



XI. Other Programs Managed by the CDMRP



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 FY03–04, the CDMRP has been responsible for executing or managing 17 institutionally based research programs, 10 of which are new to the CDMRP in FY04.

Background

Over the past decade, increased public interest in health care issues has influenced the funding of scientific research. From fiscal year 1995 (FY95) to FY04, 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 40 research programs, 32 of which are characterized by a one-time appropriation and/or are institutionally based programs. Table XI-1 lists these other programs and the fiscal year(s) that the CDMRP has managed them.

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 FY03–04, the CDMRP has been responsible for executing or managing 17 institutionally based research programs, 10 of which are new to the CDMRP in FY04. FY03–04 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 the other programs that the CDMRP has been responsible for managing or executing in FY03–04. Appendix B, Table B-8, summarizes the directions from Congress and the investment strategy for these FY03–04 initiatives.

Alcoholism Research

From FY00 to FY04, Congress appropriated \$29.1 million (M) for alcoholism research. The FY00–03 funds have been used to support 19 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 also is being recognized nationally and internationally through publications in the most highly respected scientific journals. Some of 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 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.
- The drug Ibogaine is helpful in treating addiction, but has major side effects. Gallo investigators have shown that Ibogaine



activates a specific signaling pathway in the brain. This discovery will enable the development of new drugs with Ibogaine's therapeutic characteristics, but without its detrimental 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. If human and mouse variants also show alcohol resistance, it would suggest the possibility of developing a drug that would help people become resistant to the effects of ethanol.
- Studies of the brain's opioid receptors and their binding molecules are producing new insights into whether the balance of 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.
- A major problem for alcoholics seeking treatment is the high rate of relapse. 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 FY04 congressional appropriation of \$4.5M, four proposals in this area have been both peer and programmatically reviewed. Awards are currently being negotiated.

Breast Cancer Imaging Research

In FY03, Congress appropriated \$6M for breast cancer imaging research. The House Appropriations Committee Report No. 107-532 directed the DOD to focus these funds on the development of new imaging techniques aimed at the early detection of breast cancer. Breast cancer imaging by mammography (x-ray examination of internal breast structure) is believed

Table XI-1. Other Programs Managed by the CDMRP

Program	Fiscal Year ^a
Advanced Cancer Detection ^b	97–99
Alcoholism Research	00–04
Arthropod-Borne Infectious Disease Control Research	02
Breast Cancer Imaging Research	03
3D Imaging and Genomic Analysis for Breast Cancer Management	04
Cancer Center of Excellence	01–02
Cancer Research	01
Center for Prostate Disease Research	97–04
Coastal Cancer Control ^b	95
Computer-Aided Diagnosis ^b	97
Computer-Assisted Cancer Device	04
Cooperative DOD/Veterans Affairs (VA) Medical Research	99–00
Defense Women's Health Research	95
Diagnostic and Surgical Breast Imaging	99
Donor Cord Blood Demonstration	04
Electrical Impedance Scanning Device	04
Fragile X Research	02
Gallo Cancer Center	00–01, 03–04
Genetic Cancer Research	04
Genomic Medicine and Gene Therapy	04
Hepatitis C Research	02
Lung Cancer	00–04
Molecular Medicine	04
Monoclonal Antibodies Massachusetts Biological Lab	02
Muscular Dystrophy Research	03–04
National Prion Research Program	02
Neurogenetic Research and Computational Genomics	04
Osteoporosis Research	95
Pediatric Hospice	03–04
Post-Polio Syndrome Research	99–00
Preventive Medicine Research for Prostate Cancer	04
Targeted Nano-Therapeutic for Advanced Breast and Prostate Cancer	04

^a Fiscal year 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.

to reduce the number of breast cancer deaths for women ages 40 to 69, especially those over age 50.¹ Concerns about the validity of studies used to establish current mammography screening recommendations have motivated the need for improved methods of breast cancer imaging and screening.^{2,3} For the FY03 program, a total of 19 full proposals in this subject area were scientifically and programmatically reviewed and 8 were funded.

3D Imaging and Genomic Analysis for Breast Cancer Management

Congress appropriated \$1.7M in FY04 for 3D Imaging and Genomic Analysis for Breast Cancer Management. Early detection methods for breast cancer include two-dimensional x-ray mammography followed by biopsy of any suspected tumor areas. However, of the more than 1.2M breast biopsies performed annually in the United States, only 10% to 20% of women have breast cancer. Development and implementation of 3D breast imaging techniques containing the added dimension of depth would produce a sharper, more detailed image of the breast tissue and aid in 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. Implementation and testing of 3D breast imaging and genomic analysis of breast cancers are critical goals of this program. For the FY04 appropriation, a full proposal on this subject has been both peer and programmatically reviewed. An award is currently being negotiated.

Center for Prostate Disease Research

The Center for Prostate Disease Research (CPDR) received congressional appropriations totaling \$43.6M during FY97–03 and \$4.5M during FY04.⁴ 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. 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 18,000 men treated in military health facilities. This database has resulted in landmark studies of the prostate-specific antigen, including screening for prostate cancer in high-risk African American men.

The CPDR Basic Research Program laboratories, located at the Uniformed Services University of the Health Sciences in Bethesda, Maryland, continue to focus on cutting-edge molecular and cell biology research with a goal to better understand the biology of the disease and develop 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, OCT⁵-embedded frozen tissues, as well as a frozen section slide library and serum bank from more than 500 cancer patients. Blood- and bone marrow-derived RNA and DNA from 500 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 130 patients. Linkage of these

¹ National Cancer Institute, Fact Sheet 5.28.

² Olsen O and Gotzsche P. 2001. *The Lancet* 358:1340–1342.

³ National Cancer Institute, News from the NCI, February 21, 2002.

⁴ Congress appropriated funding (\$2M) in FY92 to establish the CPDR. The USAMRMC, but not the CDMRP, managed \$10.25M in FY92–95 appropriations for the CPDR.

⁵ Tissue-embedding media.

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 putative tumor suppressor gene on chromosome 6q16 locus that is frequently deleted in prostate cancer.

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 DOD, the U.S. Army, and the CPDR.

Additionally, over the past year, CPDR staff published more than 19 peer reviewed manuscripts, 38 abstracts, and several publications for patient education. Multiple peer reviewed manuscripts and book chapters are in press.

Computer-Assisted Cancer Device

Congress appropriated \$1M in FY04 for the Computer-Assisted Cancer Device Program. Breast cancer is the most commonly diagnosed cancer in women, accounting for 32% of all cancers in women.

In 2004 approximately 215,990 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.⁶ 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. A full proposal has been both peer and programmatically reviewed. An award is currently being negotiated.

⁶ American Cancer Society - *Cancer Facts and Figures*, 2004.

⁷ American Cancer Society - *Cancer Facts and Figures*, 2004.



Donor Cord Blood Demonstration

Congress appropriated \$1M in FY04 for the Donor Cord Blood Demonstration Program. In 2004, more than 33,000 cases of leukemia will be diagnosed, and more than 40,000 people are projected to die from the disease.⁷ Cord blood, the blood that remains in the umbilical cord and placenta after birth is a rich source of blood stem cells and has the ability to treat diseases of bone marrow such as leukemia with significantly less rejection. Collected cord blood can be donated to banks that make the blood and its stem cells available for use in bone marrow-derived diseases, especially in cases where tissue-matched relatives are not available for bone marrow donation. The Donor Cord Blood Demonstration Program will develop optimized procedures for the collection, storage, and uses of donor cord blood. A full proposal was received by this program and has been both peer and programmatically reviewed. An award is currently being negotiated.

Electrical Impedance Scanning Device

Congress appropriated \$1M in FY04 for the Electrical Impedance Scanning Device Program. Detection of breast cancer is especially difficult for small lesions. Although small lesions are generally the most treatable, they also are the most difficult to diagnose. 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. Refinement and clinical testing of an electrical impedance scanning device for breast cancers are critical goals of this program. A proposal has been both peer and programmatically reviewed. An award is currently being negotiated.

Gallo Cancer Center

In FY00–01, Congress appropriated a total of \$7M to provide for the initiation of a cancer center dedicated to prostate cancer research. FY00–01 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 Program in FY02, congressional language for FY03 specified \$1.05M for the Gallo Cancer Center Program. A proposal to extend the FY00–01 program was awarded in November 2003. The Gallo Cancer Center has successfully initiated programs including a center retreat, pilot grant program, and research working groups. An epidemiologist, a behavioral scientist, and three postdoctoral fellows have been recruited to the Gallo Cancer Center. Three pilot grant projects are now fully funded and under way.

Congressional language for FY04 specifies \$1M for the Prostate Cancer Research – Gallo Center. A full proposal is currently undergoing peer and programmatic review.

Genetic Cancer Research

Congress appropriated \$2M in FY04 for genetic cancer research. Hereditary cancers are thought to account for approximately 5%–10% of all cancers; the remaining cancers result from damage to genes.⁸ 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 an individual's lifetime (somatic mutations) may lead to the development of cancer. As the cells accumulate mutations in genes that govern growth and survival, normal controls are bypassed and cellular growth becomes uncontrolled. The mutations that are critical to the growth of cancer cells must be identified to understand how normally controlled cellular pathways are subverted. Identification and characterization of

these genetic defects in human cancers through analysis of an individual's entire genome are critical goals of this program. The overall goal of the Genetic Cancer Research Program is to fund scientifically meritorious research focused on the gene mutations that lead to the development of cancer. A full proposal has been both peer and programmatically reviewed. An award is currently being negotiated.

Genomic Medicine and Gene Therapy

Congress appropriated \$3.4M in FY04 for genomic medicine and gene therapy. The completion of the sequencing of the human genome provides vast possibilities in the development of personalized, genomic medicine. Genomic medicine may contribute to the treatment of the most specialized, differentiated, and crucial tissues of the human body: the brain and the heart. The promise of genomic medicine can be brought to patients with cardiovascular or neurodegenerative diseases through preclinical testing of target disease markers and clinical trials/pilot programs for their validation. Development and clinical testing of diagnostic markers and therapeutics for cardiovascular and neurodegenerative diseases such as Alzheimer's disease are critical goals of this program. A proposal has been both peer and programmatically reviewed. An award is currently being negotiated.

Lung Cancer Research

From FY00 to FY04, Congress appropriated \$33.5M for the Lung Cancer Program. FY00–03 funds were awarded to the University of Texas M.D. Anderson Cancer Center to explore multiple avenues of research, prevention, diagnosis, and therapy that would yield new treatment options for lung cancer. A full proposal for the FY04 appropriation of \$9.5M has been both peer and programmatically reviewed.

Some of the recent accomplishments of this program follow:

⁸ American Cancer Society - *Cancer Facts and Figures*, 2004.

- A technique for finding whether small clonal outgrowths of early lung tumors are present in normal tissue is being tested. Initial tests in a series of immortalized human bronchial cell lines ranging from nontumorigenic to tumorigenic in potential were used. The technique detected accumulating genetic abnormalities in the cell line series as the series progressed from nontumorigenic toward malignant phenotypes. Studies have begun on whether samples from pathology 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 if they induce programmed cell death and inhibit the growth of normal bronchial cell and non-small cell lung cancer (NSCLC) cells. One agent, suberoylanilide hydroxamic acid (SAHA), 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 intratracheally.
- Biologically relevant animal models of human lung cancer were developed for use in these studies and in other lung cancer-related studies.

Molecular Medicine

Congress appropriated \$1M in FY04 for molecular medicine. The overall goal of the Molecular Medicine Program is to fund scientifically meritorious research focused on understanding and manipulating the molecular determinants of Alzheimer's disease, in accordance with the directives received from Congress. Alzheimer's disease is a complex disease that affects the brain. Approximately 4.5M Americans have this disease, and by 2050 the number of Americans with Alzheimer's is projected to increase by almost threefold to 13.2M.⁹ No single diagnostic test can detect whether a person has Alzheimer's disease; diagnosis 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 of Alzheimer's patients would facilitate the early detection of this disease and allow for earlier treatment options to be used. Identification, characterization, and testing of the molecular imaging markers for use as early indicators of Alzheimer's disease are critical goals of this program. A full proposal for the FY04 appropriation has been both peer and programmatically reviewed. An award is currently being negotiated.

Muscular Dystrophy Research

Congress appropriated \$3.4M in FY03 and \$4.25M in FY04 for muscular dystrophy (MD) research. 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 MD each year. There is currently no prevention or cure for any of the forms of MD. However, the future looks promising due to recent advances in gene manipulation and stem cell therapy.¹⁰ 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. A full proposal for the FY04 appropriation was received and is currently undergoing peer and programmatic review.

⁹ Herbert LE, Scherr PA, Bienias JL, Bennett DA, and Evans DA. 2003. Alzheimer's disease in the U.S. population: Prevalence estimates using the 2000 Census. *Archives of Neurology* 60(8):1119-1122.

¹⁰ Muscular Dystrophy Family Foundation, Inc.

Neurogenetic Research and Computational Genomics

Congress appropriated \$1M in FY04 for neurogenetic research and Computational Genomics. 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. A pre-proposal was received and was internally reviewed. A full proposal has not yet been submitted.

Pediatric Hospice

In FY03, Congress appropriated \$1.5M to establish the Children's Hospice Program at WRAMC. The Children's Hospice Program demonstration project at 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 the U.S. military (including the Reserve components) or retired from the U.S. military. In FY04, Congress appropriated \$1M for the Pediatric Hospice Program at WRAMC. A full proposal has been both peer and programmatically reviewed.



Preventive Medicine Research for Prostate Cancer

Congress appropriated \$1M in FY04 for Preventive Medicine Research for Prostate Cancer. In 2004, approximately 230,110 men will be diagnosed with prostate cancer, and approximately 29,900 will die from the disease.¹¹ 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, early intervention methods such as primary prevention of prostate cancer also can reduce the number of deaths from prostate cancer. Development of better preventive medicine aimed at prostate cancer is a critical goal of this program. A full proposal is currently undergoing peer 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.¹² 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. A proposal was both peer and programmatically reviewed, and an award was made to Triton Systems, Inc.

¹¹ American Cancer Society - *Cancer Facts and Figures*, 2004.

¹² American Cancer Society - *Cancer Facts and Figures*, 2004.