II. CDMRP Accomplishments

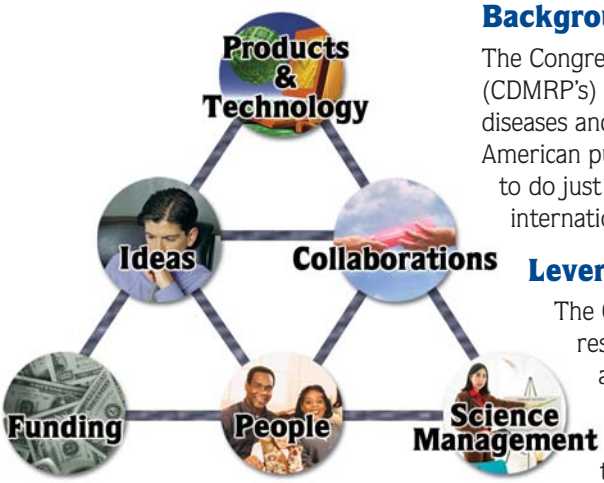

Figure II-1. Leveraging Resources to Cure Disease

Background

The Congressionally Directed Medical Research Programs' (CDMRP's) vision is to find and fund the best research to eradicate diseases and support the warfighter for the benefit of the American public. The CDMRP is a catalyst for leveraging resources to do just that and in the process is serving as a national and international model for reinventing science administration.

Leveraging Dollars to Cure Disease

The CDMRP has invested $2.3 billion (B) in biomedical research from fiscal year 1992–2003 (FY92–03) appropriations totaling $2.6B. This has resulted in 5,627 research grants, contracts, and cooperative agreements (Table II-1). The success of the programs, the work of consumer advocates, and the need for additional, focused biomedical research have led to continuing appropriations for programs managed by the CDMRP. Table II-2 is a reflection of the increase in biomedical programs, dollars, and awards administered by the CDMRP since its inception.

Leveraging People to Cure Disease

The success of the CDMRP can be attributed to the collective wisdom and dedication of the people involved – from scientists, research managers, and those who are ultimately most affected by policy and research.

Advocates, Consumers, and the CDMRP

The unique voices and experiences of survivors and their families have been a pivotal part of the establishment and growth of the CDMRP. The relentless work of thousands of advocates has resulted in almost $3B in appropriations for targeted diseases through FY04. Today, the CDMRP is a recognized leader in integrating consumers in virtually all aspects of program execution. Consumers for most of the core programs are survivors of the disease and representatives of consumer advocacy organizations. For programs such as the Neurofibromatosis Research Program (NFRP), consumers are individuals with the disease, their family members, or representatives of consumer advocacy organizations. The value of consumer involvement is derived from their firsthand experiences with the disease. This adds a perspective, passion, and a sense of urgency, which ensure that the human dimension is incorporated in program policy, investment strategy, and research focus. Approximately 600 consumers have served on scientific peer review panels since 1995. Additionally,

Table II-1. FY92–03 Awards Managed by the CDMRP

Program (Fiscal Years)	Grants Managed	Investment
BCRP (FY92–03)	4,073	$1,310.9M
PCRP (FY97–03)	1,013	$415.8M
NFRP (FY96–03)	117	$94.8M
OCRP (FY97–03)	80	$61.1M
PRMRP (FY99–03)	127	$161.8M
CMLRP (FY02–03)	28	$11.3M
TSCRP (FY02–03)	7	$2.6M
Other Programs (FY95–03)	182	$205.6M
Total	**5,627**	**$2,263.9M**

Table II-2. The CDMRP: Then and Now

	1992	2003
Number of Research Programs	1	14
Appropriation(s)	$25M	$354M
Number of Awards	26	721

consumers have served on Integration Panels (IPs) from 1993 to the present. Further, consumers are active participants in executing some research projects.

For example, consumers play a significant role in the BCRP Center of Excellence Awards by serving on research project advisory boards, assisting in patient recruitment, and promoting public education. Finally, multidisciplinary meetings held by the CDMRP, such as the Breast Cancer Research Program's (BCRP's) Era of Hope Meetings, have enabled consumers and advocates to learn about the scientific advances that their lobbying efforts have supported. Consumer participation in these meetings is substantial, from serving as members of the technical program committee to co-chairing every scientific session. For more information on consumer involvement and serving as a consumer reviewer in the first tier of review, peer review, see the consumer involvement pages on the CDMRP website (http://cdmrp.army.mil).

The Scientific Community and the CDMRP

The scientific community is essential in assisting the CDMRP to shape the future of health care. The fulfillment of program goals requires the cooperation and communication across multiple scientific and clinical disciplines. To date, over 3,000 scientists and clinicians have provided the necessary subject matter expertise on peer review panels. Approximately 200 world-renowned basic scientists, clinicians, and policymakers have participated in vision setting and programmatic review as IP members. An additional 150 scientists have served as ad hoc programmatic reviewers. Almost 100 scientists, clinicians, and professionals are currently involved in managing the CDMRP. Collectively, these scientists have assisted the CDMRP in funding over 5,000 researchers in an effort to tackle the complex causes of disease and translate this knowledge to improved disease prevention, patient survival, and quality of life.

Additionally, the CDMRP has played a major role in training scientists at all points in their careers. In the 1993 Institute of Medicine (IOM) report, it was stated that the "best investment the program can make is to stimulate talented new investigators…."[1]

The CDMRP's commitment to training the best and the brightest to eradicate human diseases is demonstrated by its portfolio of funded projects, nearly one-third of which focus on training and recruitment. The CDMRP has supported both new researchers in the field and established scientists interested in extending their expertise to the study of other diseases. Table II-3 illustrates the CDMRP's investment in training and recruitment awards that support the scientific community, a crucial force in the war against disease.

Leveraging Science Management to Cure Disease

The CDMRP has been a pioneer in exploring and mobilizing untapped research and science management opportunities, from creating award mechanisms that fulfill unique niches to developing innovative management execution processes, many of which are now being adopted by other funding agencies. Collectively, these new practices reflect the CDMRP's commitment to creating foundations on which future research can be built.

CDMRP Award Opportunities

The CDMRP has provided support for areas of highest priority and greatest need among individual programs. The CDMRP has ensured that the focus and structure of research categories and award mechanisms offered within individual programs match the unique opportunities for research breakthroughs. Approximately 30 different award mechanisms have been launched by the CDMRP to train new investigators (Table II-3), develop necessary research resources (Table II-4), and promote innovative research (Table II-5).

In the 1993 IOM report, it was noted that "research in breast cancer is impeded by the inadequate access to resources that are appropriate for sharing—including tumor samples, cell lines, animal models, DNA probes, follow-up data on women diagnosed with breast cancer, information about ongoing clinical trials, and economic data to evaluate the cost of care."[2] Based on this clear need in 1993, and the need for similar support identified by IPs in subsequent years, the CDMRP has funded research resources awards across most of its programs. These awards are designed to

[1] Institute of Medicine, *Strategies for Managing the Breast Cancer Research Program: A Report to the U.S. Army Medical Research and Development Command,* 1993.

[2] Institute of Medicine, *Strategies for Managing the Breast Cancer Research Program: A Report to the U.S. Army Medical Research and Development Command,* 1993.

provide researchers with support to (1) create or obtain materials and data from multiple sources that would otherwise be difficult to acquire or (2) establish and support centers or consortia that can provide a foundation for future research. Award mechanisms developed to enhance research resources are listed in Table II-4. Read additional information about the CDMRP's investment in training/recruitment and innovative research under Leveraging People to Cure Disease and Leveraging Ideas to Cure Disease, respectively.

Electronic Proposal Submission and Review

The CDMRP has been a leader in advancing electronic technology from disseminating funding opportunities through award notification. These strategies have improved and streamlined program management, thus saving time, saving money, and improving quality. To begin, funding opportunities for individual programs and award mechanisms are immediately posted online. Then, applicants to all CDMRP programs are required to electronically submit their proposals. To date, over 11,700 proposals have been received electronically. To facilitate the proposal review process, reviewers for both tiers of review receive their review materials in electronic format prior to the review meeting. At the meeting, electronic innovations have streamlined the review process. For instance, scientific peer reviewers utilize an electronic-based scoring system, eliminating the cost of printing, sorting, distributing, and correcting paper score sheets. Programmatic reviewers use a programmatic review database to make and track funding decisions. This database provides instantaneous information, a relevant tally of available dollars, portfolio balance, applicant information, and proposal demographics. Finally, summary statements and award notifications for each proposal are disseminated electronically to applicants.

Information Management

The CDMRP Electronic Grants System (EGS)[3] was launched in FY02 to enable real-time electronic management of CDMRP proposals from proposal receipt to award closeout. EGS is a customized business system and state-of-the-art database that allows multiple users within the USAMRMC to input data, download reports, and manage daily administrative tasks associated with grants. The implementation of EGS has allowed

Table II-3. Investing in the Best and Brightest: Summary of Training and Recruitment Awards from FY92–03

Award Mechanisms	Fiscal Year	Awards	Investment
Career Development			
BCRP	FY93–01	175	$38.9M
NFRP	FY02	1	$0.2M
Career Transition			
NPRP	FY02	4	$1.6M
Clinical Research Nurse			
BCRP	FY02–03	17	$3.0M
CTR Postdoctoral Fellowship			
BCRP	FY00	2	$0.3M
HBCU/MI Partnership Training			
BCRP	FY99–03	10	$6.8M
Health Disparity Training-Prostate Scholar			
PCRP	FY01–03	5	$0.9M
Institutional Training			
BCRP	FY93/94, 98–99	34	$19.9M
OCRP	FY02	1	$0.6M
Minority Population Focused Training			
PCRP	FY98–00	24	$1.3M
Physician Scientist Training			
BCRP	FY02–03	10	$5.2M
PCRP	FY03	5	$3.0M
Postdoctoral			
BCRP	FY93–02	480	$64.4M
PCRP	FY99–03	130	$12.2M
NFRP	FY98–02	37	N/A[a]
NPRP	FY02	30	N/A[a]
Predoctoral			
BCRP	FY93–03	678	$46.7M
NPRP	FY02	10	N/A[a]
Prion Techniques Fellowship			
NPRP	FY02	1	$0.04M
Sabbaticals			
BCRP	FY93/94, 96–97	8	$0.8M
Undergraduate Summer Training Programs			
BCRP	FY00–02	16	$2.3M
Total		**1,678**	**$208.14M**

[a] These programs offered support for postdoctoral trainees as nested traineeships within Investigator-Initiated Research Awards; therefore, dollars invested for the nested postdoctoral traineeships are not available.

[3] Formerly known as the Enterprise Data System.

CDMRP to virtually eliminate paper processing of grants, which not only saves time and money for both the proposal submitter and the government but also increases the accuracy of data management processes. In 2003, the search capability on the CDMRP website became linked to EGS, thus providing visitors to the CDMRP website with real-time data.

Leveraging Ideas to Cure Disease

In 1993, a recommendation was made to the U.S. Army Medical Research and Materiel Command (USAMRMC) by the IOM to "create an environment in which creative ideas and first-rate research can flourish and in which investigators are not afraid to gamble on risky but alluring ideas."[4] Today, the CDMRP's central philosophy is innovation. The CDMRP fills research gaps by funding high-risk, high-gain research that other agencies will not venture funding. Many of the award mechanisms offered by the CDMRP emphasize support for exploration of revolutionary ideas and concepts that could ultimately lead to a critical discovery or major development in the battle to cure disease. While each mechanism has different award requirements, all share the common goal of advancing innovative ideas, creative solutions, and breakthrough technologies.

Through FY03, the CDMRP has funded 3,041 awards across six mechanisms that specifically encourage innovative scientific ideas and approaches to disease eradication. These awards have made significant contributions to our understanding of disease processes, the development of therapeutics, and the improvement of quality of life. Table II-5 summarizes the number of awards made and the dollars invested from FY93–03 for support of novel ideas.

Table II-4. Investing in Research Resources: Summary of Research Resource Awards from FY92–03

Award Mechanisms	Fiscal Year	Awards	Investment
Behavioral Center of Excellence			
BCRP	FY00	4	$23.2M
Breast Cancer Centers of Excellence			
BCRP	FY01–03	12	$82.5M
Cancer Center Initiation/Program Projects			
BCRP	FY93–95	4	$17.8M
PCRP	FY99	4	$8.5M
OCRP	FY97, 98, 00–01	16	$30.2M
Collaborative-Clinical Translational Research			
BCRP	FY99–00, 02	3	$5.5M
Mammography/Breast Imaging Equipment			
BCRP	FY92	2	$4.1M
Natural History Studies			
NFRP	FY97	2	$5.9M
Prostate Cancer Consortium			
PCRP	FY02	2	$19.9M
Prostate Cancer Consortium Development			
PCRP	FY01	5	$0.7M
Research Resources			
BCRP	FY93/94	28	$23.4M
Special Mammography Demonstration Projects			
BCRP	FY95	8	$11.4M
Total		**90**	**$233.1M**

Leveraging Collaborations to Cure Disease

Public, private, government, and military partnerships occur in all aspects of the programs and have been key to the success of the CDMRP. We believe that these effective partnerships are leading us closer to finding cures for many diseases and are facilitating our ability to effectively address critical health issues. Illustrated in Figure II-2 are some of the collaborative efforts of the CDMRP that have played a central role in helping to shape the future of health care to prevent, control, and cure diseases. These are summarized as follows.

[4] Institute of Medicine, *Strategies for Managing the Breast Cancer Research Program: A Report to the U.S. Army Medical Research and Development Command*, 1993.

Figure II-2. Collaborative Efforts of the CDMRP

Prostate Cancer Funders' Group

The Prostate Cancer Funders' Group is composed of 14 prostate cancer funding organizations that collectively strive to eliminate prostate cancer. Some of the goals of this group are to pool resources and knowledge, establish collaborations, open the lines of communication, identify roadblocks to progress, and implement international initiatives to move prostate cancer research forward.

Common Scientific Outline (CSO) Partners

The CDMRP is a founding member of the International Cancer Research Portfolio (ICRP), a joint initiative among U.S.- and U.K.-based cancer funding organizations to classify their respective research portfolios and facilitate communication among cancer researchers, cancer funding organizations, health care policymakers, health care professionals, cancer survivors, and anyone with an interest in the most current cancer research. The ICRP represents a database of information on cancer research awards that were classified using the CSO. This outline was initiated by the National Cancer Institute (NCI) to categorize its funded research projects in a scientific and disease-related manner. The CDMRP was invited to participate in this effort in 1997 and collaborated with the NCI to develop a working model of the CSO. In subsequent years, additional cancer-funding organizations were asked to join the efforts of the NCI and the CDMRP in evaluating the utility of the CSO as a tool to facilitate the description of their respective portfolios and communication among funders. As of September 2004, the ICRP represents the portfolios of six U.S.-based funding organizations: the NCI, CDMRP, California Breast Cancer Research Program, Oncology Nursing Society Foundation, Prostate Cancer Foundation,

Table II-5. Summary of Awards from FY93–03 That Foster Novel Ideas

Award Mechanisms	Fiscal Year	Awards	Investment
Concept			
BCRP	FY99–00,[a] 02–03	612	$58.3M
Exploration			
BCRP	FY02	20	$4.4M
Hypothesis Development			
PCRP	FY03	34	$3.9M
CMLRP	FY03	18	$1.7M
Idea/Idea Development			
BCRP	FY93–03	1,445	$505.0M
PCRP	FY97–03	507	$256.6M
NFRP	FY99–03	25	$10.0M
OCRP	FY99, 02–03	39	$19.4M
NPRP	FY02	17	$7.8M
TSCRP	FY02–03	7	$2.6M
Innovator			
BCRP	FY01–03	8	$26.8M
New Investigator			
PCRP	FY97–03	262	$82.5M
NFRP	FY99–03	24	$11.8M
OCRP	FY99–00, 03	23	$10.1M
Total		**3,041**	**$1,000.9M**

[a] Concept Awards offered by the FY99 BCRP were supported by both FY99 and FY00 appropriations.

and Susan G. Komen Breast Cancer Foundation as well as 15 funding organizations that are members of the U.K. National Cancer Research Institute. The ICRP website was launched in 2003 to allow the public at-large to view and browse the most current information about research supported by these cancer-funding organizations (http://www.cancerportfolio.org/).

Collaborative Research Mechanisms

The CDMRP has supported several different award mechanisms that foster strong partnerships and collaborations in the scientific community. Since 1997, $170.7M has been invested across the programs to establish 45 Consortia, Centers, and Program Projects. Some common features of these award mechanisms include building lasting collaborations, establishing both multidisciplinary and multi-institutional teams of researchers and consumers, addressing overarching problems in disease and accelerating solutions, establishing synergistic research efforts, and fostering real-time communication and data sharing. In addition, 14 awards totaling $6.7M were also awarded to Historically Black Colleges and Universities/Minority Institutions (HBCU/MI) under different mechanisms that support collaboration. (See the section on working with special populations on page II-7 for more information on these mechanisms.)

Era of Hope Meetings

The BCRP has sponsored three major international scientific meetings, called the Era of Hope, to provide a forum for thousands of scientists, clinicians, health care providers, and consumers to communicate ideas and promising new directions in breast cancer research. These meetings have provided unprecedented opportunities for developing future collaborations and disseminating program information. The next Era of Hope meeting is planned for June 2005 in Philadelphia, Pennsylvania.

Gynecological Cancer Foundation Allied Support Group

The CDMRP is a member of the Gynecological Cancer Foundation Allied Support Group, a group composed of 8 major ovarian cancer funders and 14 advocacy organizations to facilitate synergy among organizations that share goals of prevention and early detection of gynecological cancers. This group collaborates on educational, advocacy, and research projects including the following:

- Educational kits/brochures for medical professionals and the lay public
- An ovarian cancer product guide
- Newspaper/magazine articles
- Efforts to increase consumer participation in gynecologic clinical trials

Military Health Research Forum

The Peer Reviewed Medical Research Program (PRMRP) sponsored its first Military Health Research Forum in April 2004 to provide a means for investigators funded by the program to present their research findings, products, and technologies and to develop future collaborations related to military health research. In addition, the forum emphasized ways to expedite transition from research to rapid, field-usable products/methods. Read more about the Military Health Research Forum in Section VII, page VII-6 of this report.

Working with Special Populations

In 1998, the CDMRP established the Special Populations Program (SPP) to enhance the ability of the CDMRP to address the significant disparities that exist in the incidence, morbidity, and mortality among different ethnic groups[5] in many of the diseases for which the CDMRP provides support. The purpose of the SPP is to address disparities in underserved, understudied, and underrepresented communities. Its mission is to enhance the CDMRP's efforts in this area by creating new award mechanisms, reaching out to communities through improved communication, and partnering with other agencies. For example, the BCRP and Prostate Cancer Research Program (PCRP) have

[5] American Cancer Society-*Cancer Facts and Figures*, 2004.

developed numerous health disparity and HBCU/MI partnership awards to create collaborative partnerships and direct research toward elucidating disease mechanisms in underserved populations and building resources at minority institutions. In total, the CDMRP has made 58 health disparity and HBCU/MI partnership awards totaling $19.1M.

To effectively disseminate funding opportunities in these areas, the SPP has established and maintains a contact list of investigators conducting research at HBCU/MI and on minority populations. These intensive efforts have resulted in meaningful partnerships to address health disparities among ethnic groups. Additionally, relationships with minority scientists and consumers have been fostered by attendance at conferences sponsored by such groups as the Intercultural Cancer Council, the Society for the Advancement of Chicanos and Native Americans, the Department of Defense (DOD) HBCU/MI Technical Assistance Conference, and the Minority Health Professions Foundation. The CDMRP has also formed affiliations with organizations such as the Hispanic Association of Colleges and Universities and the National Association of Native American Physicians.

Leveraging Technology for Product Development to Cure Disease

The CDMRP's vision is to find and fund the best research to eradicate diseases and support the warfighter for the benefit of the American public. As highlighted throughout this section and in the subsequent program sections, the CDMRP has designed a number of cutting-edge award mechanisms and subsequently funded over 5,600 research grants, contracts, and cooperative agreements (see Table II-1) to enable the nation to cure disease. Over 6,000 publications and 130 patents/licensures (including applications) have been produced by CDMRP-funded investigators. The following are examples of some of the products and technologies resulting from CDMRP support that have impacted global health issues such as breast, prostate, and ovarian cancers; neurofibromatosis; military health; and prion diseases.

Breast Cancer Research Program

Over the years, the BCRP has emphasized innovative, high-risk/high-gain research and support for translational research. The following examples represent some of the most notable products and technologies supported by the program that are accelerating the discovery of new therapies for breast cancer and the eradication of this disease:

- The development of Herceptin, a revolutionary breast cancer therapeutic agent. Herceptin is a breast cancer therapeutic agent based upon an anti-HER2 antibody. HER2 is a proto-oncogene that is overexpressed in approximately 25%–30% of all breast cancers. Women with this genetic alteration have a more aggressive form of breast cancer and a poorer prognosis compared to women with HER2 negative breast cancer. An FY93 BCRP-supported investigator, Dr. Dennis Slamon, studied the effects of HER2 overexpression and the impact of antibodies to HER2 in normal and cancerous breast tissue. Since Herceptin was approved for use in 1998, over 125,000 women have received Herceptin for the treatment of HER2-positive breast cancer.[6]
- The development of an FDA-approved device for conducting ductal lavage. Ductal lavage is a washing procedure used to collect cells that line the milk ducts, the site where virtually all breast cancer begins. Dr. Susan Love was awarded an FY03 Idea Award to examine the feasibility of collecting and analyzing precancerous ductal cells through a ductoscope. At the time, her "idea was unconventional."[7] Today, ductal lavage is being used as a risk assessment tool in women at high risk for developing breast cancer.
- Support for clinical trials to advance new breast cancer interventions. For instance, the international trial called ATLAS (Adjuvant Tamoxifen Longer Against Shorter) headed by Dr. Richard Peto received its original funding through the BCRP in FY93 to define the optimal duration of adjuvant tamoxifen

[6] The number of women treated with Herceptin from 1998 through September 2004 provided by Genetech.

[7] Institute of Medicine, *Strategies to Leverage Research Funding: Guiding DOD's Peer Reviewed Medical Research Programs,* 2004.

treatment. Although tamoxifen is the most widely prescribed anticancer agent, there is uncertainty on how long to continue adjuvant treatment with tamoxifen. The ATLAS trial seeks to definitively answer this question, and results from this trial could affect the management of breast cancer treatment for hundreds of thousands of women worldwide.

- Support for the discovery and development of short hair-pinned RNAs (shRNAs). shRNAs are the latest revolution in RNA interference (RNAi) – a technique by which the expression of genes can be silenced. Over the past 5 years, use of RNAi in biological research has exploded, dramatically increasing our understanding of cellular processes. The discovery of shRNAs was spearheaded by BCRP-supported investigator Dr. Gregory Hannon. This novel molecular targeting technology allows researchers to spatially and temporally control RNAi expression, thereby increasing the usefulness of RNAi in vitro and giving new hope for safe, effective transgenic therapies.

Prostate Cancer Research Program

The PCRP has emphasized funding for groundbreaking ideas and support for clinical research, and PCRP awardees are pushing the boundaries and advancing discoveries in the field of prostate cancer, as evidenced by the accomplishments summarized in the following list:

- The development and evaluation of a radioactive antibody specific to prostate specific membrane antigen (PSMA). PSMA is a membrane glycoprotein that is expressed in all prostate cells; however, it is further expressed in higher grade prostate cancer, metastatic disease, and hormone-refractory prostate cancer. Dr. Shankar Vallabhajosula was awarded an Idea Award in FY97 and FY00 to evaluate the diagnostic and therapeutic potential of a radioactive antibody that binds to the PSMA molecule on prostate cancer cells. This radiolabeled monoclonal antibody specific to the extracellular domain of PSMA was first evaluated in the laboratory and in mice bearing prostate cancer tumors. It was subsequently tested in a Phase 1 clinical trial and found to be well tolerated and specific for targeting prostate tumors. Administration of the drug resulted in a significant antitumor response. This is the first major clinical trial that tested the potential of a radiolabeled monoclonal antibody for the treatment of prostate cancer, and Phase 2 clinical trials are planned for the future.
- The discovery that selenium supplementation reduces prostate cell DNA damage. Evidence suggests that the trace element selenium may help protect men against prostate cancer. In fact, the NCI is sponsoring the largest ever prostate cancer prevention trial called Selenium and Vitamin E Chemoprevention Trial (SELECT). Originally, scientists believed that selenium helped enhance the function of the body's antioxidants and rid the body of potentially damaging agents. However, several studies funded by the PCRP are changing our understanding of how selenium protects men from prostate cancer. For example, Dr. Yan Dong was awarded an FY01 Posdoctoral Traineeship to examine what mechanisms are involved in the cancer preventive activity of selenium. Dr. Dong showed that selenium supplementation reduces prostate cell DNA damage, a presumed precursor to prostate cancer. These results are providing supportive information to SELECT by contributing to our knowledge of just how selenium confers protection against prostate cancer.

- The identification of genes that play critical roles in the development of prostate cancer. PCRP-supported investigators including Dr. William Isaacs, Dr. George Prendergast, and Dr. John Witte have found and are continuing to search for additional genes that play critical roles in the development of prostate cancer. Three genes discovered through PCRP funding (HPC2/ELAC2, HPCX, and RNASEL) are implicated in hereditary prostate cancer. Another gene, Bin 1, was found to be frequently deleted in nonhereditary metastatic prostate cancers indicating that it plays an important role in suppressing the spread of prostate cancer. Research supported by the PCRP on these and other genes is ongoing and is expected to contribute substantially to the development of more precise early detection methods and more effective therapies.

Neurofibromatosis Research Program

The overall goal of the NFRP is to decrease the impact of neurofibromatosis and schwannomatosis through the development of improved treatments. The NFRP supports all phases of the therapeutic development process, from basic studies of underlying molecular and cellular mechanisms, identification and validation of therapeutic targets, through preclinical and clinical evaluations of new drugs. This integrated approach ensures both a continuous advancement in the understanding of neurofibromatosis and schwannomatosis and translation of this knowledge into the development of new therapetics. The following are some of the most promising therapeutic development projects funded by the NFRP:

- The elucidation of a key role of merlin. Merlin is a tumor suppressor protein encoded by the neurofibromatosis 2 (NF2) gene whose loss of function leads to tumor development. FY98 NFRP-supported investigator Dr. Andrea McClatchey identified a key role of merlin in contact inhibition, a type of growth arrest that occurs when cells touch one another. Loss of contact inhibition is a critical step in tumor progression and metastasis, suggesting that therapeutics that mimic or enhance merlin function may impair the growth of not only NF2-associated tumors but other cancers as well.
- The development and preclinical testing of novel drugs to suppress nonsense mutations in neurofibromin. Neurofibromin is a tumor suppressor protein encoded by the neurofibromatosis 1 (NF1) gene. Nonsense mutations result in the production of truncated, nonfunctional proteins. Through an FY02 Therapeutic Development Award, NFRP supported researcher Dr. Westley Friesen is examining whether compounds that suppress such mutations will restore normal neurofibromin function in cultured cells and animals. These studies have promising therapeutic implications and are laying the foundation for future human drug trials.
- Clinical trials of Pirfenidone for the treatment of progressive plexiform neurofibromas in children with NF1. Pirfenidone is an antifibrotic agent that targets certain growth factors elevated in plexiform neurofibromas. Plexiform neurofibromas are tumors that arise from the coverings of multiple nerves and are a common manifestation in patients afflicted with NF1. Dr. Roger Packer was supported by the NFRP in FY01 to determine whether Pirfenidone can be used in the management of children with NF1 and progressive plexiform neurofibromas. Phase 1 studies to determine the optimal dose of Pirfenidone have been completed, and Phase 2 trials of efficacy are about to commence. Because there are no effective treatments for progressive plexiform neurofibromas other than surgery, this research has the potential to greatly benefit many children with NF1.

Ovarian Cancer Research Program

The Ovarian Cancer Research Program (OCRP) seeks to support innovative, integrated, multidisciplinary research efforts that will lead to better understanding, detection, diagnosis, prevention, and control of ovarian cancer. The following are examples of some of the most notable advances and products supported by the OCRP:

- The identification of a biomarker that can be used to recognize early-stage ovarian cancer. Most women are diagnosed with ovarian cancer during late stages of the disease. A way to detect this

disease in the early stages would save thousands of lives each year. FY98 OCRP-supported investigator Dr. Samuel Mok identified a potential biomarker, termed osteopontin, which has the potential to be used clinically to identify women with early stages of ovarian cancer.

- A synthesized peptide that slows down angiogenesis or the formation of new blood vessels. FY98 OCRP award recipient Dr. Ramakrishnan Sundaram and colleagues were able to successfully redesign antiangiogenic proteins and a peptide named anginex that displayed the ability to slow down the growth of new blood vessels. In a human ovarian cancinoma mouse model, anginex inhibited tumor growth by 70%, a discovery that holds promising therapeutic implications for the treatment of ovarian cancer.
- The use of the Sindbis vector to combat ovarian cancer. The use of gene therapy to treat cancer has gained much attention over the past 10 years. A particular type of gene therapy utilizes vectors or specific DNA sequences that can be used to transport genetic material to the host cell. These vectors can be constructed to target diseased cells in the body. FY00 OCRP researcher Dr. Daniel Meruelo is determining whether a vector based upon the Sindbis virus can be used to kill ovarian cancer cells. Dr. Meruelo observed that administration of Sinbis in conjunction with interleukin 12 (a protein capable of producing an immune response) in ovarian cancer cells resulted in cell death. In a mouse model of ovarian cancer, treatment of Sindbis–interleukin 12 extended the life of mice by 2 weeks compared to untreated mice. Although clinical trials in humans still need to be conducted, preliminary results indicate that the Sindbis–interleukin 12 combination may be a valuable treatment avenue for ovarian cancer.

Peer Reviewed Medical Research Program

The Peer Reviewed Medical Research Program (PRMRP) aims to improve the health of our military forces, and the technology stemming from this program is improving warfighter health and readiness. Examples of some of the products developed and supported by the PRMRP include the following:

- Field-deployable ultrasensitive portable immunoassay system for detection of biological toxins **(Armed Forces Institute of Pathology)**
- A new animal model to evaluate a new vaccine for dengue fever **(Naval Health Research Center)**
- An Internet-based, in-home asthma-monitoring system **(Tripler Army Medical Center)**
- An advanced frozen blood-processing system **(Mission Medical, Inc)**
- A handheld ultrasound prototype for battlefield medical imaging **(GE Global Research)**
- A bioengineered gene therapy system with potential to heal war wounds **(Johns Hopkins University)**
- The Services Tobacco Addiction Recovery (STAR) Project, a smoking cessation research program **(University of Minnesota)**
- Development of a bovine milk immunoglobulin supplement that prevents traveler's diarrhea **(Naval Medical Research Center)**
- An implantable biochip for monitoring glucose and lactate during hemorrhage **(Virginia Commonwealth University)**
- A portable system for triage and treatment of shock **(University of Massachusetts Medical School)**

Refer to Section VII for more information about this program and the scientific and technical innovations stemming from it.

National Prion Research Program

An important feature of the National Prion Research Program (NPRP) is that the program is product-driven. The mission of the NPRP is to develop a rapid, sensitive, and reproducible test for the detection of prions suitable for use as an antemortem diagnostic test as well as a screening assay. Although prion diseases are relatively rare in humans, the health threats posed by prion disease currently appear to involve food and possibly blood supplies, including those in overseas deployment zones. Thus, these health threats put military beneficiaries in affected areas overseas at risk. The NPRP is supporting investigators from 30 institutions, including 14 previously established

prion disease researchers, 40 pre- and post-doctoral trainees, and 15 scientists in other fields to develop the technology to detect the presence of prion disease.

Institutionally Based Research Programs

Since its inception, the CDMRP has managed 28 institutionally based research programs. These programs support leaders and innovators across many specialties to impact the eradication of cancer and cardiovascular, neurodegenerative, and other life-threatening diseases. From discovery to development, the institutionally based research programs are advancing products and technology for the benefit of the American public. See Section XI for more information on these programs and the technology developed and supported to cure disease.

Small Business Innovation Research/Small Business Technology Transfer Programs[8]

The Small Business Innovation Research/Small Business Technology Transfer Programs (SBIR/STTR) Programs are designed to harness the innovative talents of U.S. small businesses for our country's military and economic strength. The SBIR/STTR programs fund early-stage research and development efforts to support projects that fulfill a DOD need and have the potential for commercialization in the military and private sector markets. These programs are product-driven with the intent that a technology, product, or service will be developed that the government can potentially use and that the small business or research institution can commercialize outside the SBIR/STTR programs. The SBIR/STTR programs utilize a three-phase process, reflecting the high degree of technical risk involved in developing and commercializing cutting-edge technologies.

The CDMRP has participated in the SBIR program since FY00, while FY04 marks the first year of CDMRP participation in the STTR program. The SBIR/STTR programs have been leveraged to support research and products not supported elsewhere by the CDMRP. Through the SBIR/STTR programs, the CDMRP has supported an additional $9.3M of research in 5 years across breast, prostate, ovarian, and lung cancer, as well as supported work in angiogenesis and detection of biologicals (readily translatable to the Army mission).

Shaping Tomorrow

Solving today's health crises remains a challenge, but the CDMRP believes that by continuing to leverage resources, diseases will be cured. In 2005, the CDMRP will continue to change the course of science and medical discovery in targeted diseases. Together, we will enable the nation to cure.

[8] The SBIR Program is mandated by Public Laws 97-219, 99-43, and 102-564.