama Masilamani, Ph.D.	Sex Hormone-Mediated Regulation of Kidney Transporters and Blood Pressure Control	$94,607	$31,220	$125,827
Virginia Commonwealth University	Zendra Zehner, Ph.D.	The role of the Oncogene Stat3 and Tumor Suppressor ZBP-89 in Tumor Metastasis	$100,000	$33,000	$133,000
Total 2007/2008 CHRB Grant Awards			**$1,105,585**	**$512,493**	**$1,618,078**

Abstracts for 2007/2008 Grant Awards (July 1, 2007 to June 30, 2008)

Dianne Daniel, Ph.D.
Eastern Virginia Medical School
Grant Title: MCM7 and MCM8 in the Control of DNA Replication in Ovarian Cancer

Project Summary: In the United States and in Virginia, ovarian cancer has the highest mortality rate of gynecologic malignancies and, for women, ranks the fifth most common cancer. At diagnosis, most tumors have spread beyond the ovary. A hallmark of this cancer is the loss of control of cell proliferation. Mini-chromosome maintenance (MCM) proteins have been identified as essential for licensing the DNA for duplication in a controlled manner as the cell proliferates. Several MCM family members have been implicated as markers for epithelial-derived cancers. In 2003, we discovered a new family member, MCM8. In ovarian cancer, variation in MCM8 and elevated expression of MCM7 may be preferential indicators of tumor progression. This study of MCM7 and MCM8 will help elucidate the relationship between control of DNA replication and tumor progression in ovarian cancer.

Jason Rife, Ph.D.
Virginia Commonwealth University
Grant Title: Arm/Rmt ribosomal methylation and antibiotic resistance

Project Summary: Widespread antibiotic resistance now severely limits treatment options, particularly in patients hospitalized with life-threatening conditions such as burns and cystic fibrosis. The opportunistic gram-negative pathogens, such as *Pseudomonas aeruginosa* and *E. coli*, are commonly treated with aminoglycoside (AG) antibiotics. A recently discovered, new form of AG resistance in these pathogens has now rendered even front-line AGs, such as amikacin, clinically useless. This new resistance is conferred by a plasmid-borne gene, called *arm* or *rmt*, which codes for an RNA methylase enzyme that modifies the bacterial ribosome at the site where AGs bind. This new form of AG resistance presents challenges to circumvention that have not previously been confronted. The goal of this proposal is to fully characterize this newly discovered methylase enzyme at the molecular level. Data from our studies will be used for the design and discovery of inhibitor drugs that will neutralize this resistance mechanism and assure the continued effectiveness of AGs.

Geraldine Grant, Ph.D.
George Mason University
Grant Title: The Role of FRZB1 and KLF4 on the Differentiation of Normal Chondrocytes in vitro

Project Summary: A relatively new cartilage repair technique used to treat osteoarthritis and repair damaged joints involves removing some of a patient's own normal cartilage cells, growing them outside the body in culture, and then transplanting them into the joint defect. While the technique is somewhat successful, there are differences between the new cartilage and the surrounding cartilage. The replanted cartilage is more fibrous, prone to deterioration, and poorly integrated with the surrounding tissue, and thus the implants sometimes fail. Preliminary studies in cultured cartilage cells have revealed a consistent decrease in the expression of two specific genes. The proposed research is a more detailed study of how these two genes affect the cartilage cells grown in culture. The results of this study will aid in devising ways to control the changes in these cells in order to improve transplant success, and will open new avenues of research in cartilage engineering.

John J. Beck, Ph.D.
Sweet Briar College: 2002 CHRB grant recipient for a project entitled, *Syntheses and Structure-Activity Relationship Studies of Aromatic Side-Chain (z)-Ligustilide Derivatives: A Natural Product from Ligusticum Species.*

"Funds from the CHRB supported research that provided positive results of an initial investigation into a line of antibacterial compounds. These positive results provided evidence for a new line of antibacterial compounds. These new compounds will be the subject of a grant proposal to the NSF."

As a result of the CHRB grant award: Dr. Beck was awarded a National Science Foundation (NSF) grant award in the amount of $254,066 for the period September 2002 to September 2005.

Abstracts for 07/08 Grant Awards

George Kulik, Ph.D.
University of Virginia: 2001 CHRB grant recipient for a project entitled, *Molecular Targets for Cancer Therapy by Proteomic Analysis of Antiapoptotic Signaling Pathways.*

As a result of the CHRB grant award, Dr. Kulik leveraged grant funds from the Department of Defense Prostate Cancer Research Program *Anti-apoptotic signaling in prostate cancer cells* in the amount of $330,000 for the period January 1 2002 – December 31, 2005.

Frank Castora, Ph.D.
Eastern Virginia Medical School: 2001 CHRB grant recipient for a project entitled, *Alzheimer Disease linked to a mutation in mitochondrial DNA.*

"The CHRB award can be instrumental in allowing exciting research projects that may lack the preliminary data to warrant national funding to begin to obtain the data necessary for successful application for NIH or similar national funding."

Jorge Jacot, Ph.D.
Eastern Virginia Medical School

Grant Title: Functional/Structural Capillary Rarefaction Associated with Pericyte Degeneration a Plausible Novel Mechanism in the Early Development of Diabetic-like Retinopathy

Project Summary: Diabetic retinopathy is the leading cause of blindness in the industrialized world. Despite many existing theories describing the events underlying the early stages of diabetic retinopathy, there is still much debate as to the underlying causes of this microvascular eye disease. One of the earliest blood vessel changes in diabetic retinopathy is the death of the pericyte cell and the development of capillaries that become occluded. The mechanism(s) underlying these changes are not fully understood. Therefore, we will explore the relationship of the death of the pericyte to the development of capillary loss in the retina. This relationship will be investigated by identifying candidate genes and proteins that potentially contribute to these early blood vessel changes. The success of this study would provide a new understanding of the early events that could benefit the development of clinical treatments aimed at slowing the progression of this debilitating disease.

Terrie Rife, Ph.D.
James Madison University

Grant Title: Understanding Transcriptional Changes of Nitric Oxide Synthase 1 Leading to Diabetes

Project Summary: Decreased levels of the enzyme, Nitric Oxide Synthase 1(NOS1) due to diet may play a role in the increased susceptibility of obese individuals to diabetes type-2. Reduced production of NOS1 decreases glucose absorption and elevates blood glucose. Cultured rat brain and muscle tissues will be used to provide insights into which of NOS1's twelve promoters are responsible for the lowered NOS1 found in diabetics. Cultured tissue will be treated with insulin and advanced glycolation end stage products which are increased in type-2 diabetics. Secondly, rats fed high fat and carbohydrate diets that lead to the development of diabetes type-2 symptoms will be examined to understand what changes in NOS1 protein and mRNA expression occur during the development of the disease. These studies will lead to a better understanding of why obese individuals are more susceptible than the normal population to the development of diabetes type-2.

Joanna Goldberg, Ph.D.
University of Virginia

Grant Title: A novel vaccine approach to combat pathogenic bacteria: a focus on the category B biothreat agents causing meliodiosis and glanders

Project summary: The need to have reliable and adaptable strategies of response in place to combat bacterial pathogens is more critical than ever before. *Burkholderia mallei* and *Burkholderia pseudomallei* are category B select biothreat agents that are responsible for glanders and meliodiosis, respectively. These are both highly virulent organisms, and would pose serious health threats, if intentionally released; there are currently no approved vaccines available for either of these pathogens. The ability of these bacteria to be weaponized as well as the increased travel of our military personnel and tourists to endemic sites prompts us to develop a vaccine to protect our citizens from these agents. The long-term goal of this project is to develop effective vaccines for these infectious agents as well as validate our approach to potentially combat any pathogenic bacteria, including hospital and community acquired antibiotic resistant bacteria, and disease-causing bacteria in contaminated foods.

Abstracts for 07/08 Grant Awards

Dongmin Liu, Ph.D.
Virginia Polytechnic Institute and State University
Grant Title: Phytochemical genistein and pancreatic islet function

Project Summary: In both type I and type II diabetes, the deterioration of glucose control over time is primarily caused by an inadequate mass and dysfunction of beta-cells in which insulin is produced. Therefore, induction of beta-cell growth and prevention of its dysfunction is an essential strategy to prevent diabetes. We recently found that genistein, a plant-derived compound, is a novel growth factor and protector for clonal insulin-secreting cells. We further observed that dietary supplementation of genistein can effectively prevent the development of diabetes in mice. However, it is unknown how genistein exerts such as anti-diabetic effect. This application is thus aimed at investigating whether genistein directly stimulates growth and promotes survival of the islet beta-cells, thereby improving the beta-cell mass, function and preventing diabetes. A support for this research will facilitate our effort to develop novel, natural agents to prevent and treat human diabetes, a growing problem in this country including Virginia.

Henri Parson, Ph.D.
Eastern Virginia Medical School
Grant Title: Characterization of Diabetic Neuropathy and Genetic Differences in African-Americans (second year of a two-year grant awarded in FY 2006/2007)

Project Summary: Diabetes mellitus is the leading cause of non-traumatic lower extremity amputations (LEAs) and ulcerations in the United States. Recent studies paradoxically indicate that while rate of neuropathy in the African-American (AA) population is lower than in the Caucasian population, lower extremity amputations and ulcerations are more prevalent in AA. Our preliminary data indicates that AAs with diabetes may have an altered vascular system that potentiates abnormal blood flow and causes decreased skin nutrition and nerve integrity which may lead to a greater prevalence of ischemia, loss of sensation, foot ulcers and amputations. We suspect that the reasons AA have a higher frequency of amputation, despite lower rates of neuropathy is not only due to differences in access and disparities regarding health care, but also physiologic and possibly genetic differences which may predispose them to severe diabetic neuropathy and its complications. These facts underscore the need to understand the racial differences in the pathophysiology of diabetic neuropathy.

Paul Matherne, M.D.
University of Virginia
Grant Title: Evaluation of metabolic remodeling in the prevention of left ventricular hypertrophy with A1 adenosine receptors (second year of a two-year grant awarded in FY 2006/2007)

Project Summary: Myocardial hypertrophy (thickening of the heart) is a serious consequence of congenital heart defects in children (including aortic stenosis), high blood pressure and heart attacks. Hypertrophy of the heart can in turn impair the ability of the heart to function well, causing heart failure. For this reason it is important to develop effective strategies to prevent hypertrophy of the heart. Adenosine is a naturally occurring compound which we think can prevent a heart from becoming enlarged. This study will use state of the art imaging techniques developed at UVA to investigate how adenosine prevents hypertrophy. These findings will support future national grant applications to develop effective treatments to protect the hearts of children born with congenital heart defects, and in adults with cardiovascular disease.

Abdelali Haoudi, Ph.D.
Eastern Virginia Medical School: 2002 CHRB grant recipient for a project entitled, *Novel Cancer Gene Therapy for Prostate Cancer.*

"Funding from the CHRB was instrumental for establishing the grounds for a novel scientific finding in the area of cancer gene therapy. Further investigations are needed to clearly establish this exciting finding and further clarify its mechanism of action and control therefore opening a new avenue for a potential cancer gene therapy."

As a result of the CHRB award, Dr. Haoudi leveraged additional grant support from the Elsa U. Pardee Foundation for the period of Sept 2004-Sept 2006 for the amount of $125,000.

Abstracts for 07/08 Grant Awards

Talissa Altes, M.D.

University of Virginia: 2001 CHRB grant recipient for a project entitled, *Hyperpolarized Helium-3 Diffusion Weighted MR of the Lung: An New Technology to Assess the Lung Microstructure.*

"Thank you very much for your support! It was integral to our getting started in what has turned out to be a very productive and interesting area of research."

As a result of the CHRB award, Dr. Altes was able to leverage additional grant support from the following sources: (1) *Assessment of the variability of hyperpolarized helium-3 gas magnetic resonance imaging in patients with chronic obstructive pulmonary disease*, GlaxoSmithKline (GSK), 11/1/03-10/31/04, $363,069; and (2) *A New Method to Detect Early Changes of Emphysema in Persons Exposed to Second Hand Cigarette Smoke*, Flight Attendant Medical Research Institute (FAMRI), 7/1/04- 6/31/07, $317,000.

Diane Duffy, Ph.D.
Eastern Virginia Medical School

Grant Title: Aspirin, Eggs and Pregnancy: A New Method of Birth Control? (second year of a two-year grant awarded in FY 2006/2007)

Project Summary: Prostaglandins are produced by the ovary around the time of ovulation, and prostaglandin synthesis inhibitors can reduce fertility in women. This project will determine if prostaglandins act directly at the oocyte to stimulate the maturation and fertilization of the oocyte, steps which are essential for successful reproduction. PCR, immunofluorescence, and measurements of intracellular messengers will be utilized to determine if oocytes express functional receptors for prostaglandins. Studies will also test the hypothesis that prostaglandin treatment increases oocyte maturation and fertilization in vitro. If prostaglandins enhance oocyte maturation and fertilization, then prostaglandin synthesis inhibitors such as aspirin and ibuprofen (Advil, Motrin) may prevent these essential steps, resulting in an effective pre-fertilization contraceptive.

Shyama Masilamani, Ph.D.
Virginia Commonwealth University

Grant Title: Sex Hormone-Mediated Regulation of Kidney Transporters and Blood Pressure Control (second year of a two-year grant awarded in FY 2006/2007)

Project Summary: One out of three Virginians have been told by a health care provider that they have hypertension. The prevalence of hypertension is greater in men than premenopausal women (men=24%, women=13%; 35-44 age group). The long- term goal of this study is to enhance our understanding of the molecular mechanisms that are involved in the sex related difference in the development of hypertension. Our hypothesis is that premenopausal female DOCA-salt hypertensive rats retain less sodium and fluid compared to males due to a lower expression of epithelial sodium channels (ENaC) and aquaporin 2 (AQP2) water channels. Further, this sex difference is mediated by differential regulation of ENaC and AQP2 by gender hormones. This study will use an integrated physiologic approach, utilizing both in vivo and in vitro studies to examine the regulation of ENaC and AQP2 by sex hormones in the DOCA-salt hypertensive rat.

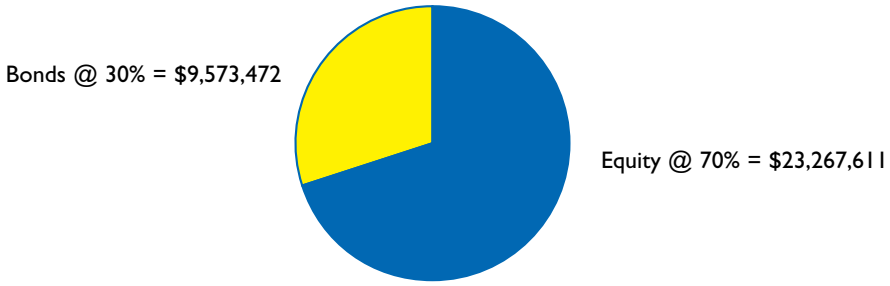
Zendra Zehner, Ph.D.
Virginia Commonwealth University

Grant Title: The role of the Oncogene Stat3 and Tumor Suppressor ZBP-89 in Tumor Metastasis (second year of a two-year grant awarded in FY 2006/2007)

Project Summary: There is no doubt that cancer is a major health threat. Statistics show that 1 in 3 Americans will experience some form of cancer in their lifetime. Most, if not all, cancers originate from epithelial cells, which during tumor progression leave the confines of the primary tumor, invade the interstitial tissue, and disseminate to secondary sites. In this process the epithelial cell is modified making it receptive to new directives. It is thought that by understanding the requirements for this transition, new targets will be uncovered, which, if blocked, could prevent tumor progression. We propose one such target is the oncogene Stat3, which we have shown stimulates gene expression by overcoming the tumor suppressor ZBP-89. Ultimately, we propose to restore the repressor activity of the tumor suppressor ZBP-89, in the hopes that this will serve to control cell growth and halt tumor progression.

Investment of Funds

The Virginia Retirement System invests the Commonwealth Health Research Fund (CHRF). The estimated value of the CHRF as of June 30, 2007 was $32.8 million. The CHRF is a very straightforward account that consists of a combination of equity (70%) and bonds (30%). This asset mix results in a relatively low risk profile when viewed over a market cycle. This account has performed very well over time and has benefited from low investment management fees.



Grant funding is calculated by an amount not to exceed six percent of the moving average of the market value of the CHRF calculated over the previous five years or since inception, whichever is shorter, on a one-year delayed basis, net of any administrative fee assessed pursuant to subsection E of Section 51.1-124.36, may be expended in a calendar year for any purpose permitted by this chapter.

Commonwealth Health Research Board
Fiscal Year 2007 budget for the period – January 1, 2007 to December 31, 2007

Grant Budget for Calendar Year 2007

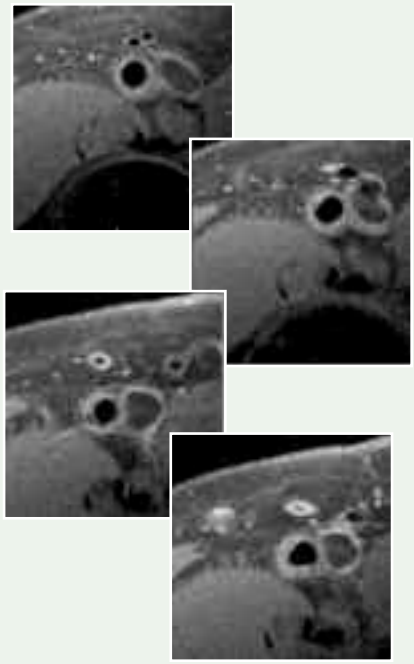
Calendar Year		***Market Value @ 12/31/06***
January 1 - December 31, 2001	Year 1	$26,150,016
January 1 - December 31, 2002	Year 2	$22,273,551
January 1 - December 31, 2003	Year 3	$26,449,255
January 1 - December 31, 2004	Year 4	$28,010,649
January 1 - December 31, 2005	Year 5	$28,637,870
	Average Market Value	$26,304,268
		5.00%
Funds available for 2007 grants based on average market value:		$1,315,213
Less Estimated Administrative Expenses:		
Estimated Mellon Custodial Fee		$ 5,100
Estimated VRS Management Fee		$ 4,600
Estimated State Street Management Fee		$ 3,600
Total Estimated Administrative Expenses		$13,300
Funds available for 2007 grants less estimated administrative expenses:		$1,301,913

Methodology:
The valuation date for market values will be 12/31/XX of each year.
Each annual calculation will be made based on the previous five calendar years, with a one year delay.

Christopher Kramer, M.D.
University of Virginia: 2001 CHRB grant recipient for a project entitled, *Imaging Inflammation within Atherosclerotic Plaque with magnetic resonance.*

"The CHRB grant was instrumental in completing the project, publishing a manuscript, and the data accrued served as preliminary data for an NIH R01 application that was subsequently funded."

As a result of the CHRB grant award, Dr. Kramer was awarded a National Institutes of Health (NIH) National Heart, Lung and Blood Institute (NHLBI) R01 grant, *Comprehensive Magnetic Resonance in Peripheral Arterial Disease* for the period 9/22/03-8/30/08, in the amount of $3.7 million total costs including $2.6 million direct costs.



Representative sequential black blood magnetic resonance images (upper left to lower right) obtained with the use of a surface coil from the femoral artery of a subject with mild to moderate peripheral arterial disease with both the luminal and adventitial border clearly delineated. Note the slice to slice variation in plaque morphology. This technique can be used to reduce sample sizes for clinical trials of novel approaches to reducing atherosclerotic plaque burden.

George Kunos, M.D., Ph.D. Virginia Commonwealth University: 1999 CHRB grant recipient for a project entitled, *Development of Novel Drugs for the Treatment of High Blood Pressure Disease.*

"I am grateful for the CHRB for the support I received. There is considerable foresight on the part of CHRB in supporting research with potential practical implications, such as the development of novel therapeutic agents."

Jennifer Wayne, Ph.D. Virginia Commonwealth University: 2000 CHRB grant recipient for a project entitled, *Mechanical function predicted by MRI parameters in cartilage.*

"I am truly grateful for the award from the CHRB which allowed me to explore a new avenue of research and establish collaborations with additional colleagues. The CHRB clearly has foresight in advancing science and technology by supporting research within the Commonwealth for the benefit of Virginians and society as a whole."

Dr. Wayne's continuing work was funded by The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) of NIH, 9/2002-2005, for $326,500.

Eligibility for CHRB Grant Funding

The following Virginia-based entities may apply for a grant from the Commonwealth Health Research Board (CHRB):

- State-supported institutions of higher education,
- Private, not-for-profit institutions of higher education established in Virginia,
- Agencies of the Commonwealth of Virginia, whose mission is to conduct health or health related research, and
- Nonprofit organizations exempt from income taxation under Section 501 c (3) of the Internal Revenue Code and with their principal offices and programs in the Commonwealth of Virginia whose mission is to conduct health or health related research.

CHRB Grant Application Process

As part of the Commonwealth Health Research Board (CHRB) grants application process, there are three steps that take place in the review process. More details regarding the required information as part of the submission of a concept paper or a full proposal to the CHRB can be found at www.chrb.org under the heading of CHRB Grant Guidelines.

Step One: Submission of a concept paper. Concept papers are normally due October 1st. Concept papers (excluding the cover page) must be no longer than five typewritten, double-spaced pages. In general, concept papers will provide information on the problem, need or opportunity that the project will address and the anticipated results or impact of the project. Concept papers will also include estimated total project costs and the amount of funding the applicant is seeking from the CHRB as well as a timeframe for conducting the research. Each concept paper undergoes scientific and technical merit review.

Step Two: Submission of a full proposal. The Board requests those applicants whose concept papers have been judged, in Step one, to have potential for successful research outcomes, to submit full proposals. Only applicants whom the Board has invited to develop a full proposal may submit a full proposal to the Board. Full proposals are normally due February 1st. The full proposal, excluding the cover page, must be no longer than 12 typewritten, double-spaced pages. In general, full proposals will provide similar information as provided in the concept paper except in greater detail. As in Step One, each full proposal receives in-depth review.

Step Three: Presentation to the CHRB. The Board invites finalists from Step two to make a presentation in-person to the Board. Presentations to the Board are normally scheduled for the May meeting. Presentations, including questions and responses, should take no longer than 15 minutes. The presentation should elaborate on the information contained in the concept paper and formal proposal.

CHRB Grant Guidelines

CHRB grant guidelines are updated annually and posted to the CHRB website at www.chrb.org by August 1st of each year. The grant guidelines are designed to help individuals determine if the research project or initiative for which financial support is sought is a good match with the CHRB purposes and criteria. The guidelines also describe the kinds of research projects and activities the CHRB funds - and does not fund, and tells how and when to apply for a grant. The CHRB website also provides a description of past and current CHRB grant awards and grant abstracts.

Grant Criteria

Maximum CHRB Grant Award

Applicants may request funding to support projects over either a one-year or a two-year period. The maximum amount of a one-year award is $100,000. The maximum amount for a two-year award is $200,000. However, no more than $100,000 will be provided in either the first or second year. The number of one-year and two-year awards that the CHRB anticipates it will make, is dependent upon the amount of funds available and the number of requests received for each category.

Required 33% Matching Funds from Grantee Institution/Organization

The grantee institution must agree to provide 33% in required matching funds for the CHRB grant award. For example, if the grantee institution requests $100,000 in CHRB grant funds, then the 33% matching funds would amount to $33,000.

Other Grant Requirements

- The starting date for all projects awarded CHRB grant funds shall be July 1st of the funding year.
- Requests for funding will be reviewed according to criteria that are consistent with the CHRB's purposes and goals.
- Individuals applying for funding may submit no more than one application per funding cycle.
- The CHRB will accept no more than 15 applications from any one organization or institution of higher education per funding cycle.
- Grantees are responsible for meeting federal, state, and local health and safety standards and for establishing and implementing necessary measures to minimize their employees' risk of injury or illness in activities related to CHRB grants. Grantees are further responsible for meeting all applicable federal, state, and local regulations, requirements, and standards related to human subjects and vertebrate animals.
- Grantees are responsible for obtaining the appropriate approvals by any internal or external institutional review boards when the use of human subjects or vertebrate animals is proposed. Written documentation must be provided that the approvals have been obtained prior to the release of any CHRB grant funding. If these approvals are not in place by July 1 of the funding year, an award will not be made and the applicant will be required to reapply at a subsequent date for CHRB funding.

CHRB Grant Criteria

Concept papers and full proposals will be reviewed in accordance with the following criteria:

- **Significance:** Does the research address an important problem? If the aims of the application are achieved, how will scientific or other knowledge be advanced? What will be the effect of this research on the concepts, methods, or practices in this field?

Paul H. Ratz, Ph.D.
Eastern Virginia Medical School: 2000 CHRB grant recipient for a project entitled, Regulation of detrusor smooth muscle contraction by CA2+ and CA2- sensitization.

"Funds provided by the Commonwealth Health Research Board of Virginia enabled my laboratory to acquire a substantial amount of high-quality data that was included in an NIH RO1 grant application. Our goal with this research is to provide a cellular mechanistic approach for the design of new therapeutic agents that will reduce the incidence of urinary incontinence, a chronic disorder that is more prevalent than diabetes. Organizations exist to support research on specific life-threatening disorders such as hypertension, cancer and diabetes, but research on many non-life-threatening disorders is under funded. Support by the CHRB addresses this issue by providing funds of sufficient magnitude and duration for investigators with diverse interest to pursue their medical research problems in a meaningful and significant way."

As a result of work funded by the CHRB, Dr. Ratz was funded for 4 years at $730,000 by the National Institute of Diabetes and Digestive and Kidney Diseases at the National Institutes of Health.

Grant Criteria

Glenda E. Gillaspy, Ph.D. Virginia Polytechnic Institute and State University: 2001 CHRB grant recipient for a project entitled, *Isolation of Genes for Transgenic Production of a Diabetes Treatment.*

"The CHRB funding I received was critical in starting a new research project in my laboratory in 2002. I really appreciate this opportunity, and hope the CHRB can continue to fund "seed" projects of Virginia scientists. Although we did not accomplish our intended goal of cloning a chiro inositol epimerase gene from plants, we did find a really exciting connection between inositol and Vitamin C. This finding allowed us to pursue studies currently funded by the National Science Foundation."

Based on preliminary data funded by the CHRB, Dr. Gillaspy was awarded the following grants from the NSF:

National Science Foundation, Sole Principal Investigator, *Inositol Synthesis and Catabolism in Plants*, for the period 9/01/03- 8/31/06 in the amount of $380,000; and, National Science Foundation, Sole Principal Investigator, *REU: Inositol Synthesis and Catabolism in Plants*, for the period 9/01/03- 8/31/05 in the amount of $11,250.

- **Collaboration:** Will the initiative employ useful collaborative arrangements among two or more institutions of higher education or organizations either within or outside the Commonwealth of Virginia?
- **Leverage:** How will funding provided by the CHRB be used to leverage additional support from other federal or private organizations? The Board gives priority to those research efforts where support can be leveraged to foster contributions from federal agencies or other entities.
- **Approach:** Are the conceptual framework, design, methods and analyses adequately developed, well integrated, and appropriate to the aims of the project?
- **Innovation:** Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?
- **Experience and Qualifications of Research Team:** Does the Principal Investigator have the proper training and experience to direct and manage the project? What percentage of time will the Principal Investigator contribute to the project? Has the Principal Investigator conducted research related to this project? Through training and experience, is the research team qualified to conduct this research? Is the research team experienced with research evaluation processes?
- **Unique Virginia Considerations:** Are there unique Virginia research resources or facilities that will be utilized?

Conditions for CHRB Grant Acceptance

Conditions for grant acceptance include a grant agreement between the principal investigator and the grantee institution and the CHRB. Each grantee must sign a Grant Agreement with the CHRB that delineates the terms and specific objectives of the project. Each grantee receiving a one-year or two-year CHRB grant award will be required to submit scientific and fiscal reports at specific times. Specific grant reporting dates are specified in the individualized grant agreement. Also provided are general dates for the distribution of CHRB grant funds over the course of the grant project.

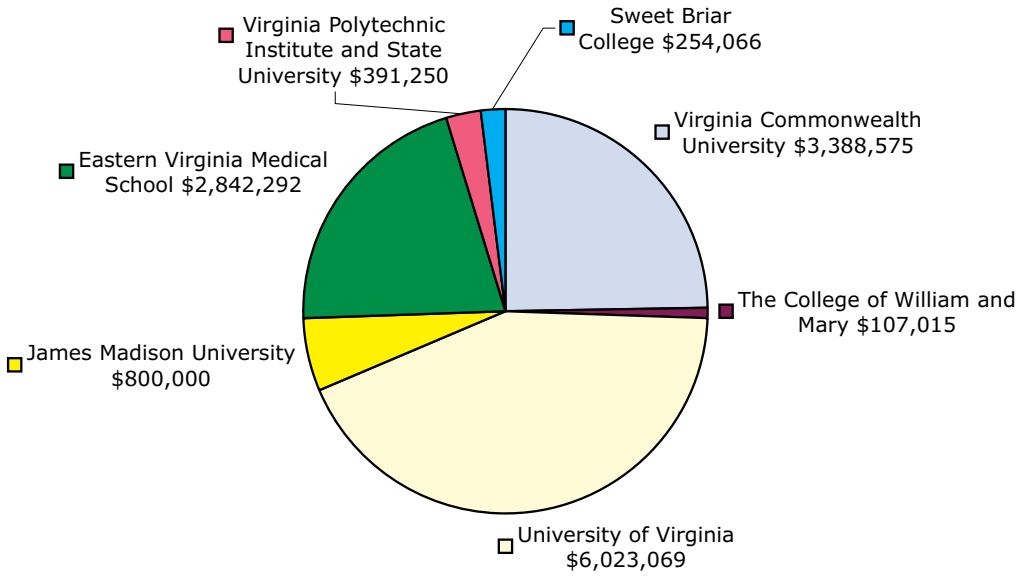
Grant Evaluation

Post Award Reporting Requirements

For a period up to five years, the recipient organization agrees to notify the CHRB of any future grant awards that are received as a result of research funded with grant funds from the Commonwealth Health Research Board.

The CHRB submits an annual report to the Governor and the General Assembly on the Board activities to include an executive summary of the grant process. It also provides information on grants funded in prior years and their success in leveraging additional grant funding from federal or private foundation funding sources.

Additional Funds Leveraged Total $13.8 million (based upon evaluation responses received)



Cynthia S. Kelly, M.D. Eastern Virginia Medical School: 2000 CHRB grant recipient for a project entitled, EZ Breathers: Partnership for Asthma Awareness and Prevention in Head Start children.

"Funding provided by the Commonwealth Health Research Board not only helped us to improve care for preschool-aged children with asthma in our community but it provided us with the outcome data necessary to successfully compete for national funding from the Robert Wood Johnson Foundation so that we could expand our program to asthmatic children of all ages in Hampton Roads."

As a result of work funded by the CHRB, Dr. Kelly was successful in obtaining one of eight awards for an "Allies Against Asthma" program funded by the Robert Wood Johnson Foundation, in a competition of 250 investigators. The grant is in an amount of $1,500,000 over four years.

Geoffrey Krystal, M.D., Ph.D. Virginia Commonwealth University: 1999 CHRB grant recipient for a project entitled, *Inhibition of P13K as a Novel Therapeutic Strategy for the Treatment of Small cell lung cancer (SCLC).*

Preliminary data generated as a result of the CHRB award was used to obtain a Merit Review Award from the Department of Veteran's Affairs Research Service of $689,800 over the period of 2001-2006. The complete set of data also served as a cornerstone for the renewal of the Merit Review Award that will run from 2006-2010 at total direct cost of $535,200.

Commonwealth Health Research Board

2007 Annual Report

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