



The Office of the Congressionally Directed Medical Research Programs (CDMRP) has built a diverse portfolio totaling 6,193 awards and almost \$3.4 billion (B) in congressional appropriations. The CDMRP is accountable for the expenditure of these appropriations to consumer advocates, the scientific community, Congress, the Department of Defense (DOD), and the American public. Accordingly, a program evaluation division has been established to assess research productivity and outcomes. (Refer to the program evaluation section detailed in Section I.) Products, defined as tangible research outcomes that may lead to clinical and/or public health application, are of particular importance to both the CDMRP and its stakeholders. The program evaluation division has developed an innovative electronic classification scheme (taxonomy) that enables our staff to identify, catalog, and track products developed using CDMRP funding. This products taxonomy summarized in Table III-1 classifies each product by type, stage(s) of development funded by the CDMRP, and family (group of related but different products).

CDMRP began using the products taxonomy to retrospectively classify products developed with funding from six of its core programs—Breast Cancer Research Program (BCRP), Prostate Cancer Research Program (PCRP), Neurofibromatosis Research Program (NFRP), Ovarian Cancer Research Program (OCRP), Chronic Myelogenous Leukemia Research Program (CMLRP), and Peer Reviewed Medical Research Program (PRMRP)—from each program’s year of inception through fiscal year 2002 (FY02). Data were derived from the review of annual and/or final progress reports submitted by the Principal Investigators. Each product was assigned only one type or category but could have multiple stages. For example, if a gene were to be identified, characterized as a potential inducer of apoptosis, and tested in an animal model for potential therapeutic efficacy through a BCRP Idea Award, it would be classified as a biological molecule and staged as discovery and development and animal validation. The same products were often identified in multiple grants, both within and between programs, since many investigators conduct research on the same genes, animal models, or drugs. All products are stored in an electronic database that allows for easy retrieval of data. These data may be used to highlight gaps in the CDMRP portfolio that would benefit from additional support, assist Integration Panels in crafting award mechanisms that meet the needs of their programs, and inform our stakeholders of CDMRP-funded advances via updates on our website and in the annual reports. Thus, the products database will assist the CDMRP in fulfilling its mission of guarding the public trust and may ultimately lead to further advances in disease prevention, treatment, and management.

CDMRP’s efforts have resulted in the development of many new products to support the warfighter and revolutionize disease prevention, management, and treatment. The CDMRP will continue to support innovative research with the ultimate goal of eradicating diseases.



Table III-1. CDMRP Products Taxonomy

Product Type

Animal Model - non-human animal system, such as a knockout mouse model, that mimics specific biological processes

Biological Molecule - human molecular substance, such as a gene, hormone, or protein

Biological Resource - biological material, such as a cell line, used for research purposes

Clinical or Public Health Assessment - potential or tested biological procedure, such as biomarker assays and risk assessments

Clinical or Public Health Intervention - potential or tested medical and/or behavioral procedure, such as a surgical technique or diet modification program

Data Resource - database or other collection of data used for research, such as a database of patient medical information or a collection of digital mammography images

Device - instrument, equipment, or other apparatus, such as digital mammography, used for medical purposes

Drug - natural or synthetic compound not of human origin, such as taxol[®]

Methodological Resource - process or procedure, such as informatics techniques and statistical models, used for research

Stage (Phase) of Development

Discovery and/or Development - initial product design, identification, and/or synthesis, or product development and/or testing in in vitro systems including cell lines to determine product characteristics

Animal Validation - assessing product characteristics and effects in non-human animal models

Human Validation - preclinical assessment of product characteristics and effects in human subjects

Phase 1 Clinical Trial[®] - assessment of administration characteristics, such as route of administration, frequency, dosing, device settings, device tolerances, drug metabolism, and acute side effects. Phase 1 trials typically involve a small number of healthy volunteers (between 10 and 80)

Phase 2 Clinical Trial[®] - assessment of product safety, preliminary efficacy, and trial methods. Phase 2 trials usually focus on a specific disease, involve more participants (100–300), and involve those who have the disease or condition that the product seeks to address

Phase 3 Clinical Trial[®] - assessment of product efficacy and side effects in comparison to a standard treatment or approach. Phase 3 trials typically involve large numbers of participants having the disease or condition (1,000–3,000) and randomization to study groups

Family (selected examples)

Animal Models

Biomarkers

Detection and Diagnostic Tools

Military Health and Readiness

Pharmacologic and Therapeutic Interventions

^a Clinical trials are classified by phase based on definitions established by the U.S. Food and Drug Administration (FDA) for prospective studies of drugs, biologics (e.g., vaccines), and devices. The CDMRP expanded the FDA definitions for the products taxonomy to encompass procedures, dietary and behavioral interventions (including complementary and alternative medicine), and educational interventions.



Retrospective product coding has been completed for all programs and prospective coding of grants awarded from FY02 forward is ongoing.

A total of 11,812 products have been identified from 4,841 awards.

These products are summarized by type and phase in Table III-2.

Table III-2. CDMRP Products by Type and Phase

Type/Phase	BCRP	PCRP	NFRP	OCRP	CMLRP	PRMRP	Totals
Biological Molecules	3,991	1,189	232	161	40	44	5,657
Discovery &/or Development	3,705	1,052	213	111	39	44	5,164
Animal Validation	545	178	29	30	11	14	807
Human Validation	421	209	35	59	3	7	734
Phase 1 Clinical Trial	5	3	-	-	-	-	8
Phase 2 Clinical Trial	4	1	-	-	-	-	5
Phase 3 Clinical Trial	-	-	-	-	-	-	0
Drugs	705	440	22	27	15	34	1,243
Discovery &/or Development	638	388	20	17	12	33	1,108
Animal Validation	220	156	6	18	4	12	416
Human Validation	24	15	-	1	2	1	43
Phase 1 Clinical Trial	19	7	1	-	1	-	28
Phase 2 Clinical Trial	5	1	1	1	-	1	9
Phase 3 Clinical Trial	-	-	-	-	-	-	0
Devices	190	36	0	0	0	10	236
Discovery &/or Development	185	34	-	-	-	9	228
Animal Validation	23	10	-	-	-	-	33
Human Validation	48	9	-	-	-	2	59
Phase 1 Clinical Trial	5	1	-	-	-	-	6
Phase 2 Clinical Trial	-	-	-	-	-	-	0
Phase 3 Clinical Trial	-	-	-	-	-	-	0
Clinical or Public Health Assessments	63	10	0	0	0	1	74
Discovery &/or Development	56	7	-	-	-	1	64
Animal Validation	2	-	-	-	-	-	2
Human Validation	37	6	-	-	-	1	44
Phase 1 Clinical Trial	-	-	-	-	-	-	0
Phase 2 Clinical Trial	-	-	-	-	-	-	0
Phase 3 Clinical Trial	1	-	-	-	-	-	1





Table III-2. CDMRP Products by Type and Phase (cont.)

Type/Phase	BCRP	PCRP	NFRP	OCRP	CMLRP	PRMRP	Totals
<i>Clinical or Public Health Interventions</i>	288	55	0	3	3	5	354
<i>Discovery &/or Development</i>	232	35	-	2	3	5	277
<i>Animal Validation</i>	85	27	-	1	3	1	117
<i>Human Validation</i>	95	10	-	1	-	2	108
<i>Phase 1 Clinical Trial</i>	21	-	-	-	-	-	21
<i>Phase 2 Clinical Trial</i>	2	1	-	-	-	-	3
<i>Phase 3 Clinical Trial</i>	-	-	-	-	-	-	0
<i>Animal Models</i>	543	164	61	7	6	14	795
<i>Discovery &/or Development</i>	532	164	61	7	6	14	784
<i>Animal Validation</i>	79	28	-	-	-	-	107
<i>Human Validation</i>	-	-	-	-	-	-	0
<i>Phase 1 Clinical Trial</i>	-	-	-	-	-	-	0
<i>Phase 2 Clinical Trial</i>	-	-	-	-	-	-	0
<i>Phase 3 Clinical Trial</i>	-	-	-	-	-	-	0
<i>Biological Resources</i>	2,002	635	122	59	14	27	2,859
<i>Discovery &/or Development</i>	1,981	620	122	58	14	27	2,822
<i>Animal Validation</i>	157	99	7	3	4	1	271
<i>Human Validation</i>	14	21	-	4	-	-	39
<i>Phase 1 Clinical Trial</i>	-	-	-	-	-	-	0
<i>Phase 2 Clinical Trial</i>	-	-	-	-	-	-	0
<i>Phase 3 Clinical Trial</i>	-	-	-	-	-	-	0
<i>Methodological Resources</i>	675	138	72	21	1	34	941
<i>Discovery &/or Development</i>	661	136	72	21	1	34	925
<i>Animal Validation</i>	54	15	5	4	1	-	79
<i>Human Validation</i>	96	21	26	7	-	3	153
<i>Phase 1 Clinical Trial</i>	1	-	-	-	-	-	1
<i>Phase 2 Clinical Trial</i>	1	-	-	-	-	-	1
<i>Phase 3 Clinical Trial</i>	-	-	-	-	-	-	0
<i>Data Resources</i>	181	85	12	6	0	11	295
<i>Discovery &/or Development</i>	156	83	12	6	-	11	268
<i>Animal Validation</i>	5	2	-	-	-	1	8
<i>Human Validation</i>	65	34	-	2	-	4	105
<i>Phase 1 Clinical Trial</i>	-	1	-	-	-	-	1
<i>Phase 2 Clinical Trial</i>	-	-	-	-	-	-	0
<i>Phase 3 Clinical Trial</i>	-	-	-	-	-	-	0



The remainder of this chapter showcases some of the most promising and exciting products resulting from CDMRP support. Products range from basic and preclinical outcomes (such as mouse models) to novel therapeutic agents in clinical trials. Together, these products demonstrate the profound impact that the CDMRP has had in global health issues, namely, breast, prostate, ovarian, and other cancers; neurofibromatosis (NF); prion diseases; and military health.

ANIMAL MODELS OF DISEASE

Animal models of human disorders provide a powerful means for researchers to study disease mechanisms and test new therapeutics before human clinical trials. The CDMRP has funded the development of animal models through both the NFRP and the OCRP that have revolutionized NF and ovarian cancer research and allowed investigators to conduct important studies that were not possible previously.

Mouse Models of NF1 and NF2

The NFRP sponsored the creation of mouse models of myeloproliferative disorder and several common NF1- and NF2-associated solid tumors, including plexiform neurofibromas, malignant peripheral nerve sheath tumors, astrocytomas, meningiomas, ependymomas, and schwannomas. These models, developed by a team led by Dr. Kevin Shannon of the University of California, San Francisco, are being used to identify novel drug targets and study the effectiveness of experimental agents, with the ultimate goal of improving the clinical management and treatment of NF.^{1,2,3,4}

Animal Models of Ovarian Cancer

- ◆ **Monkey.** The OCRP sponsored research in monkeys that provided important insights into ovarian cancer prevention. Dr. Andrew Berchuck and colleagues at Duke University demonstrated the protective effects of oral contraceptives,⁵ and Dr. David Gershenson led an M.D. Anderson Cancer Center team that tested the vitamin A analog fenretinide.⁶ Fenretinide is currently in clinical



¹ Le DT, Kong N, Zhu Y, et al. 2004. Somatic inactivation of *Nf1* in hematopoietic cells results in a progressive myeloproliferative disorder. *Blood* 103:4243–4250.

² Weiss B and Shannon K. 2003. Mouse cancer models as a platform for performing preclinical therapeutic trials. *Curr Opin Genet Dev* 13:84–89.

³ Zhu Y, Ghosh P, Charnay P, et al. 2002. Neurofibromas in *NF1*: Schwann cell origin and role of tumor environment. *Science* 296:920–922.

⁴ Kalamirides M, Niwa-Kawakita M, Leblais H, et al. 2002. *Nf2* gene inactivation in arachnoidal cells is rate-limiting for meningioma development in the mouse. *Genes Dev* 16:1060–1065.

⁵ Rodriguez GC, Nagarsheth N, Rex C, et al. 2002. Progestin induction of apoptosis in the macaque ovarian epithelium is associated with differential regulation of transforming growth factor-beta. *J Natl Cancer Inst* 94:50–60.

⁶ Brewer M, Utzinger U, Satterfield W, et al. 2001. Biomarker modulation in a nonhuman rhesus primate model for ovarian cancer chemoprevention. *Cancer Epidemiol Biomarkers Prev* 10:889–893.

**DON'T MISS THESE
OTHER EXCITING
OUTCOMES AND
ADVANCES**

“Little Fish, Big Potential,” page IX-3.

“Dissecting the Molecular and Genetic Mechanisms of Learning Disabilities in TSC,” page X-3.



trials for ovarian cancer prevention sponsored by the Gynecologic Oncology Group and M.D. Anderson Cancer Center.

- ◆ **Chicken.** Chickens are the only animals that develop spontaneous ovarian cancer at a high rate. The FY99 OCRP funded the development of a chicken model of ovarian cancer by Dr. Patricia Johnson and colleagues at Cornell University.⁷
- ◆ **Mouse.** The FY03 OCRP funded several promising mouse models of tissue-specific gene expression. These included a model developed by Dr. Denise Connolly of Fox Chase Cancer Center using the ovarian epithelial-specific promoter Mullerian inhibitory substance type II receptor (MISIIR) and research by Dr. Rong Wu of the University of Michigan using the MISIIR promoter to model ovarian endometrioid carcinoma. The OCRP provided funding to Dr. Louis Dubeau at the University of Southern California to test his hypothesis that ovarian cancer could arise in cells other than the epithelial cells where it is most often detected. Dr. Dubeau's finding that inactivating the BRCA1 oncogene in ovarian granulosa cells did indeed lead to the development of epithelial ovarian cancer in mice has significant implications for understanding the development of ovarian cancer.⁸ Read more about Dr. Dubeau's research on pages VII-7–VII-9.

BIOMARKERS

Biomarkers may be defined as molecules (such as genes or proteins) whose presence and/or levels in cells, tissues, or body fluids may serve as an indicator of the predisposition, presence, or progression of disease or of a patient's response to treatment. As described in this section, CDMRP-funded research has resulted in the identification and characterization of biomarkers for multiple diseases.

Biomarkers of Prostate Cancer Susceptibility

The risk of developing prostate cancer—the most common cancer in American men—is influenced by genetic factors, but many of the genes involved have not yet been identified. Consequently, the PCRFP has sponsored research focusing on the identification and analysis of biomarkers of prostate cancer susceptibility.

- ◆ ***Nkx3.1***. Brief exposure of rodents to estrogens early in development can permanently alter prostate development and increase the incidence of precancerous prostate lesions with aging. Dr. Charles

⁷ Giles JR, Shivaprasad HL, and Johnson PA. 2004. Ovarian tumor expression of an oviductal protein in the hen: A model for human serous ovarian adenocarcinoma. *Gynecol Oncol* 95:530–533.

⁸ Chodankar R, Kwang S, Sangiorgi F, et al. 2005. Cell-nonautonomous induction of ovarian and uterine serous cystadenomas in mice lacking a functional *Brca1* in ovarian granulosa cells. *Curr Biol* 15: 561–565.



Bieberich of the University of Maryland found that estrogen exposure altered the expression of several prostate genes, including the developmental gene *Nkx3.1*. These studies may provide insight into the early molecular events that predispose men to prostate cancer in later life and ultimately aid in the identification of individuals at enhanced risk of developing the disease.

- ◆ **Kruppel-like factor 6 (KLF6).** The KLF6 transcription factor is expressed in most normal cells and tissues but is mutated or deleted in a large percentage of human prostate cancers. Dr. John Martignetti of the Mount Sinai School of Medicine determined in a study of 3,411 men that a type of mutation known as a single nucleotide polymorphism in KLF6 was associated with increased prostate cancer risk. One particular mutant, IVS A, might be responsible for up to 5.4% of prostate cancers. Ongoing PCR-supported studies of KLF6 and prostate cancer progression may lead to advances in the early detection of the disease as well as the development of new drug targets and therapies.

Ovarian Cancer Biomarkers

Ovarian cancer is rarely associated with obvious symptoms until late in its progression, so most women are diagnosed at late stages of the disease. While the 5-year survival rate for women diagnosed with early-stage ovarian cancer is 94%, the 5-year survival rate for those with late-stage disease is 29%. Development of a routine screen for the early-stage detection of ovarian cancer, analogous to the Pap test for cervical cancer, could save thousands of lives every year. The OICRP has supported several promising projects focused on the identification of candidate ovarian cancer biomarkers that could potentially be used for diagnostic screening. Many of these studies exploit advances in high-throughput screening technologies that have enhanced the ability to identify candidate biomarkers. Dr. Amy Skubitz of the University of Minnesota used gene expression arrays of ovarian tumors, normal ovarian tissue, and normal and diseased tissues from other organs followed by immunocytochemistry to identify three candidate biomarkers—beta 8 integrin subunit, claudin-4, and S100 calcium-binding protein A1—from among 12,000 genes studied.⁹ Dr. Samuel Mok has performed extensive work in identifying and evaluating biomarkers. Dr. Mok and colleagues at Brigham and Women's Hospital have identified numerous proteins, including protease M, cyclin E, human epididymis protein 4, creatine kinase B, prostasin, epithelial cell adhesion molecule haptoglobin subunit alpha, and osteopontin, as being overexpressed in ovarian cancer. Because the secreted protein osteopontin can easily be detected in urine,

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“Novel Serum Biomarkers for the Detection of Ovarian Cancer,” page VII-6.



⁹ Hibbs K, Skubitz KM, Pambuccian SE, et al. 2004. Differential gene expression in ovarian carcinoma: Identification of potential biomarkers. *Am J Pathol* 165:397–414.



it holds great promise as a marker that could be used for routine screening.^{10,11,12,13,14} Study of ovarian cancer etiology has also led to discovery of biomarkers for detection and diagnosis. The three major subtypes of epithelial ovarian cancer (EOC)—serous, endometrioid, and mucinous—are distinguished by their distinct patterns of histologic differentiation. Dr. Honami Naora and colleagues at the University of Texas M. D. Anderson Cancer Center have identified three homeobox-containing (Hox) genes not expressed in normal ovarian tissue, but each expressed specifically in one subtype of EOC. These Hox genes control the development of each of the three major histological subtypes of epithelial ovarian cancer.¹⁵

Predictors of Symptom Development in NF1

In addition to identifying individuals who are predisposed to developing prostate cancer or other disorders, biomarkers are useful for predicting the risk of developing specific symptoms in people already living with a disease. Such biomarkers are especially important for a disorder such as NF1. Clinical manifestations and symptom severity vary greatly among individuals with this disease, even within families, making it difficult for physicians to predict the risk of developing particular disease features in individual patients. NFRP-supported research has significantly improved our understanding of predictors of symptom development in NF1.

◆ **Statistical associations between clinical features.** Dr. Jan Friedman of the University of British Columbia and colleagues analyzed the medical records of over 4,400 individuals with NF1 and identified associations between multiple sets of clinical symptoms. For example, individuals with plexiform neurofibromas exhibited an increased risk of developing scoliosis, and individuals with learning disabilities or mental retardation were more likely to experience seizures than those without cognitive deficits. Additionally, a separate study of over 3,700 patients revealed associations among café-au-lait spots, freckling, and Lisch nodules and cutaneous, sub-

¹⁰ Mok S, Ye B, and Cramer DW. 2005. Methods of detecting ovarian cancer based on osteopontin. U.S. patent application 20050009120.

¹¹ Ni X, Zhang W, Huang KC, et al. 2004. Characterization of human kallikrein 6/protease M expression in ovarian cancer. *Br J Cancer* 91:725–731.

¹² Schorge JO, Drake RD, Lee H, et al. 2004. Osteopontin as an adjunct to CA125 in detecting recurrent ovarian cancer. *Clin Cancer Res* 10:3474–3478.

¹³ Kim JH, Herlyn D, Wong KK, et al. 2003. Identification of epithelial cell adhesion molecule autoantibody in patients with ovarian cancer. *Clin Cancer Res* 9:4782–4791.

¹⁴ Kim JH, Skates SJ, Ueda T, et al. 2002. Osteopontin as a potential diagnostic biomarker for ovarian cancer. *J Amer Med Assoc* 287:1671–1679.

¹⁵ Cheng W, Liu J, Yoshida H, et al. 2005. Lineage infidelity of epithelial ovarian cancer is controlled by HOX genes that specify regional identity in the reproductive tract. *Nat Med* 11:531–537.



cutaneous, and plexiform neurofibromas. These findings may lead to the development of improved diagnostic profile tools for NF1.¹⁶

- ◆ **Biomarkers of cognitive function.** Dr. Kathryn North of the Children's Hospital at Westmead in Australia has identified predictors of cognitive and social function in young children with NF1. Cognitive deficits are a common complication of NF1 associated with academic underachievement, psychosocial and behavioral problems, and poor self-image in children. Additionally, these deficits continue to have a significant negative impact in adulthood, contributing to failure to complete higher education and limited career choices. The presence of lesions known as T2 hyperintensities on magnetic resonance images of the brains of 8- to 16-year-old children with NF1 was found to be predictive of cognitive deficits during both childhood and adulthood. Moreover, the presence of attention deficit hyperactivity disorder (ADHD) was found to be the primary risk factor for poor social functioning in children with NF1, suggesting that social skills training combined with ADHD medication may be an effective treatment for psychosocial problems in NF1. The use of these and other biomarkers to identify "at-risk" youth with NF1 for early cognitive, psychosocial, and therapeutic intervention has great potential to improve long-term functioning and quality of life in these children.^{17,18}

Biomarkers of Breast Cancer Treatment Response

Biomarkers are also powerful for predicting response to treatment in diseases such as breast cancer. Tamoxifen, an estrogen blocker, is used to treat estrogen receptor-positive breast tumors. However, nearly one-third of tamoxifen-treated patients do not exhibit a prolonged response to treatment. BCRP-funded investigator Dr. Dennis Sgroi recently demonstrated that measuring the activity of two genes, HOXB13 and IL17BR, can predict the outcome of tamoxifen treatment in patients with early-stage breast cancer. "The higher the expression levels of HOXB13 and the lower the expression of IL17BR, the greater the chance of recurrence," explained Dr. Sgroi. Using an initial set of 20 patients, the predictive power of this two-gene signature was 80%. In a cohort of lymph node-negative breast cancer patients, the predic-

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"Single Cell Protein Profiles for Improved Diagnosis and Treatment of Breast Cancer," page IV-7.



¹⁶ Szudek J, Evans DG, and Friedman JM. Patterns of associations of clinical features in neurofibromatosis 1 (NF1). *Hum Genet* 2003;112:289–297.

¹⁷ Barton B and North K. 2004. Social skills of children with neurofibromatosis type 1. *Dev Med Child Neurol* 46:553–563.

¹⁸ Hyman SL, Gill DS, Shores EA, et al. 2003. Natural history of cognitive deficits and their relationship to MRI T2-hyperintensities in NF1. *Neurology* 60:1139–1145.



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“Magnetic Resonance Imaging of Prostate Cancer,” on page V-3 and “MR Spectroscopy May Be Superior for Determining Prostate Cancer Prognosis” on page V-15.

“Advancing Radiation-Based Treatments for Prostate Cancer” on page V-10.



tive power was approximately 78%. Dr. Sgroi will continue to test this pattern with the goal of adding other genes that may improve the predictive power of this test. Further development and validation of this and other tests will allow physicians to identify patients who are most likely to be helped by specific drugs as well as those who might benefit more from other therapies.¹⁹

DETECTION AND DIAGNOSTIC TOOLS

Early detection and/or diagnosis of disease can significantly improve the odds of successful treatment and enhance overall patient outcomes. The CDMRP has supported the development of improved diagnostics for cancer and neurofibromatosis. The CDMRP has also funded the development of diagnostic tests for prion diseases, with the ultimate goal of protecting the food and blood supplies and reducing the occurrence of human transmissible spongiform encephalopathies. Selected examples of CDMRP-supported diagnostics are described in this section, many of which were funded by the Small Business Innovation Research/Small Business Technology Transfer (SBIR/STTR) program. The SBIR/STTR program is described in greater detail on page II-12.

Cancer Diagnostics

- ◆ **A handheld device for at-home breast cancer screening.** This device, tentatively named “iFind,” may someday allow women to screen themselves for breast cancer in the privacy of their homes. Although this is not a full diagnostic device, it can provide an indication of early signs of breast cancer that need to be followed up by a doctor. iFind detects oxygenation and monitors the difference in blood oxygen ratios in growing cancers and normal tissues. If potential early signs are picked up, the user will be alerted with a light or vibration. Additionally, iFind has a longitudinal memory so that the woman can bring the device with her to her doctor who will then have the results from every time it has been used. See the related In The News article on “iFind” on page III-22.
- ◆ **Protein biomarker diagnostics.** Protein markers are increasingly being used for the early detection and diagnosis of cancer and other diseases. The following products are the results of studies focused on protein biomarkers for cancer:
 - ◇ A device for the simple, rapid, and inexpensive measurement of lysophosphatidic acid, a marker of early-stage ovarian cancer. This technology may be easily adapted for the detection of other disease markers (Lynntech, Inc.).

¹⁹ Ma XJ, Wang Z, Ryan PD, et al. 2004. A two-gene expression ratio predicts clinical outcome in breast cancer patients treated with tamoxifen. *Cancer Cell* 5:607–616.



- ❖ An ultrasensitive multiphoton detection method for measuring blood levels of a prostate cancer biomarker called prostate-specific antigen (PSA). The test was able to discriminate between normal prostate tissue and prostate cancer in preliminary studies. This assay may also be useful for monitoring therapeutic responses and detecting disease recurrence after prostatectomy (Biotraces, Inc.).
- ❖ A high-throughput assay for the analysis of multiple cancer biomarkers in patient blood samples (Bioscales, Inc.).
- ❖ A high-throughput system for the quantitation of metalloproteinases, a specific class of cancer biomarkers (PhysicalOptics Corporation).
- ❖ A new technology, termed Dual Immunostaining Mediated Subtractive Cloning, for detecting markers expressed on the outside of tumor cells (Epitomics).
- ❖ The SeroFAS assay for the detection of intact and fragmented fatty acid synthase, a tumor-associated biomarker, in blood samples. This assay may also be useful in guiding therapeutic choices and assessing treatment responses (FASGen Diagnostics).
- ◆ **Pathology-based diagnostics.** RedPath Genetics developed five genetic assays for cancer detection that use material excised from patient tumor samples with a technique known as microdissection.
- ◆ **Aptamer diagnostics.** Kumetrix is developing a device for the detection of cancer biomarkers. This diagnostic tool consists of a fragment of DNA (known as an oligonucleotide) attached to the surface of a silicon chip fabricated with gold.
- ◆ **Radiolabeled targeted molecules for imaging ovarian cancer.** OCRP-funded investigator Dr. Janina Baranowska-Kortylewicz of the University of Nebraska is developing a noninvasive imaging system for ovarian cancer detection in which radioactive iodine targeted to ovarian carcinoma cells is visualized by a gamma camera. Radiolabeled iododeoxyuridine is targeted to ovarian cancer cells by linking it to dihydrotestosterone, which binds selectively and tightly to the androgen receptor, overexpressed in 90% of ovarian cancers. The gamma rays emitted by radioactive iodine isotopes have high energy, making them useful for imaging in the peritoneal cavity. Studies of biodistribution of the radiolabeled ligand in tumor-bearing mice have demonstrated effective targeting to tumors and shown no toxicity at doses that provide good imaging.





- ◆ **Near-infrared (NIR) technology for the detection of cancer.** The following products are aimed at improving NIR imaging technology for cancer detection:
 - ◇ Design and testing of a prototype integrated NIR diffusion optical tomography (DOT) system with built-in 3-dimensional imaging capability in a single hardware platform. Phase 2 studies are under way to test and optimize the prototype system's hardware and software (Genex Technologies).
 - ◇ Optimization of dynamic NIR optical tomography specifically for the detection of cancer. Clinical trials of this system are under development (NIRx Medical Technologies).

NF2 Diagnostics

The clinical diagnosis of NF2 is based on family history and the presence of bilateral vestibular schwannomas and other characteristic tumors. The disease may also be diagnosed in presymptomatic individuals using assays to detect mutations or deletions in Merlin, the NF2 tumor suppressor gene. Although mutation detection assays are relatively efficient, there is a critical need for improved methodology for the detection of NF2 deletions. NFRP-funded investigator Dr. Jan Dumanski of Uppsala University, Sweden, used his expertise in the cutting-edge field of array-comparative genomic hybridization to develop a high-resolution diagnostic assay for detecting disease-causing NF2 deletions. This assay can be used to analyze segments of the NF2 gene that are nearly impossible to assess using current methods. Dr. Dumanski is currently working to enhance the assay with the support of an award from the FY03 NFRP.²⁰

Prion Disease Diagnostics

- ◆ Rural Technologies, Inc. developed a follicular dendritic cell (FDC)-based diagnostic assay for prion disease. Phase 2 studies are in progress to confirm the diagnostic utility of this assay for samples from infected animals. Upon completion of Phase 2, Rural Technologies, Inc. will have a technology ready for commercial use.
- ◆ Nomadics, Inc. is developing a cell culture-based assay for elk chronic wasting disease. Their innovative approach involves bio-engineering a cow B-lymphocyte cell line to constitutively surface express high levels of elk PrPc fused to yellow fluorescent protein.



²⁰ Mantripragada KK, Buckley PG, Jarbo C, et al. 2003. Development of NF2 gene specific, strictly sequence defined diagnostic microarray for deletion detection. *J Mol Med* 81:443-451.



PHARMACOLOGIC AND THERAPEUTIC INTERVENTIONS

Several examples of drugs, biologics, and complementary treatments developed as a result of CDMRP funding are described in this section. The CDMRP also has supported the application of the burgeoning field of nanotechnology to cancer treatment. Additionally, the CDMRP has sponsored the development of non-pharmacologic interventions including breast reconstruction procedures, exercise regimens, and behavior modification programs.

Drugs, Biologics, and Complementary Treatments

- ◆ **WX-UK1, a breast cancer anti-metastatic agent.** WX-UK1 is a serine proteinase inhibitor that impairs tumor growth and metastasis in a rat model of breast cancer. Dr. Olaf G. Wilhelm and Dr. Bernd Muehlenweg of Wilex Biotechnology in Munich, Germany are conducting a Phase 1 clinical trial to evaluate the safety of this drug. Although the trial is still in progress, preliminary results indicate that WX-UK1 is well tolerated. Recruitment of additional patients to evaluate the safety of a larger dose of the drug is in progress.
- ◆ **Retinoic acid metabolism blocking agents for cancer therapy.** Differentiating agents, such as all-trans retinoic acid (ATRA), also known as Tretinoin, have shown some success as chemotherapeutic agents. However, studies suggest that the changes in the metabolism of ATRA may result in resistance to ATRA treatment. Therefore, compounds that inhibit ATRA metabolism may serve as improved chemotherapeutic agents. BCRP-funded investigator Dr. Vincent C. Njar synthesized over 50 retinoic acid metabolism blocking agents (RAMBAs) and tested their ability to block ATRA metabolism. The majority of the compounds were highly potent inhibitors of ATRA metabolism in liver microsomes and in human breast cancer cell lines. The most potent inhibitor, VN12-1, is 670,000-fold more potent than liarozole, a previously identified inhibitor of ATRA metabolism and the only RAMBA to have undergone clinical trials in both breast and prostate cancer patients. Therefore, these new compounds may be strong candidates for development as therapeutic agents for cancer treatment.
- ◆ **Guanosine-rich oligonucleotides.** Dr. Paula Bates and Dr. Donald Miller developed a new chemotherapeutic agent with the support of the PCRCP that may provide a new treatment option for prostate cancer. AS1411 (formerly, AGRO100) is an oligonucleotide that binds to nucleolin, an RNA binding protein involved in nucleic acid metabolism. This protein is localized on the surface of malignant cells and its expression is regulated by androgen. The binding of AS1411 to nucleolin inhibits growth and promotes cell death (apoptosis) in cultured tumor cells but does not affect non-malignant cells. Administration of AS1411 to mice



DON'T MISS THESE OTHER EXCITING OUTCOMES AND ADVANCES

“The Wealth of the Rain Forest,”
page IV-5.

“Soy and Breast Cancer: Food for Thought,” page IV-6.

“An Antibiotic That Kills Breast Cancer Cells,” page IV-9.

“U-M Researchers Identify a Small Molecule That Inhibits Protein Involved in Cancer,” page IV-16.

“Prostate Cancer Vaccine Development,” page V-7.

“A New Genetic Link to Increased Prostate Cancer Risk,” page V-14.

“Phase 2 Trials Under Way for NF1 Treatment,” page VI-4.

“Squalamine and Cisplatin: Potential Ovarian Cancer Therapeutic Agents,” page VII-7.

“Pre-Clinical Evaluation of PD166326, a Potential New CML Therapeutic Agent,” page IX-3.



bearing pre-established DU145 prostate tumors caused significant regression of the tumor masses. AS1411 was detectable in the bloodstream of mice for as long as 4 hours after injection, which is considerably longer than other similar agents, with no detectable toxicity. Clinical trials are in progress in patients with advanced solid tumors. Among 17 patients with advanced tumors that were unresponsive to treatment, 7 showed stable disease for 2 months or more after treatment and 1 patient had a near complete response.

- ◆ **Combined 13-cis retinoic acid, (alpha) interferon, taxotere, and estramustine (RITE) treatment.** Conventional therapies are ineffective for advanced hormone refractory prostate cancer (HRPC). Mechanisms of drug resistance include overexpression of the Bcl-2 oncogene and mutations in the p53 tumor suppressor gene. PCR-supported investigator Dr. Robert DiPaola found that a combination of 13-cis retinoic acid and alpha interferon downregulated the expression of Bcl-2. A combined Phase 1/Phase 2 trial of patients with HRPC revealed that this regimen, in combination with the chemotherapeutic agents docetaxel (Taxotere[®]) and estramustine (Emcyt[®], Estracyte[®]) was well tolerated and resulted in decreases in Bcl-2 levels. PSA levels decreased in all nine patients. Phase 2 clinical trials are under way.
- ◆ **Angiogenesis inhibitors.** Angiogenesis, the formation of new blood vessels, is required for the growth of all types of tumors. Luna Innovation Corporation has identified 12 small-molecule modulators of focal adhesion kinase (FAK) activity that plays a role in angiogenesis. Analysis of the effects of these modulators on cell migration and angiogenesis in cell culture and in animal models is in progress.
- ◆ **Combined breast cancer therapy using antibodies against HER2/Neu and vascular endothelial growth factor (VEGF).** Serum levels of VEGF, a protein involved in the formation of new blood vessels (angiogenesis), are elevated in invasive breast cancer. BCRP-funded investigator Dr. Mark Pegram is evaluating the combined therapeutic effects of two humanized monoclonal antibodies: trastuzumab (Herceptin[®]; directed against HER2/Neu) and bevacizumab (Avasatin[®], directed against VEGF). Preclinical studies using human breast cancer cells grown in mice revealed a nearly threefold reduction in tumor volume in trastuzumab + bevacizumab-treated mice. Results from the Phase 1 dose escalation portion of a clinical trial showed that the antibody combination is well tolerated with few serious adverse events. Also, preliminary evidence suggests encouraging clinical efficacy of the antibody combination. A multi-institutional Phase 2 trial to evaluate the efficacy of the combination therapy is being planned.



- ◆ **Prostate cancer vaccines.** With the support of the PCRP, Dr. Douglas McNeel and Dr. David Peace are independently developing vaccines for the treatment of prostatic cancer using an immune system attack on prostate cancer cells. Read more about these vaccines on pages V-7–V-9. Furthermore, VectorLogics is developing adenoviral vaccines targeted to dendritic cells for prostate cancer immunotherapy.
- ◆ **Oncolytic herpes viruses for the treatment of NF tumors.** The treatment of many NF-associated nerve tumors is limited to surgery and radiation, both of which are associated with serious side effects and recurrences. Gene therapy using vectors derived from the herpes simplex virus (HSV), including one known as G207, represents a promising strategy for treating nervous system tumors in human patients with minimal toxicity. A team of leading investigators from Massachusetts General Hospital received awards from the NFRP in FY99, FY01, and FY03 to develop HSV-based gene therapy approaches for NF tumors. Drs. Xandra Breakefield, Robert Martuza, and Samuel Rabin examined the therapeutic effectiveness of G47-delta, a vector derived from G207 that grows more efficiently in NF1 and NF2 tumor cells but has the same safety profile as the parent vector. G47-delta killed cultures of human schwannoma cells and substantially reduced the size of human NF2 schwannoma tumors implanted into mice. G47-delta also reduced tumor size in mice genetically engineered to develop schwannomas. The group plans to assess the efficacy of G207 and G47-delta in treating NF2 meningiomas and ultimately seeks to test the vectors in clinical trials of individuals with NF. The development and testing of HSV vectors and other therapeutics will hopefully lead to new, less invasive treatment strategies for NF tumors.
- ◆ **Targeted drug delivery technology.** SibTech is developing “molecular vehicles” for targeted therapeutic delivery, consisting of a tumor-specific monoclonal antibody attached to a drug compound. This technology will potentially have wide applicability in the treatment of a variety of tumor types.
- ◆ **Spices may add a spice to life—dietary components and breast cancer progression.** Curcumin, a component of the spice turmeric, may impact cancer progression. Dr. Bharat Aggarwal at M.D. Anderson Cancer Center in Texas is evaluating the efficacy of curcumin against breast cancer metastasis in a mouse model of human breast cancer. The incidence of lung metastasis was significantly decreased in mice treated with curcumin alone or in combination with the chemotherapy drug paclitaxel. These data combined with results from studies of other cancers suggest that curcumin may be a safe and effective co-therapy in the treatment and prevention of breast cancer.





Nanotechnology

- ◆ **Nanoshells for breast cancer treatment.** Researchers from Rice University have recently demonstrated the first use of a single bio-imaging tool for both diagnosis and therapy of breast cancer. Dr. Naomi Halas and her team have developed gold-shelled nanoparticles that target HER2-expressing cells. In preclinical tests using low-powered lasers, these “nanoshells” scatter light allowing researchers to image cells with high HER2 levels. With higher power, the nanoshells convert light into heat that kills the cancer cells without harming the nearby healthy tissue. Follow-up studies will be conducted in a mouse model with the ultimate goal of applying this technology in the clinic as a noninvasive cancer treatment.
- ◆ **Biomagnetic imaging and treatment of ovarian cancer using magnetic nanoparticles.** SBIR/STTR-funded Senior Scientific, Inc., is developing a novel technology that can rapidly detect ovarian cancer and localize the cancer site for treatment. The technology uses biomagnetic sensors (magnetic nanoparticles linked to antibodies recognizing ovarian cancer cells and angiogenic molecules) that bind to cancerous or precancerous lesions and are detected via imaging with Superconducting Quantum Interference Detector (SQUID) magnetic sensors. Studies are under way to examine the use of these particles for targeted drug delivery.
- ◆ **Nanoparticle self-lighting photodynamic therapy for ovarian cancer treatment.** Nomadics is creating a new efficient treatment modality for cancer by combining radiotherapy and photodynamic therapy (PDT), which may be more effective, cheaper, simpler, and more convenient than conventional PDT. They have designed and synthesized scintillation nanoparticles with strong, self-luminescence. Self-luminescence will be a critical component of this therapy especially for the treatment of ovarian cancer as to date it has not been possible to externally excite nanoparticles at a distance from the skin to the ovaries. Preliminary data indicate that this therapy is a promising modality for cancer treatment.
- ◆ **Nanocapsules for cancer gene therapy.** GeneSegues, Inc., is developing a nonviral gene therapy agent for the targeted treatment of advanced prostate cancer using the vertebrate *Sleeping Beauty Transposon DNA* system (SB-Tn System). The traditional gene therapy approach using viral vectors to replace defective genes with functional ones is problematic due to the host’s response to the viral vectors and the protein itself. The vertebrate SB-Tn System, prepared from Salmonid fish, is commercially available and has attractive features for use as a vector for gene therapy. GeneSegues, Inc., is using this DNA system to deliver a functional gene to replace a defective gene for the treatment of prostate



cancer. GeneSegues, Inc., is also generating nanocapsules made of Tenfibgen. Currently, GeneSegues, Inc., is evaluating the nanocapsulated transposon DNA system in mouse prostate TRAMPC 2 in vitro cell culture. A preclinical mouse model implanted with prostate TRAMPC-2 cells will be tested after a proof of concept is demonstrated.

Other Therapeutic Interventions

- ◆ **Breast reconstruction using tissue engineering.** Dr. Charles Patrick Jr. is exploring new techniques for breast reconstruction. He is developing a tissue engineering process in which a woman's own precursor fat cells are implanted under the skin of the chest to regrow the breast mound. When isolated cells are cultured, they tend to grow in flat sheets, so a three-dimensional support must be provided. Dr. Patrick developed a biodegradable support from plastic-like gels with a consistency similar to that of human fat tissue. The gels are inexpensive and can easily be molded to fit the specific shape of a tissue cavity resulting from mastectomy or lumpectomy. In addition, these gels have been formulated to contain a biochemical adhesion signal and a target for fat cell enzymes to eventually degrade the gel, leaving only the fat cells. When subcutaneous fat cells were seeded into the gel network, they were able to attach and grow before breaking down the network. These results are very promising for the development of tissue engineering to rebuild breast tissue after mastectomy.
- ◆ **Exercise and the repair of chemotherapy-induced damage to the immune system.** Dr. Andrea M. Mastro studied the effects of exercise on the immune system following chemotherapy for breast cancer. Women who entered the study were assigned to one of two groups: (1) a group that incorporated exercise into their recovery routine and (2) a group that did not initiate an exercise routine. The results of this study demonstrated that the exercisers had an increased maximum oxygen uptake and increased upper body strength. In addition, inflammation was decreased in the exercise group. Furthermore, data showed that the replenishment of responsive immune cells (lymphocytes) that had been eliminated during chemotherapy was faster in individuals in the exercise group when compared to the non-exercise group. Thus, exercise resulted in quicker replenishment of the immune system, less inflammation, and overall improved strength and stamina following chemotherapy for breast cancer.
- ◆ **Prostate cancer—What patients can do for themselves.** There are a number of excellent prostate cancer support groups that exist for prostate cancer patients. However, many prostate cancer patients feel that they are powerless to do anything themselves to directly





combat the disease. Two recent products of a PCRP-funded researcher, Dr. James Hebert of University of South Carolina, distill data from Dr. Hebert's own research as well as that of others into two guides that can be used at home by patients who desire to play an active role in fighting their disease: a *Prostate Cancer Intervention Manual* and a *Prostate Cancer Cookbook*. The intervention manual provides 12 weeks of lessons combining instruction in nutrition, mindfulness-based stress reduction, physical activity, and behavior change models that are known to decrease disease impact. The cookbook was prepared in collaboration with a chef and nutritionist to minimize foods implicated to exacerbate prostate cancer while at the same time making healthful and appetizing meals.

PRODUCTS TO IMPROVE MILITARY HEALTH AND READINESS

A key objective of the CDMRP is to fund research with direct relevance to military health that supports and improves the overall readiness and well-being of military service personnel. CDMRP-supported research, funded primarily through the PRMRP, has begun to yield products and technologies aimed at enhancing the health and readiness of service personnel and their families. For example, the PRMRP's Advanced Technology Development Award Mechanism, which was introduced in FY03, is expected to facilitate the advanced development and military acquisition of many valuable products with great potential to improve the health of our military forces, their families, and in many cases the civilian population.

The following are examples of exciting products and technologies that are being developed by PRMRP-supported investigators. More information on these and additional military relevant products can be found in Section VIII.

- ◆ **Field-deployable assay system to detect biological toxins.** Biological toxins are extremely lethal at very small concentrations and pose a major threat to military personnel deployed in hostile peacekeeping and combat situations. Thus, the ability to detect biological toxins at extremely low concentrations and at high specificity is paramount for the protection of our military personnel. Dr. Jeffrey Mason of the Armed Forces Institute of Pathology is generating a simple and reliable field-deployable assay system for detecting biological toxins with high specificity at low levels using immunoliposome-DNA amplification hybrids. Read more about this development on page VIII-7.
- ◆ **Advanced closed-loop frozen blood processing system.** Dr. Thomas Robinson and colleagues at Mission Medical Inc. have developed a self-contained, frozen blood processing system that





provides an efficient, more rapid, sterile process of glycerolization and deglycerolization of red blood cells for use in supplying blood to military personnel in remote military locations and on board naval ships. This processing system allows frozen blood to be available for use within 30–40 minutes and to be refrigerated for 21 days prior to use, as opposed to previous methods requiring 60 minutes of processing and allowing refrigeration for only 1 day prior to use.

- ◆ **Minirobot design for military telesurgery.** Remote surgical capability (i.e., telesurgery) is needed in the battlefield to improve the care of wounded military personnel in the critical hour after injury. However, current research and commercial robots are too large and heavy to effectively deploy military needs. Dr. Blake Hannaford and colleagues at the University of Washington are at the forefront of developing and evaluating a dramatically smaller surgical robot system to improve general and combat casualty care. It is hoped that this new system will be able to administer immediate care to soldiers wounded in battle and ultimately to save lives.
- ◆ **Implantable biochip for monitoring during hemorrhage.** Lactate levels have been shown to increase following injuries that result in tissue hypoxia. Lactate levels have also been found to correlate with the severity of injury, including hemorrhage and whole-body hypoxia. Thus, small molecules, such as lactate, can serve as important markers of severe hemorrhage. Dr. Anthony Guiseppi-Elie of Clemson University (formerly of Virginia Commonwealth University) is developing an implantable biochip that senses lactate levels. The biochip, implanted in injured combatants, would be capable of telemetered-reporting of local lactate levels and thereby improve triage and allocation of medical resources. Initial studies being conducted by investigators at the Virginia Commonwealth University are focused on implanting the biochips into skeletal muscle beds of animals. Lactate levels will then be continuously monitored during periods varying from several hours to 3 months after implantation. The biochip will eventually be tested in an animal model of severe hemorrhagic shock.
- ◆ **Supplement that prevents traveler's diarrhea.** Traveler's diarrhea represents a major problem in deployed U.S. forces as it is a leading cause of disease and temporary incapacitation. Dr. Stephen Savarino and researchers at the Naval Medical Research Center are developing bovine milk immunoglobulins as a supplement with activity against enterotoxigenic *Escherichia coli*, the predominant cause of traveler's diarrhea. Additional details about this research can be found on page VIII-6.





- ◆ **Portable sensor system to measure tissue perfusion.** Shock occurs when there is insufficient tissue perfusion to support cellular function. However, there are currently no methods or systems to assist medics in identifying when they have provided adequate resuscitation from shock. A project headed by Dr. Babs Soller of the University of Massachusetts Medical School, in collaboration with Luxtex Corporation, is supporting the development and testing of a prototype, portable sensor system based on near infrared spectroscopy to noninvasively measure tissue perfusion. More information about this prototype device can be found on page VIII-4.
- ◆ **Orthopaedic nail to prevent bone infections.** Bone infections arising from skeletal injuries represent a major health issue in the military. To prevent bone infections both during the initial stages of fracture stabilization and during fracture fixation, Dr. Irving Shapiro of Thomas Jefferson University is developing a bactericidal orthopaedic nail to which an antibiotic is chemically tethered and as such serves to eradicate both early and late infections. In addition, the tethered surface is coated with sol-gel film that releases antibiotic immediately following nail implantation. By preventing long-term infection as well as initiating antibiotic prophylaxis, these surfaces facilitate a quick recovery and return to duty.
- ◆ **Compact electroporation gene therapy system for improved wound healing.** Wounds are an inescapable consequence in battle, and impaired healing of war wounds remains a serious problem for the military. Dr. John Harmon and colleagues at Johns Hopkins University are examining electroporation-facilitated gene therapy with growth factors to improve wound healing. The investigators developed a small, compact device that is suitable for deployment in a military setting. The technique involves the application of electrical fields to make the cell membrane permeable and allow the entrance of macromolecules into cells. As a result, the electrical field causes small transient pores to open in the insulating lipid bilayer of the cells' membranes thereby enhancing cell membrane permeability. Using this novel bioengineered gene therapy system in a rodent combat wound model, preliminary data suggest that the delivery of growth factors by electroporation is a promising model for wound healing.
- ◆ **Adenoviral-based vaccine against malaria.** Malaria causes millions of deaths each year worldwide and poses a specific infectious threat to military personnel deployed to malaria-endemic regions. A project led by CAPT Thomas Richie, M.D., Ph.D., of the Naval



Medical Research Center is supporting the development of an adenoviral-based vaccine against malaria infection. The investigators plan on assessing the safety of the malaria vaccine in laboratory animals, followed by an Investigational New Drug (IND) application to the FDA. Clinical trials will then proceed in human volunteers for protective efficacy against malaria challenge and will conclude with final down-selection of ideal vaccine regimens for further field testing. Clinical trials are expected to begin in 2006.

- ◆ **Antiviral drugs for the treatment of hantavirus.** Hantaviruses cause two serious human diseases, hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS). Both of these diseases pose infectious threats to military personnel. However, there are currently no approved antiviral drugs for the treatment of either illness. Dr. Colleen Jonsson of Southern Research Institute is synthesizing and screening antiviral drugs for therapeutic intervention of hantavirus infections.
- ◆ **Telemedicine-based cardiac ultrasounds for use in infants.** Early detection of neonatal heart abnormalities in infants born at remote health care facilities can be limited due to inadequate equipment and expertise to conduct echocardiography. Dr. David Sahn and researchers at Oregon Health & Science University and Madigan Army Medical Center (MAMC) are collaborating to determine whether a combination of telemedicine and cardiac ultrasound can be used by trained primary care practitioners or nurses, with telemedicine supervision, to detect heart disease in infants born in remote health care facilities where on-site pediatric echocardiography is unavailable. Personnel at remote sites have been trained at MAMC for 2 or 3 days and given high performance hand-held ultrasound systems that have been set up to image infants. When necessary, they are connected to the pediatric cardiologists (echo experts) on a live videotelemedicine link running over NIPRNET Data links. The supervising pediatric cardiologist can see the examiner and the images and can control and fine tune the ultrasound system parameters. It is anticipated that results from this study could result in the expansion of qualified personnel who can perform echocardiography, thus impacting diagnosis, outcomes, and costs associated with infants suspected of having congenital heart disease. This proven technology could be used in the future to assist in diagnosis and treatment of military personnel deployed to remote areas of the world.





LOOKING AHEAD

CDMRP's efforts have resulted in the development of many new products to support the warfighter and revolutionize disease prevention, management, and treatment. The CDMRP will continue to support first-rate research with the ultimate goal of eradicating diseases.

IN THE NEWS

August 18, 2005

by Army Sgt. Sara Wood, American Forces Press Service,
dcmilitary.com, *The Journal*

Defense-Funded Device May Help Breast Cancer Fight

A device for detecting early stages of breast cancer is being developed at the University of Pennsylvania and partly funded by the Defense Department.

Officials say the device has the potential to save some of the thousands of lives breast cancer claims each year.

The device, a pager-sized handheld unit known as "iFind," has been in the development process since 1993, and a prototype is now being tested, said Army Col. Janet Harris, director of Congressionally Directed Medical Research Programs at Fort Detrick, MD.

The device is designed to be an accessory to self-breast exams, Harris said. It works by sending a near-infrared light through the breast tissue, looking for areas of high blood flow, sometimes indicating an abnormality. Britton Chance, emeritus professor of physics and radiology at the University of Pennsylvania Medical School in Philadelphia and developer of the device, said the light is absorbed by the extra blood in cancerous areas, therefore sending less light back to the device. If an abnormality is found, the device sounds an alarm and records the data and can be taken to a doctor for evaluation, Harris said.

The near-infrared light is safe and can be used often without risk, Harris said.

The goal is to market the device as a home-care item available in drug stores and convenience stores, Chance said. If research continues as planned, the device, which will probably cost about \$100, could be available in one or two years, he said. Initial results from research on the device have shown to be accurate more than 90 percent of the time, Harris said. This device promises to be a very useful tool in the fight against breast cancer, she said.

"The research has been very, very promising," she said. "If we can detect problems earlier, there is a greater chance we can successfully treat them."



The funding for this device is part of the Defense Breast Cancer Research Program, which began in 1992 when the Breast Cancer Coalition lobbied Congress for additional funding for research and prevention of breast cancer, Harris said. The program was assigned to the Defense Department because of its long history of biomedical research, she said.

Each year, an integration panel made up of scientists, breast cancer survivors and other experts meets to determine where the gaps are in research about breast cancer, Harris said. Based on these findings, a program announcement is put out soliciting proposals from scientists. The list of proposals then goes back to the integration panel and the members decide which proposals best meet the program's goal of detecting, preventing and treating breast cancer, she said.

The program's unique partnership between the military, breast cancer survivors and scientists makes for strong, well-rounded results, Harris said.

"Our belief is individuals working together and disciplines working together have a better chance of finding answers than one scientist alone," she said.

