REPORT TO THE U.S. CONGRESS

U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND

CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

PEER REVIEWED CANCER RESEARCH PROGRAM

8 February 2010

Peer Reviewed Cancer Research Program
Report to Congress

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BACKGROUND and PURPOSE OF REPORT

The US Army Medical Research and Materiel Command (USAMRMC) is a major subordinate Command of the United States Army Medical Command. The USAMRMC manages biomedical research and development programs that are part of the Department of Defense (DOD) and Army Science and Technology Master Plans. The Commanding General (CG), USAMRMC, is assigned authority as the Executive Agent for a number of medical research, development, and acquisition programs. Congressional appropriations totaling $5.4 billion for fiscal years 1992 to 2009 (FY92-09) assigned to USAMRMC are managed by the Office of the Congressionally Directed Medical Research Programs (CDMRP), a subordinate organization within the USAMRMC. Biomedical research supported by these funds include research in breast, prostate, lung, ovarian, melanoma and genetic cancers; pediatric brain tumors, neurofibromatosis; tuberous sclerosis complex; autism; Gulf War illness; psychological health and traumatic brain injury; deployment-related medical; and other research. The CDMRP is responsible for planning, coordinating, integrating, programming, budgeting, and executing the research programs. The CDMRP's flexible execution and management cycle includes the receipt of annual congressional appropriations, new research programs stakeholders meeting, vision setting, release of request for preproposals or proposals, preproposal screening and invitation to submit full proposals, full proposal receipt and review, recommendation of grants for funding, and oversight of research grants.

Following receipt of appropriations, each program's Integration Panel, an external advisory board of leading scientists, clinicians, military members, and disease survivors (consumers), recommends an investment strategy for the upcoming year that meets the unique needs of the research field, consumer community, and the military. The investment strategy is unique to each program and to each fiscal year cycle. By revisiting the investment strategy yearly, the program is able to explore innovative scientific ideas and research gaps spanning from basic laboratory science to clinical trials. Program announcements requesting research proposals through specific award mechanisms are subsequently prepared and released. Integration Panel members are not allowed to be involved either as collaborators or participants in the proposal processes including, but not limited to, concept design, proposal development, and conduct of research.

To ensure that each program's research portfolio reflects not only the most meritorious science, but also the most programmatically relevant research, the CDMRP developed a unique proposal review model based upon recommendations from the Institute of Medicine (IOM) 1993 report.[1] The IOM recommended a two-tier review procedure for research proposals composed of a scientific peer review and a separate programmatic review. The scientific peer review is conducted by an external panel recruited specifically for each peer review session. It involves the expertise of scientists, clinicians, and consumers. The peer review process includes evaluation of the proposals based on a criterion process as delineated in the program announcements. Each proposal is judged on its own scientific and technical merit with respect to the described criteria. The second tier of review, the programmatic review, is conducted by the Integration Panel. The Integration Panel is charged with reviewing the proposals based on the

scientific peer review ratings, a balanced portfolio, programmatic intent, and relevance to the congressional language. Scientifically sound proposals that best meet the program's interests and goals are recommended to the CG, USAMRMC, for funding. Once the CG approves the funding recommendations, awards are made in the form of 1- to 5-year grants, contracts, or cooperative agreements, and assigned to grants managers for full-cycle support of research and outcomes. The programs that comprise the CDMRP are scientifically sound, innovative, and responsive to congressional intent and the needs of the public. The USAMRMC and CDMRP have been praised by the IOM, which issued a report in 1997 stating it was favorably impressed with the processes implemented by the CDMRP and supported its continuation.[2]

In the Consolidated Security, Disaster Assistance, and Continuing Appropriations Act, 2009, a "peer-reviewed cancer research program" was appropriated for $16 million (M). In November 2008, the Peer Reviewed Cancer Research Program was assigned to USAMRMC and to the CDMRP for execution by the Assistant Secretary of Defense for Health Affairs, Force Health Protection. Continuing to support a peer reviewed cancer research program, the House Appropriations Committee on Defense 2010 has recommended funding of $20M. The House Appropriations Committee on Defense 2010 has directed that a report on the status of the FY10 Peer Reviewed Cancer Research Program as to the relevance of this type of research for service members and their families be provided to the congressional defense committees 8 February 2010. The current report details the status of the FY09-10 Peer Reviewed Cancer Research Program and the relevance of this type of research for service members and their families.

FY09 PEER REVIEWED CANCER RESEARCH PROGRAM

The Consolidated Security, Disaster Assistance, and Continuing Appropriations Act, 2009, directed that $16M be appropriated for the FY09 Peer Reviewed Cancer Research Program. Specific topics were noted and funds allocated for each topic area. The funds and directed topic areas included: $4M for research of melanoma and other skin cancers as related to deployments of service members to areas of high exposure; $2M for research of pediatric brain tumors within the field of childhood cancer research; $8M for genetic cancer research and its relation to exposure to the various environments that are unique to a military lifestyle; and $2M for research into noninvasive cancer ablation treatment including selective targeting with nano-particles. A stakeholders meeting was held on 23-24 February 2009. Participants included leading scientists, clinicians, military members, and consumers. Working groups from each topic area discussed gaps in scientific knowledge and research with respect to the state of the science, consumer concerns, and military medicine. Participants also recommended members for the External Advisory Board or Integration Panel. The Integration Panel was established and met on 28 April 2009 to conduct vision setting to review the recommendations made at the stakeholders meeting, and to craft a vision and mission of the program to represent the program priorities. The vision of the Peer Reviewed Cancer Research Program is to improve quality of life by significantly decreasing the impact of cancer on service members, their families, and the American public. In order to attain this goal, the mission is to foster groundbreaking research, team science, and partnerships for the development of better prevention, earlier detection, and more effective treatments for cancer. Program priorities were defined with respect to each topic area. The investment strategies for each topic area were designed to answer the gaps as defined by the stakeholders and Integration Panel. Several different program announcements, reflecting the

program priorities of each topic area, were released in June 2009. The two levels of review have been completed for the program announcements for grants that are relatively short in duration and modest funding amounts. Larger and longer awards require the investigator more time to prepare; as such, the final reviews will be completed in March 2010. Award negotiations are underway for those awards already recommended for funding, and final award agreements for all awards are expected to be in place no later than 30 September 2010.

FY10 PEER REVIEWED CANCER RESEARCH PROGRAM

Continuing to support a peer reviewed cancer research program, the House Appropriations Committee on Defense 2010 has recommended funding of $20M for a peer reviewed cancer research program that would research cancers not addressed in the breast, prostate, lung, and ovarian cancer research programs currently executed by the DOD and, specifically, the USAMRMC. Specific topics were noted to include melanoma and other skin cancers, pediatric brain tumors within the field of childhood cancer research, genetic cancer research and genomic medicine, kidney cancer, blood cancer, colorectal cancer, *Listeria* vaccine for infectious disease, and cancer and radiation protection utilizing nanotechnology.

An Integration Panel consisting of members of the FY09 Peer Reviewed Cancer Research Program Integration Panel and new members to represent the congressional target areas will be convened. The Integration Panel will meet on 26 March 2010 to reassess the vision and mission of the Peer Reviewed Cancer Research Program with respect to the new congressional language. Following any revisions of the vision and mission, the Integration Panel will discuss and recommend an investment strategy to meet the goals of the program and the congressional language. It is anticipated that program announcements will be released by April/May 2010, with scientific peer review in January 2011, and programmatic review in March 2010. Award negotiations will proceed and final award agreements are expected to be in place no later than 30 September 2011.

RELEVANCE TO SERVICE MEMBERS and THEIR FAMILIES

The House Appropriations Committee on Defense 2010 has directed that a report on the status of the FY10 Peer Reviewed Cancer Research Program as to the relevance of this type of research for service members and their families be provided to the congressional defense committees 8 February 2010. Multiple epidemiological studies have shown an increased incidence in several cancers in military populations, as compared to similar non-military populations. Members of the military are exposed to hazardous environments due to the nature of their service and deployments and, thus, are at risk for the development of different types of cancers.[3] The Veterans Health Administration (VHA) identified malignancies that may be associated with military service (VHA-Directive 2003-34 Attachment B). The Automated Central Tumor Registry of the DOD published data demonstrating that the incidence of melanoma was higher in the US military population in comparison to the US general population[4] A meta-analysis using published epidemiological data on cancer risk in male military pilots, civilian pilots, and flight attendants revealed a higher standardized incidence ratio for melanoma and other skin cancers in those with exposure to specific physical, chemical, or biological factors (electromagnetic fields,

jet fuel, volatile organic materials, etc). In addition, studies of common military exposures such as aircraft maintenance have been associated with an increased risk of cancer.[6]

Yamane reported that the most frequent cancers diagnosed in Air Force service members between 1989 and 2002 were different from the general US population, with a higher[7,8] incidence of melanoma, testicular, thyroid, cervical, and vulvar cancers in the Air Force population,[7] particularly cervical and vulvar cancer. Hodgkin's disease, a blood cancer, was the most common cancer diagnosis in men requiring a Physical Evaluation Board in the Navy.[9] Another review demonstrated a higher rate of prostate cancer in the military beneficiary population compared to the general population.[10]

The Selected Cancers Cooperative Study Group showed that veterans of the Vietnam War had a 50% increase in risk of Hodgkin's disease as compared to subjects who had not served in Vietnam.[11] Evidence links an increased risk for soft tissue sarcomas, non-Hodgkin's lymphoma, Hodgkin's disease, and chronic lymphocytic leukemia to Vietnam War service and exposure to herbicides such as Agent Orange.[12] Cancer patterns of Vietnam War military women nurses in comparison to non-Vietnam War military women nurses and the general population showed that site-specific cancer patterns were different, with excess deaths from pancreatic and uterine corpus cancers in the Vietnam War military women nurses.[13] As the configuration of the military population changes to include more women, consideration into research on their risks and exposures is critical.

Military families may also be at risk for developing cancers due to environmental exposures as shown by investigations into leukemia clusters near military aviation facilities.[14] Additionally, transgenerational occupational exposures may lead to increased risk of cancer development in progeny. Children of Vietnam War veterans have an increased risk of developing acute myeloid leukemia.[12] As shown by Hicks et al,[15] children of fathers in the Air Force had a higher incidence of tumors of the central nervous system (brain and spinal cord) and lymphatic system. It is known that pediatric brain tumors are the leading cause of death from childhood cancers.[16] The VHA acknowledged the toll of cancer on service members and their families when releasing its National Cancer Strategy in 2003 (VHA-Directive 2003-34). A serious illness in a family member, such as cancer, may have consequences on the warfighter's ability to complete the mission. A healthy family unit, free of serious illnesses, allows the service member to focus on his or her role as a warfighter and facilitates the overarching military mission. There are a total of 355,442 military beneficiaries with a cancer diagnosis, for a prevalence of 4.1%, comprised of over 60 different cancer types.[17] The cost of cancer care within the Military Health System in FY02 was over $1 billion.[17] Funding studies on the detection, diagnosis, treatment, and prevention of these diseases benefits both the warfighter and the American public, ultimately leading to increased survival rates and decreased costs of medical care.

In summary, the CDMRP, USAMRMC, manages the FY09-10 Peer Reviewed Cancer Research Program using its established and highly recognized management process. Members of the various services will provide input and recommendations to assist in the request for militarily relevant research proposals. The FY10 Peer Reviewed Cancer Research Program directly impacts military welfare by providing research into cancers that may develop due to exposure in various uniquely military environments. Pursuant to congressional direction, the Peer Reviewed

Cancer Research Program will focus on militarily relevant areas of cancer research. The CDMRP will plan, execute, and manage the FY09-10 Peer Reviewed Cancer Research Program with the same rigor and integrity it has demonstrated for other research programs.

REFERENCES

1. Strategies for Managing the Breast Cancer Research Program: A Report to the U.S. Army Medical Research and Development Command (1993) Committee to Advise the Department of Defense on Its Fiscal Year 1993 Breast Cancer Program, Institute of Medicine, National Academy Press, Washington, DC.

2. A Review of the Department of Defense's Program for Breast Cancer Research (1997) Committee to Review the Department of Defense's Breast Cancer Research Program, Institute of Medicine, National Academy Press, Washington, DC.

3. Bullman TA and Kang HK. 1994. The effects of mustard gas, ionizing radiation, herbicides, trauma, oil smoke on US military personnel: The results of veteran studies. *1994 Annu Rev Public Health* 15:69-90.

4. Department of Defense Automated Central Tumor Registry, http://www.afip.org/consultation/actur/data00

5. Buja A, Lange JH, Perissinotto E, Rausa G, Grigoletto F, Canova C, and Mastrangelo G. 2005. Cancer incidence among male military and civil pilots and flight attendants: An analysis of published data. *Tox Ind Health* 21:273-282.

6. D'Este C, Attia JR, Brown AM, Gibberd R, Tavener M, Guest M, Horsley K, Harrex W, and Ross J. 2008. SHOAMP Study Team. 2008 Cancer incidence and mortality in aircraft maintenance workers. *Am J Ind Med* 51:16-23.

7. Yamane GK. 2006. Cancer incidence in the U.S. Air Force: 1989-2002. *Aviat Space Environ Med* 77:789-794.

8. Surveillance Epidemiology and End Results, http://seer.cancer.gov/.

9. Ajene A, Bohnker B, Malakooti MA, Riegodedios A, and Sack DM. 2004. Neoplasms in the Navy, 1998-2000: A descriptive analysis of the Physical Evaluation Board database. *Military Medicine* 169:707-711.

10. Zhu K, Devesa SD, Wu H, Zahm SH, Jatoi I, Anderson WF, Peoples GE, Maxwell LG, Granger E, Potter JF, and McGlynn KA. 2009. Cancer incidence in the U.S. Military population: Comparison with rates from the SEER Program. *Cancer Epidemiol Biomarkers Prev* 18:1740-1745.

11. The Selected Cancers Cooperative Study Group. 1990. The association of selected cancers with service in the US military in Vietnam. I. non-hodgkin's lymphoma. *Arch Intern Med* 150:2473-2483.

12. Frumklin H. 2003. Agent orange and cancer: An overview for clinicians. *CA Cancer J Clin* 53:245-55.

13. Dalanger NA, Kang HK, and Thomas TL. 1995. Cancer mortality patterns among women who served in the military: The Vietnam Experience. *J Occup Environ Med* 37:298-305.

14. Steinmaus C, Lu M, Todd RL, and Smith AH. 2004. Probability estimates for the unique childhood leukemia cluster in Fallon, Nevada, and risks near other U.S. Military aviation facilities. *Environ Health Perspect* 112:766-771.

15. Hicks N, Zack M, Caldwell GG, Fernbach DJ, and Falletta JM. 2006. Childhood cancer and occupational radiation exposure in parents. *Cancer* 53:1637-1643.

16. Pediatric Brain Tumors Program Review Group, http://prg.nci.nih.gov/pediatrics

17. Crawford RS, Wu J, Park D, and Barbour GL. 2007. A study of cancer in the military beneficiary population. *Military Medicine* 172:1084-1088.