XI OTHER PROGRAMS MANAGED BY THE CDMRP

Over the past decade, increased public interest in health care issues has influenced the funding of scientific research. From fiscal year 1995 (FY95) to FY05, Congress has directed the Department of Defense (DOD) to manage numerous targeted research initiatives. As the manager for these initiatives, the U.S. Army Medical Research and Materiel Command's (USAMRMC's) Office of the Congressionally Directed Medical Research Programs (CDMRP) has executed 54 research programs, 47 of which are characterized by a one-time appropriation and/or are institutionally based programs. Table XI-1 lists these other programs and the FY(s) that the CDMRP has managed them.

The goal of the CDMRP in managing these programs is to fund scientifically meritorious research that addresses the topic areas specified by Congress. For FY04 through FY05, the CDMRP has been responsible for executing or managing 32 institutionally based research programs, 14 of which are new to the CDMRP in FY05. FY04 through FY05 awards were made following proposal submission in response to the USAMRMC 99-1 Broad Agency Announcement and an external peer review for scientific merit.

This section contains information on other programs managed by the CDMRP in FY04 through FY05. Appendix B, Table B-8, summarizes the directions from Congress and the investment strategy for these initiatives.

The goal of the CDMRP in managing the other programs is to fund scientifically meritorious research that addresses the topic areas specified by Congress. For FY04 through FY05, the CDMRP has been responsible for executing or managing 32 institutionally based research programs, 14 of which are new to the CDMRP in FY05.

3D IMAGING AND GENOMIC ANALYSIS FOR BREAST CANCER MANAGEMENT

Congress appropriated $1.7 million (M) in FY04 for 3D Imaging and Genomic Analysis for Breast Cancer Management and an award was made to General Electric (GE) Global Research to implement and test 3D breast imaging and genomic analysis of breast cancers. Early detection methods for breast cancer include 2D x-ray mammography followed by biopsy of any suspected tumor areas. However, the more than 1.2 million breast biopsies performed annually in the United States yield positive results only in 10% to 20% of women tested. Development and implementation of 3D breast imaging techniques containing the added dimension of depth would produce sharper, more detailed images of the breast tissue and aid in the interpretation of the images. The additional interpretation would increase the detection rate of early-stage cancers and reduce the number of unnecessary biopsies for women. Where biopsies are warranted, genomic analysis of the tissue can assist in the description of the tumor and focus treatment options for the best decisions for the patient.

Table XI-1. Other Programs Managed by the CDMRP

Program	Fiscal Year[a]
3D Imaging and Genomic Analysis for Breast Cancer Management	04
Advanced Cancer Detection[b]	97–99
Advances in Breast Cancer Therapy Research	05
Alcoholism Research	00–05
Arthropod-Borne Infectious Disease Control Research	02
Breast Cancer Imaging Research	03
Cancer Center of Excellence	01–02
Cancer Research	01
Cancer Vaccine Research	05
Cancerous Brain Tumors Drug Research	05
Center for Prostate Disease Research	97–05
Coastal Cancer Control[b]	95
Comprehensive Bioactive Products for Breast Cancer Research	05
Computer-Aided Diagnosis[b]	97
Computer-Assisted Cancer Device	04–05
Cooperative DOD/Veterans Affairs (VA) Medical Research	99–00
Defense Women's Health Research	95
Diagnostic and Surgical Breast Imaging	99
Diagnostic and Therapeutic Cancer Care Equipment	05
Donor Cord Blood Demonstration	04
Electrical Impedance Scanning Device	04
Fragile X Research	02
Gallo Cancer Center	00–01, 03–05
Genetic Cancer Research	04–05
Genomic Medicine and Gene Therapy	04–05
Hepatitis C Research	02
Life Sciences Research Initiative	05
Lung Cancer Research	00–05
Molecular Medicine	04
Monoclonal Antibodies, Massachusetts Biological Lab	02
Muscle Research Consortium	05
Muscular Dystrophy Research	03–05
Myeloproliferative Disorders Research	04
National Prion Research	02, 05
Neurogenetic Research and Computational Genomics	04
Neutron Therapy Research	05
Orphan Disease Drug Discovery Research	05
Osteoporosis Research	95
Pediatric Brain Tumor and Neurological Disease Research	05
Pediatric Hospice	03–04
Post-Polio Syndrome Research	99–00
Preventive Medicine Research Institute	05
Preventive Medicine Research for Prostate Cancer	04–05
Spinal Muscular Atrophy Research	05
Targeted Nano-Therapeutic for Advanced Breast and Prostate Cancer	04–05
Tripler Cancer Care	05
Veterinary Manpower Development	05

[a] FY(s) that the CDMRP was responsible for managing the listed programs.

[b] Award period of performance has been completed or responsibility for managing this program is no longer handled by the CDMRP.

ADVANCES IN BREAST CANCER THERAPY RESEARCH

Congress appropriated $1.3M in FY05 for an Advances in Breast Cancer Therapy Research Program. Breast cancer, the most commonly diagnosed cancer in women, accounts for 32% of all cancers in women. In 2005, approximately 211,240 women in the United States will receive a diagnosis of invasive breast cancer, and more than 40,000 are projected to die from the disease.[1] The benefits of the research from this program will extend to warfighters and their family members. In 2003, breast cancer treatment accounted for more than $56M in direct care costs throughout the Military Health System. These costs are expected to increase by almost 50% by the end of the decade, with projections exceeding $75M in breast cancer direct care costs in 2009.[2] Surgery, chemotherapy, and radiation treatment are the established methods of combating breast cancer. New advances in breast cancer prevention, treatment, and care will offer improvements in the fight against this disease. The Advances in Breast Cancer Therapy Research Program seeks to develop and validate host and tumor genetic factors that can predict response to chemotherapy to assist the selection of the most effective chemotherapy for the individual patient. A full proposal was scientifically and programmatically reviewed. A recommendation for funding has been requested from the Commanding General, USAMRMC. Pending the Commanding General's approval, an award is anticipated by October 2005.

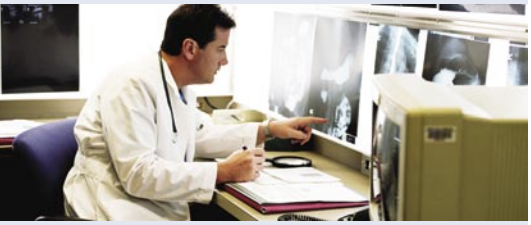
ALCOHOLISM RESEARCH

Alcoholism research received congressional appropriations totaling $29.1M in FY00 through FY04 and $3.75M during FY05. The FY00 through FY04 funds have been used to support 23 research projects at the Ernest Gallo Clinic and Research Center in San Francisco, California. These research projects are related to the Center's theme of studying neuroscience in models of addiction, particularly alcoholism. The Gallo Center's multidisciplinary approach links genetics, physiology, behavioral studies, and molecular and cell biology in model systems and uses coherent team approaches to study the complex problems of alcohol abuse. The work from the Ernest Gallo Clinic and Research Center is being recognized nationally and internationally through publications in highly respected scientific journals. The highlights of this research include the following:

- Dopamine and adenosine receptors are important in neuronal signaling and are highly expressed in specific portions of the brain. Investigators have shown that the proteins dopamine and adenosine work synergistically in a region of the brain known to

[1] *American Cancer Society,* Cancer Facts and Figures, *2005.*

[2] *TRICARE Management Activity Selected Disease Report for its FY04 Program Objective Memorandum.*



be important in alcohol and other addictions. This finding suggests that low-dose combinations of drugs, each of which affects one of these proteins, could be highly specific in altering human drinking behaviors.

- Ibogaine is a drug known to be helpful in treating addiction, but it has severely detrimental side effects. Gallo investigators have shown that Ibogaine activates a specific signaling pathway in the brain. This discovery may lead to the development of new drugs that have Ibogaine's therapeutic characteristics but not its negative side effects.
- A gene (*slo-1*) has been identified in a model organism, the nematode *Caenorhabditis elegans*, that when inhibited creates resistance to alcohol. Work continues to identify and characterize *slo-1* gene variants in the mouse and human. The possibility of developing a drug that would help people become resistant to the effects of ethanol would be suggested if mouse and human variants also show alcohol resistance.
- Studies of the brain's opioid receptors and their binding molecules are producing new insights into whether particular types of opioid receptors can reinforce addictive behaviors. Changing treatment regimens toward therapeutics that affect the most responsive opioid receptors may increase the effectiveness of alcoholism treatment programs.
- The high rate of relapse is a major problem for alcoholics seeking treatment. Investigators have developed a neurosteroid that prevents relapse drinking in rats. The discovery of this drug suggests a pathway to the development of a new generation of drugs that could be helpful in long-term recovery from alcoholism.

For the FY05 congressional appropriation of $3.75M, six proposals have been both scientifically and programmatically reviewed. Awards are currently being negotiated.

CANCER VACCINE RESEARCH

Congress appropriated $3.4M in FY05 for the Cancer Vaccine Research Program. Vaccines have been used primarily to prevent infectious diseases by stimulating the immune system to recognize particular antigens. Vaccines for cancer can be developed that will recognize and destroy cancer cells as soon as they develop. The goal of the Cancer Vaccine Research Program is to develop vaccines that will prevent primary or secondary occurrences of some cancers and infectious diseases and also have use in biodefense involving genetically modified Listeria bacteria. A pre-proposal for the FY05 program was received and internally reviewed. A full proposal is currently undergoing peer review.

CANCEROUS BRAIN TUMORS DRUG RESEARCH

Congress appropriated $1M in FY05 for cancerous brain tumors drug research. In 2005, approximately 18,500 people in the United States will receive a diagnosis of primary brain cancer, and nearly 12,760 people are projected to die from the disease.[3] Primary brain tumors are the leading cause of death from childhood cancers.[4] Adequate treatment is not available for most brain tumors and the likelihood for long-term survival is poor. Treatment of brain tumors generally has been surgery, radiation treatment, chemotherapy, or a combination of these treatments. The goal of the Cancerous Brain Tumors Drug Research Program is to develop novel therapeutics for brain tumors. A full proposal was scientifically and programmatically reviewed and subsequently approved for funding. Negotiations are under way and an award is anticipated by October 2005.

CENTER FOR PROSTATE DISEASE RESEARCH

The Center for Prostate Disease Research (CPDR) Program received congressional appropriations totaling $58.35M in FY92 through FY04 and $4.3M during FY05.[5] The CPDR was initially established in response to a growing concern over the incidence of prostate cancer and the controversy over treatment choices at the various stages of the disease. The program is administered under the auspices of the Uniformed Services University of the Health Sciences (USUHS). The CPDR has been devoted to the study and cure of prostate disease and cancer and comprises three major emphasis programs: the Tri-Service Multicenter Prostate Cancer Database, the Basic Sciences Research Program, and the Clinical Research Center. These programs strive to fight diseases of the prostate as well as foster training in basic sciences and clinical research.

The CPDR Program has developed and is actively maintaining and expanding, a tri-service prostate cancer comprehensive clinical research database involving nine military treatment sites and numerous military and civilian researchers and support staff. Heralded as a unique national resource by the Scientific Oversight External Advisory Committee, the CPDR Program database maintains relevant prostate disease data on more than 19,000 men treated in military health care facilities. This database has resulted in landmark studies of the prostate-specific antigen (PSA), including screening for prostate cancer in high-risk African American men.

[3] *American Cancer Society,* Cancer Facts and Figures, *2005.*

[4] *Pediatric Brain Tumors Progress Review Group, http://prg.nci.nih.gov/brain/pediatrics.html.*

[5] *Congress appropriated funding ($2M) in FY92 to establish the CPDR Program. The USAMRMC, but not the CDMRP, managed $10.25M of FY92 through FY95 appropriations for the CPDR Program.*

The CPDR laboratories, located at the USUHS in Bethesda, Maryland, continue to focus on cutting-edge molecular and cell biology research with the goals of better understanding the biology of the disease and developing novel diagnostic and prognostic biomarkers for prostate cancer. The CPDR laboratories, in collaboration with the Walter Reed Army Medical Center (WRAMC) and the Armed Forces Institute of Pathology, continue to develop and expand unique bioresources for prostate cancer research, which now include paraffin-embedded whole-mount prostates, OCT®-embedded frozen tissues, and a frozen section slide library and serum bank from more than 600 cancer patients. Blood- and bone marrow-derived RNA and DNA from 700 cancer patients and 300 controls have been prepared. The CPDR laboratories also developed a new DNA and RNA bank from laser capture microdissected normal and tumor cells of 150 patients. Linkage of these biomaterials to well-defined clinico-pathologic features, patient demographics, and treatment responses has provided promising new opportunities in the discovery of prostate cancer-specific biomarkers using genomic and proteomic approaches.

Prostate cancer gene discovery efforts using state-of-the-art global gene expression profiling and positional cloning strategies at the CPDR laboratories are uncovering novel gene alterations in prostate cancer. The current focus is on the identification of the common gene expression and mutational alterations in prostate cancer. The CPDR has identified Ets-related gene (ERG) proto-oncogene overexpression as one of the most common changes described in prostate cancer thus far. The CPDR is also involved in multicenter cohorts evaluating the diagnostic utility of serum protein profiling.

In the past year, CPDR's progress and accomplishments have been recognized. Both the Agency for Healthcare Research and Quality and the National Cancer Institute invited the CPDR to key advisory panels related to prostate cancer, bringing great recognition to the DOD, the U.S. Army, and the CPDR. Two patents have been issued to CPDR researchers, and three patent applications are pending.

COMPREHENSIVE BIOACTIVE PRODUCTS FOR BREAST CANCER RESEARCH

Congress appropriated $1M for a comprehensive bioactive products program for breast cancer and an additional $1M for a bioactive products program for breast cancer. The USAMRMC decided to consolidate these appropriations into one program for execution. Breast cancer, the most commonly diagnosed cancer in women, accounts for 32% of all cancers in women. Approximately 211,240 women in the United States will receive a diagnosis of invasive breast cancer in 2005.

More than 40,000 women are projected to die from the disease this year. Currently, there are more than 2 million women in the United States who have been treated for breast cancer.[6] Bioactive products are extranutritional constituents that occur in small quantities in foods, and often are from plant sources. Many bioactive products, from aspirin, which was isolated from willow bark, to paclitaxel (Taxol®), isolated from the stunted North American yew, are now commonly used medicinal compounds. A comprehensive investigation of possible bioactive compounds including profiles of chemical, bioactivity, and anticancer properties would increase the number of bioactive product treatment or prevention avenues for women with breast cancer. The benefits of the research from this program will extend to warfighters and their family members. In 2003, breast cancer treatment accounted for more than $56M in direct care costs throughout the Military Health System. These costs are expected to increase by almost 50% by the end of the decade, with projections exceeding $75M in breast cancer direct care costs in 2009.[7] A full proposal was scientifically and programmatically reviewed and subsequently approved for funding. Negotiations are under way and an award is anticipated by October 2005.

COMPUTER-ASSISTED CANCER DEVICE

Congress appropriated $1M in FY04 and $1.1M in FY05 for the Computer-Assisted Cancer Device Program. Some breast cancers go undetected on standard screening mammograms, and false negatives can occur. Better methods are needed to make tumors on mammograms more conspicuous. Computer-assisted detection technology can provide radiologists with a "second opinion," enhancing the identification of suspicious areas that may have been missed by a standard imaging technique. Identification and implementation of a computer-assisted detection device are critical goals of this program. An award was made to Henry M. Jackson Foundation for WRAMC; iCAD, Incorporated (Nashua, New Hampshire); and the Windber Research Institute (Windber, Pennsylvania). The FY05 funds were used to extend the FY04 award as a continuation of the research.

DIAGNOSTIC AND THERAPEUTIC CANCER CARE EQUIPMENT

Congress appropriated $7.5M in FY05 for diagnostic and therapeutic cancer care equipment. Diagnostic and therapeutic medical equipment includes magnetic resonance imagers, computed tomography scanners, and radiation therapy equipment. It also may include other diagnostic and therapeutic equipment such as ultrasound devices, diagnostic x-ray

[6] *American Cancer Society,* Cancer Facts and Figures, *2005.*

[7] *TRICARE Management Activity Selected Disease Report for their FY04 Program Objective Memorandum.*

machines, and medical and surgical equipment. The ability of patients to have early access to diagnostic and therapeutic equipment can lead to earlier detection, diagnosis, and treatment for cancers. The Diagnostic and Therapeutic Cancer Care Equipment Research Program seeks to examine the diagnostic and therapeutic effect of emerging technologies in imaging and radiation oncology and the effect of equipment access on the quality of patient care. A pre-proposal for the FY05 program was received and was internally reviewed. A full proposal has been submitted and is currently undergoing scientific review.

DONOR CORD BLOOD DEMONSTRATION

Congress appropriated $1M in FY04 for the Donor Cord Blood Demonstration Program and an award was made to Wayne State University to continue to establish a bank of donor cord blood from minority populations and to assess outcomes of umbilical cord blood transplants in this patient population. In 2005, more than 34,810 cases of leukemia will be diagnosed, and more than 22,000 people are projected to die from the disease.[8] More than 100,000 people have been cured from these potentially fatal hematological diseases using transplantation of blood stem cells. However, finding a genetic match for blood stem cells becomes very difficult when the recipient is a member of a minority population. It is imperative that strategies be implemented to increase the success rate of blood stem cell transplantation among these populations through enhanced participation in donor programs. Cord blood, the blood that remains in the umbilical cord and placenta after birth, is a rich source of blood cell stem cells and can be used to treat diseases of bone marrow such as leukemia with significantly less rejection than conventional bone marrow transplantation.

ELECTRICAL IMPEDANCE SCANNING DEVICE

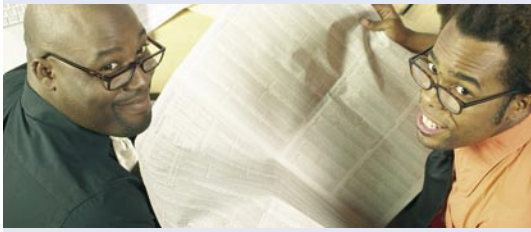
Congress appropriated $1M in FY04 for the Electrical Impedance Scanning Device Program and an award was made to the Henry M. Jackson Foundation to work with TransScan and WRAMC to refine and clinically test an electrical impedance scanning device for breast cancer. Detection of breast cancer is especially difficult for small lesions, although small lesions are generally the most treatable. Electrical impedance scanning-based systems use measurements based on how tissues affect the flow of electricity. Malignant tumor tissue will have one impedance "signature," whereas the surrounding normal tissue will present a different pattern. Thus, electrical impedance scanning-based systems may provide an improved image of small breast tumors aiding in their early diagnosis.

[8] *American Cancer Society,* Cancer Facts and Figures, *2005.*

GALLO CANCER CENTER

In FY00 through FY01, Congress appropriated a total of $7M to provide for the initiation of a cancer center dedicated to prostate cancer research. FY00 through FY01 funds were awarded to the University of Medicine and Dentistry of New Jersey to support the Dean and Betty Gallo Prostate Cancer Center at the Cancer Institute of New Jersey. While Congress did not appropriate funds for the Gallo Cancer Center in FY02, appropriations continued in FY03 through FY05, with $1M appropriated for FY05. Through FY05, a total of $10.05M has been specified for the Gallo Cancer Center to fund scientifically meritorious research focusing on cancer of the prostate and to align this civilian research initiative with military research and clinical needs in accordance with directives received from Congress. The Gallo Cancer Center has initiated programs successfully including a center retreat, pilot grant program, and research working groups. Three pilot grant projects are now fully funded and under way. Work from the Gallo Cancer Center is being recognized nationally and internationally through publications in highly respected scientific journals. Some of the highlights of this research include the following:

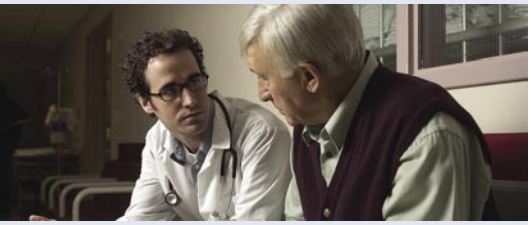
- Transgenic mice that carry an Nkx3.1-lacZ knock-in have been developed. These mice have enabled the development of a novel prostate cancer explant culture system that reproducibly allows the growth and differentiation of prostatic epithelium in vitro.
- Work examining the effect of insulin-like growth factor binding proteins (IGFBPs), which are necessary for PSA, on prostate cancer has shown that prostate cancer can be exacerbated by IGFBP.
- A clinical trial for hormone refractory prostate cancer using epothilone and estramustine was initiated. Several genes, including p53, MAP4, and MRP, will be assayed to determine whether they can predict sensitivity to epothilones in the clinic.
- The Outreach and Education Program has collaborated with the 100 Black Men of New Jersey as well as several other groups to provide community partnerships for prostate cancer education and outreach. During 2003, the Gallo Cancer Center participated in more than 65 prostate cancer educational programs.



For the FY05 congressional appropriation of $1M, a pre-proposal has been internally reviewed. A full proposal is anticipated by October 2005.

GENETIC CANCER RESEARCH

Congress appropriated $2M in FY04 for genetic cancer research and an award was made to the Cold Spring Harbor Laboratory to study gene mutations that lead to or occur during the progression of cancer.



The genetic changes that cause cancer susceptibility or occur during the development, progression, and metastasis of cancer are only now becoming understood. Mutations in genes inherited from parents (germline mutations) as well as mutations that are acquired during the course of an individual's lifetime (somatic mutations) may lead to the development of cancer. Once cancer has started, additional mutations may occur that can increase the severity of the disease. Hereditary cancers are thought to account for approximately 5%–10% of cancers in women; the remaining 90%–95% of women's cancers expected to be diagnosed in 2005 (affecting more than 600,000 women) will be the result of the spontaneous, often unknown, genetic abnormalities that cause cancer.[9] In 2004 cancer treatment and prevention accounted for more than $365M in direct care costs throughout the Military Health System. By 2009, projections for cancer treatment and prevention increase to more than $450M in direct care costs.[10] In FY05, Congress appropriated $1.5M for genetic cancer research in women. A proposal was received, internally reviewed, and found to contain sufficiently meritorious science to award. The FY05 funds were used to modify an FY02 award to Cold Spring Harbor Laboratory from the DOD's Breast Cancer Imaging Research Program (also managed by CDMRP) as a continuation of that research. Research focuses on detection of the genetic mutations to predict cancer progression and drug responsiveness.

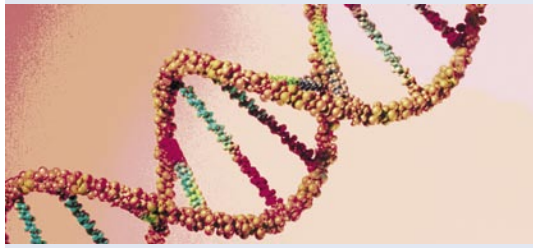
GENOMIC MEDICINE AND GENE THERAPY

Congress appropriated $3.4M in both FY04 and FY05 for genomic medicine and gene therapy and an award was made to the Guilford Genomic Medicine Project consortium, composed of Duke University, the Moses Cone Memorial Hospital, and the University of North Carolina. The completion of the sequencing of the human genome provides vast possibilities in the development of personalized, genomic medicine. As more knowledge about the genome in relation to human health and disease becomes available, outreach and educational programs will be necessary to inform physicians and medical staff at health care facilities about the concepts and practices of genomic medicine. The development of a model for the introduction of these concepts to the U.S. military and civilian health care institutions in preparation for the future of personalized medical practice is a critical goal of this program. The FY05 funds were used to expedite the research and a decision was made to negotiate both the FY04 and FY05 appropriations as one award. The complete award was made in April 2005 for multiple years of research.

[9] *American Cancer Society,* Cancer Facts and Figures, *2005.*

[10] *TRICARE Management Activity Selected Disease Report for its FY04 Program Objective Memorandum.*

LIFE SCIENCES RESEARCH INITIATIVE



Congress appropriated $500,000 in FY05 for the Life Sciences Research Initiative. The funds are directed toward research that focuses on the areas of chemoprevention, identification of novel tumor suppressor genes, and biomarkers of angiogenesis. The Life Sciences Research Initiative will integrate the three areas into the development of an integrated breast cancer research program. A pre-proposal for the FY05 program has been submitted and reviewed by the CDMRP. A full proposal is expected by the end of October 2005.

LUNG CANCER RESEARCH

The Lung Cancer Research Program received congressional appropriations totaling $33.5M during FY00 through FY04 and $9.5M during FY05. FY00 through FY04 funds were awarded to the University of Texas M.D. Anderson Cancer Center (MDACC) to explore multiple avenues of research, prevention, diagnosis, and therapy that would yield new treatment options for lung cancer. A full proposal was scientifically and programmatically reviewed and subsequently approved for funding. Negotiations are under way and an award is anticipated by October 2005.

Some of the recent accomplishments of this program follow:

- A technique is being tested to find whether small clonal outgrowths of early lung tumors are present in normal tissue. Initial tests in a series of immortalized human bronchial cell lines were completed recently. This novel technique detected accumulating genetic abnormalities as cells progressed from nontumorigenic to malignant phenotypes. Studies have now begun to determine whether samples from tissue and cell sections can be used for these analyses.
- Two agents that change the expression status of genes are being tested singly and in combination to find whether they induce programmed cell death and inhibit the growth of normal bronchial cell and non-small cell lung cancer (NSCLC) cells. One agent, suberoylanilide hyroxamic acid, inhibited NSCLC growth in culture.
- Proteins from the apical surface liquid (ASL) of normal human tracheobronchial epithelial cell cultures will be used as markers for the development of NSCLC. From the proteins present in ASL, 40 have been identified using mass spectrometry and are being analyzed for marker use.
- Farnesyl transferase inhibitors (FTIs), a novel class of compounds that inhibit expression of the mutated Ras oncogene, can induce programmed cell death of tumor cells. During treatment of cells with FTIs, 35 new proteins were identified when compared

to untreated cells. Studies continue on their identification and significance.

- Gene therapy delivery for lung cancer treatments or preventives will be improved through the use of perfluorocarbons (PFCs) to enhance pulmonary gene transfer. Initial experiments using adenovirus transfection of a reporter gene indicated that PFCs can enhance gene delivery when given endotracheally.
- Biologically relevant animal models of human lung cancer were developed for use in these studies and in other lung cancer-related studies.
- *FUS1*, a tumor-suppressor gene shown to inhibit the growth of lung tumors and reduce greatly the spread of lung cancer in animals, will be tested in a Phase 1 clinical trial in a group of later stage lung cancer patients at the MDACC to evaluate its anti-cancer activity and toxicity.

MOLECULAR MEDICINE

Congress appropriated $1M in FY04 for molecular medicine and an award was made to GE Global Research to identify, characterize, and test molecular imaging markers for use as early indicators of Alzheimer's disease and other neurodegenerative diseases. Approximately 4.5 million Americans have Alzheimer's disease, and by 2050 the number of Americans with Alzheimer's is projected to increase almost threefold to 13.2 million.[11] Currently, there is no single diagnostic test that can detect whether a person has Alzheimer's or another neurodegenerative disease; diagnosis currently consists of a combination of medical history assessment, mental status evaluation, and brain imaging. A single test that images the brain focusing on the biological changes that occur within brain cells during the development of neurodegenerative diseases would facilitate the early detection of these diseases and allow for the use of earlier treatment options.

MUSCLE RESEARCH CONSORTIUM

Congress appropriated $1M in FY04 and $3.5M in FY05 for a Muscle Research Consortium.[12] Muscular dystrophy (MD) is the common name for a group of inherited diseases characterized by progressive muscle weakness and degeneration. Each type of MD has a distinct hereditary pattern, age of onset, and rate of muscle loss. Between 50,000 and 250,000 people are affected by the different types of MD

[11] *Hebert LE, Scherr PA, Bienias JL, et al. 2003. Alzheimer disease in the U.S. population: Prevalence estimates using the 2000 Census.* Arch Neuro *60(8):1119-1122.*

[12] *USAMRMC, but not the CDMRP, was also responsible for managing a congressional appropriation of $1M in FY04 for a Muscle Research Consortium and an award was made to the Cooperative International Neuromuscular Research Group (CINRG).*

each year. No prevention or cure exists for any of the forms of MD. While the future looks promising because of recent advances in gene manipulation and stem cell therapy,[13] more clinical trials are needed to translate these advances into clinical practice methods. The CINRG was established to facilitate clinical trial development for MD and other muscle-related diseases. As a part of this facilitation, greater coordination and information dissemination are needed within the MD and muscle-related diseases research community. Integrated data systems are needed to share and analyze the clinical trial data arising from CINRG. Further development of the CINRG's data research resources will permit greater cooperation among investigators, allowing more effective means to conduct state-of-the-art clinical trials. Research that results in an increase in the number and quality of clinical trials in muscle-related disease patients, with the goal of improving muscle structure and function, is the critical objective of the CINRG program. A full proposal submitted by the CINRG that incorporates both the FY04 and FY05 funds over multiple years of research was scientifically and programmatically reviewed. A recommendation to fund this work was requested of the Commanding General, USAMRMC. Pending the Commanding General's approval, an award is anticipated by October 2005.

MUSCULAR DYSTROPHY RESEARCH

MD research received congressional appropriations totaling $7.65M in FY03 through FY04 and $2.5M during FY05. For the FY03 appropriation, the program made two awards to the Children's Hospital of Pittsburgh and another to the Children's Research Institute, Children's National Medical Center. For the FY04 program, an award was made to Children's Hospital of Pittsburgh. The four awards made in FY03 through FY04 involve the study of muscle and muscle regeneration for the treatment of MD. Multidisciplinary approaches will be used to link molecular and cell biology in model systems with an integrated data resource to study the complex problems of MD. An early accomplishment of this program is the redesign of the Public Expression Profiling Resource (PEPR) (http://pepr.cnmcresearch.org). The PEPR is available to outside users and permits gene-based queries of large Affymetrix array data sets without any specialized software. More than 200 projects that represent 100 investigators and 50 institutions have been completed in the PEPR. Of these, 54 projects containing 1,830 Affymetrix profiles have been released to the public, typically prior to publication, via the PEPR website. A full proposal was received and is currently undergoing scientific review for the FY05 program.

[13] *Muscular Dystrophy Family Foundation, Inc.*

MYELOPROLIFERATIVE DISORDERS RESEARCH

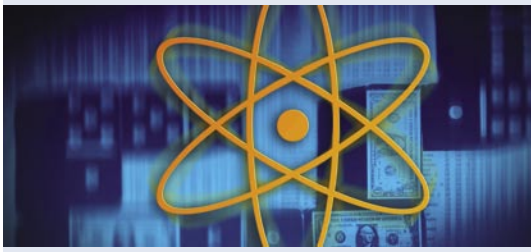
Congress appropriated $4.25M in FY04 for the Myeloproliferative Disorders Research Program (MPDRP). Myeloproliferative disorders are relatively rare forms of cancer that cause an overproduction of blood cells or alteration of bone marrow. There are four types of myeloproliferative disorders: polycythemia vera, essential thrombocytosis, primary or idiopathic myelofibrosis, and chronic myelogenous leukemia. Although these disorders of the bone marrow vary in severity by disorder and patient status, study of these malignant diseases offers promise toward understanding the pathogenesis, diagnosis, and treatment of human blood cell disorders. The FY04 MPDRP was conducted according to the two-tier review system recommended to the USAMRMC by the National Academy of Sciences Institute of Medicine. (See Section I for summary information about the two-tier review system.) Nine awards were made that focused on the specific chronic myeloproliferative disorders of polycythemia vera, idiopathic myelofibrosis, and essential thrombocytosis with direct relevance to military health.

NATIONAL PRION RESEARCH

The National Prion Research Program (NPRP) was established in FY02 by the Joint Appropriations Conference Committee Report No. 107-350, which provided $42.5M for research on prion disease. Prion diseases or transmissible spongiform encephalopathies (TSEs) refer to several apparently related diseases including Creutzfeldt-Jacob disease (CJD) and its new variant (nvCJD), kuru, bovine spongiform encephalopathy ("mad cow disease"), and others. Except for nvCJD, TSEs appear to develop progressively over many years, lead to extensive central nervous system vacuole degeneration, and are invariably fatal. At present, definitive diagnosis can only be made at autopsy. The diseases are relatively rare in humans but have been documented most extensively in hooved mammals. The current disease theory attributes TSEs to "prions," normal cell membrane proteins with atypical 3D configurations, transmitted by ingestion or possibly blood transfer. Although a Nobel Prize was awarded for the work underlying this proposed mechanism (Prusiner, 1997), it remains controversial because disease transmission is traditionally associated with an agent capable of replication. The health threats posed by TSEs currently appear to involve the food and blood supplies. These health threats put military beneficiaries in affected areas overseas at risk. The FY02 NPRP was conducted according to the two-tier review model recommended to the USAMRMC by the National Academy of Sciences

Institute of Medicine (IOM) in 1993 and resulted in 38 ongoing awards. In FY05, Congress appropriated an additional $1.5M for the NPRP. A full proposal was scientifically and programmatically reviewed and subsequently approved for funding. An award to McLaughlin Research Institute, Great Falls, Montana, was made in August 2005 to develop an in vitro bioassay for the treatment of prion infection. In December 2005, the NPRP is hosting a forum of all funded investigators who will present results of DOD-funded studies and assess progress toward the priority goal for the program, the development of a reliable ante-mortem diagnostic for the detection of prion diseases.

NEUROGENETIC RESEARCH AND COMPUTATIONAL GENOMICS



Congress appropriated $1M in FY04 for neurogenetic research and computational genomics and an award was made to the University of Southern California. Neurogenomics is the analysis of the expression and fundamental cellular mechanisms of cognitive function and the application of those principles to the discovery and design of therapeutic molecules and devices for the treatment of disorders of the nervous system. Relevant and rigorous algorithm tools are needed that are able to integrate, analyze, and visualize the output of the complex DNA and protein sequence data generated by neurogenomic research. Identification of the fundamental cellular mechanisms of cognitive function and development and implementation of computational genomic tools for the analysis of the neurogenomic data are critical goals of this program.

NEUTRON THERAPY RESEARCH

Congress appropriated $900,000 in FY05 for a Neutron Therapy Research Program. Neutron therapy is a highly effective form of radiation using neutrons rather than the electrons or photons that are used in conventional radiation treatments. Neutron therapy has been shown to be superior to other therapies for some types of cancer, including adenoid cystic carcinoma, locally advanced prostate cancer, locally advanced head and neck tumors, inoperable sarcomas, and cancer of the salivary glands. The Neutron Therapy Research Program seeks to develop applications of neutron therapy beyond its current uses through additional basic and clinical research. A full proposal was scientifically and programmatically reviewed and a recommendation for funding was requested from the Commanding General, USAMRMC. Pending the Commanding General's approval, an award is anticipated by October 2005.

ORPHAN DISEASE DRUG DISCOVERY RESEARCH

Congress appropriated $2M in FY05 for orphan disease drug discovery. Orphan drugs are products that have demonstrated some promise for the diagnosis and/or treatment of rare diseases or conditions. These diseases and conditions may include Huntington's disease, myoclonus, amyotrophic lateral sclerosis (Lou Gehrig's disease), or Tourette's syndrome. Such rare diseases and/or toxins may be turned into biological weapons that have little to no known defense. Pharmaceutical companies that develop orphan drugs expect such drugs to generate relatively small sales in relation to the drug's development costs and consequently incur financial losses. The goal of the Orphan Disease Drug Discovery Research Program is to identify and develop small molecule inhibitors for the treatment of orphan and neglected (rare) diseases for patients in the military and civilian sectors. A full proposal was scientifically and programmatically reviewed and a recommendation for funding was requested from the Commanding General, USAMRMC. Pending the Commanding General's approval, an award is anticipated by November 2005.

PEDIATRIC BRAIN TUMOR AND NEUROLOGICAL DISEASE RESEARCH

Congress appropriated $1.5M in FY05 for the Pediatric Brain Tumor and Neurological Disease Research Program. Primary brain tumors are the leading cause of death from childhood cancers.[14] The effects of brain tumors in survivors can be devastating because the tumors are located at the control centers for thought, emotion, and movement, causing physical and/or psychological disabilities throughout the course of the survivor's life. Adequate treatment is not available for most brain tumors, and the likelihood for long-term survival is poor. Treatment of brain tumors generally has been surgery, radiation therapy, chemotherapy, or a combination of these treatments. The Pediatric Brain Tumor and Neurological Disease Program will develop novel therapeutics for brain tumors. A pre-proposal for the FY05 program was received and was internally reviewed. A full proposal was scientifically reviewed and is in the process of programmatic review.

PEDIATRIC HOSPICE

In FY03, Congress appropriated $1.5M to establish the Children's Hospice Program at WRAMC and in FY04 Congress appropriated $1M to continue this program. Approximately 1 million children in the United States alone are seriously ill with progressive medical conditions. Between 75,000 and 100,000 children die each year as a result of these

[14] *Pediatric Brain Tumors Progress Review Group, http://prg.nci.nih.gov/brain/pediatrics.html.*

medical conditions. Children's Hospice International developed a Program for All-Inclusive Care for Children and Their Families (PACC®) demonstration project charged with developing and coordinating a comprehensive system of care for children with life-limiting conditions that will allow a continuum of care from the time of diagnosis through bereavement.[15] The Pediatric Hospice Program demonstration project at the WRAMC structures, implements, and provides oversight of a program serving children with life-threatening illnesses, diseases, or conditions who have parents or custodial caregivers serving in or retired from the U.S. military (including the Reserve components).

PREVENTIVE MEDICINE RESEARCH INSTITUTE

Congress appropriated $1.5M in FY05 for the Preventive Medicine Research Institute in Sausalito, California. The goal of the Preventive Medicine Research Institute Program is to develop better preventive measures aimed at cardiovascular disease, in accordance with the directives received from Congress. The principal components of cardiovascular disease are heart disease and stroke. The Centers for Disease Control and Prevention estimates that over 930,000 Americans die from cardiovascular disease each year, which amounts to one death every 34 seconds. Although these conditions are more common among people ages 65 years and older, the number of sudden deaths from heart disease among people ages 15–34 has increased.[16] In 2005, the estimated direct and indirect cost of cardiovascular disease is $393.5 billion. The increasing obesity and lack of physical activity in the American population increase the risk of cardiovascular disease in the United States.[17] A pre-proposal for the FY05 program was received and was internally reviewed. A full proposal has not yet been submitted.

PREVENTIVE MEDICINE RESEARCH FOR PROSTATE CANCER

Congress appropriated $1M in FY04 for the Preventive Medicine Research Program for Prostate Cancer and an award was made to the Preventive Medicine Research Institute in Sausalito, California, to develop better preventive medicine aimed at prostate cancer. In 2005, approximately 232,000 men will be diagnosed with prostate cancer, and approximately 30,350 will die from the disease.[18] Early detection and diagnosis of this disease can result in lower mortality. Although the causes and risk factors of prostate cancer are not well understood,

[15] *Children's Hospice International website, www.chionline.org.*

[16] *U.S. Department of Health and Human Services Centers for Disease Control and Prevention. 2004.* Preventing Heart Disease and Stroke: Addressing the Nation's Leading Killers.

[17] *American Heart Association. 2005.* Heart Disease and Stroke Statistics – 2005 Update. *Dallas, Texas: American Heart Association.*

[18] *American Cancer Society,* Cancer Facts and Figures, *2005.*

early intervention methods such as primary prevention of prostate cancer also can reduce the number of deaths from the disease. The Preventive Medicine Research Program for Prostate Cancer was continued with a congressional appropriation of $1.4M in FY05. A pre-proposal for the FY05 program was received and was internally reviewed. A full proposal has not yet been submitted.

SPINAL MUSCULAR ATROPHY RESEARCH

Congress appropriated $2.25M in FY05 for a Spinal Muscular Atrophy Research Program. Spinal muscular atrophy (SMA), the leading genetic killer of infants and toddlers, is the most prevalent genetic motor neuron disease. Over 25,000 Americans, mostly children, suffer from significant physical disability and impairment as a result of SMA. A defect in the survival motor neuron gene leads to progressive degeneration of nerve cells in the spinal cord, resulting in wasting away of muscles. No prevention or cure for any of the forms of SMA exists.[19] The goal of the Spinal Muscular Atrophy Research Program is to identify the protein defects causing SMA that will lead to potential therapeutics for SMA patients. A pre-proposal for the FY05 program was received and was internally reviewed. A full proposal was scientifically reviewed and is in the process of programmatic review.

TARGETED NANO-THERAPEUTIC FOR ADVANCED BREAST AND PROSTATE CANCER

Congress appropriated $1M in FY04 for the Targeted Nano-Therapeutic for Advanced Breast and Prostate Cancer Program. Breast cancer is the most frequently diagnosed non-skin cancer in women, and prostate cancer occupies the same position for men.[20] Many existing cancer therapeutics are designed to act systemically. Although systemic therapeutics kill the cancer, they also harm normal tissue in the process. Therapeutics that can specifically target cancer cells without harming the rest of the body would provide significant advantages for the patient's overall treatment and produce fewer toxic side effects. Identification and characterization of a targeted therapy for breast and prostate cancers using nano-therapeutics are critical goals of this program. For the FY04 program, an award was made to Triton Biosystems, Inc. The Targeted Nano-Therapeutic for Advanced Breast and Prostate Cancer Program was continued with a congressional appropriation of $1M in FY05. The FY05 funds will be used to modify the FY04 award to Triton Biosystems, Inc. as a continuation of the research.

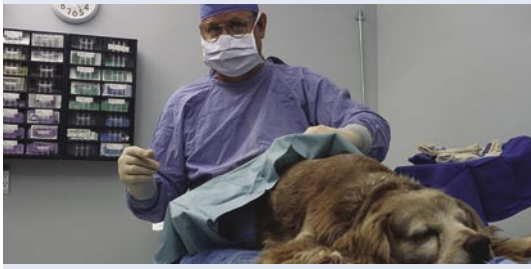
[19] *Spinal Muscular Atrophy Foundation; http://www.smafoundation.org.*

[20] *American Cancer Society,* Cancer Facts and Figures, *2005.*

TRIPLER CANCER CARE

Congress appropriated $8.5M in FY05 for Tripler Cancer Care under Defense Health Program (DHP) Operation and Maintenance. Currently, both civilian and military health care beneficiaries must relocate to the United States mainland to receive cutting-edge cancer treatments. Cancer clinical trials employing novel therapies, especially early-phase trials are generally not available in Hawaii. Moreover, patient access to more advanced clinical trials (e.g., Phase 3 trials) in the state of Hawaii is constrained by a lack of resources sufficient to sponsor many such trials. The development of an improved cancer care and research infrastructure in Hawaii will enhance patient access to cancer care. The goal of the Tripler Cancer Care Program is to improve cancer screening, treatment, and research programs in the state of Hawaii for the benefit of both DOD and non-DOD health care beneficiaries in Hawaii, and throughout the greater Pacific Basin. The appropriation was re-programmed to DHP Research, Development, Test, and Evaluation in August 2005. A pre-proposal was reveiwed and internally reviewed. A full proposal has not yet been submitted.

VETERINARY MANPOWER DEVELOPMENT



Congress appropriated $300,000 in FY05 for veterinary manpower development. Veterinarians help form the first line of defense against a bioterrorism attack.[21] It is estimated that 75% of potential bioterrorism agents are animal diseases.[22] As animal diseases have the potential to threaten the nation's health, economy, and food supply, veterinarians are in great demand to defend our country. The United States Department of Agriculture (USDA) Skills Gap Analysis has predicted a shortage of 584 veterinary medical officers at the USDA Agricultural Research Service by 2007.[23] The goal of the Veterinary Manpower Development Research Program is to develop training for veterinarians in public health skills so that they may plan and implement responses to bioterror outbreaks. A pre-proposal was received and was internally reviewed. A full proposal has not yet been submitted.

[21] *Howell JM and Prasse KW. 2002. American Veterinary Medical Association/Association of American Veterinary Medical Colleges Joint letter to the Departments of Agriculture and Health and Human Services.*

[22] *Centers for Disease Control and Prevention. Biological and chemical terrorism: Strategic plan for preparedness and response, recommendations of the CDC Strategic Planning Workgroup.* MMWR Morb Mortal Wkly Rep *2000; 49:1–14.*

[23] *USDA Research, Education and Economics Human Capital Plan FY 2003–FY 2007.*