The Defense Health Research Consortium

June 8, 2017

The Honorable Kay Granger  The Honorable Peter Visclosky
Chair  Ranking Member
Subcommittee on Defense  Subcommittee on Defense
Committee on Appropriations  Committee on Appropriations
H-405 Capitol Building  1016 Longworth House Office Bldg
Washington, DC 20515  Washington, DC 20515

Dear Madame Chairman Granger and Ranking Member Visclosky:

As you begin work on the Fiscal Year 2018 (FY18) Defense Appropriations bill, we write to request your continued support for the critical and highly successful defense health research programs funded through the Congressionally Directed Medical Research Programs (CDMRP) at the Department of Defense (DoD). We deeply appreciate your support in a challenging fiscal environment for these programs during the FY17 budget process. As in previous years, you both exhibited extraordinary leadership in ensuring continuity in funding and operations for defense health research programs.

The highly innovative research portfolio supported by the CDMRP fuels scientific discovery by funding high impact research not sponsored by the National Institutes of Health (NIH), the Department of Veterans Affairs (VA) and other federal agencies. Many of the programs’ award mechanisms propel the exploration of revolutionary ideas and concepts, and focus on the potential of having a significant impact upon both their respective fields of research and support and treatment for members of the military. Defense health research programs are worthy of continued federal support for the following reasons:

- **Directly relevant to DoD-prevalent conditions:** The medical research programs at DoD directly impact the health and lives of the U.S. military, their families, veterans and the public. Programs provide groundbreaking research on psychological health, Gulf War Illness, spinal cord injury, and hearing and vision loss (which comprise a significant portion of current battlefield injuries). Research also focuses on infectious diseases that may threaten operational readiness and health security, and why diseases like ALS and multiple sclerosis occur at greater rates in those who have served in the military. The DoD’s defense health research program has also funded the orthopedic research program that has resulted in new limb-sparing techniques to save injured extremities, avoid amputations, and preserve and restore the functions of injured extremities.

Equally important, this disease-specific approach includes important medical research programs related to several forms of cancer (breast, blood, colorectal, kidney, melanoma, pancreatic, brain tumors, lung, ovarian, prostate, stomach, liver and cancers related to radiation exposure) and other disorders (like neurofibromatosis and tuberous sclerosis complex) that have led to breakthroughs on nerve regeneration, traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD).
Complementary – and not duplicative – of other federal research: Defense health research program grants neither duplicate nor supplant NIH or VA research efforts, but rather enhance those efforts. They fund highly innovative projects – support that is typically unavailable. For example, programatically related VA research funding is only available to VA employees (at least 0.625 full-time equivalent). CDMRP funds the best-qualified proposals from researchers and research teams at top research universities and medical centers. The NIH and DoD medical research portfolios have symbiotic relationships, allowing NIH-funded basic research to serve as a foundation for groundbreaking, disorder-targeted research at DoD. NIH and DoD program officers meet regularly to ensure collaboration and prevent duplication.

Cutting-edge and focused on cures: While the NIH funds primarily high-quality basic biomedical research, the defense health research programs provide essential emphasis on and support for finding innovative cures or new therapeutics for medical conditions. For several disorders, DoD breakthroughs have led to new clinical trials, new drug products, and novel procedures that are making a difference in the everyday lives of affected patients and families. For example, research funded by DoD led to the development of the only treatment for tuberous sclerosis complex approved by Food and Drug Administration. The ALS Research Program is supporting translational research and has developed four potential treatments for the disease, for which an effective treatment currently does not exist.

Agile, adaptable, and collaborative: Each of the separate programs is guided by a specific vision and mission statement, which in addition to incorporating Congressional direction, reflect rapid change in knowledge, address research gaps, and prevent overlaps. Annual funding prevents out-year budget commitments, which in turn further enhances programmatic flexibility. Many DoD programs find (or even work to develop) and fund collaborative and consortium-based research, helping to bring unique, interdisciplinary, inter-institutional, collaborative efforts to bear on complex medical research issues unlikely to be solved though the inherent limits of individual researchers.

Competitive and unique peer review process: While Congress allocates funding through the annual Defense Appropriations Act to specific medical conditions, it does not direct the programs’ dollars to specific researchers. These programs utilize an efficient multi-tiered process that includes multiple stages of peer review, including two levels of formal peer review of final proposals. Proposals are scored in a number of key areas such as scientific merit and impact for patients and the military, providing a robust comparative basis for helping accomplish the program’s mission of finding and funding the best research related to these important medical conditions.
• Consumer review: All defense health research programs incorporate the full and equal participation of consumer reviewers at every stage of the multi-tiered review process – a novel and valuable practice in medical research funding. Consumers – people actually affected by the disease or medical condition – help ensure the program’s funded research will have the greatest impact on those who are affected. Consumer reviewers also help inform and educate their disease advocacy communities and others.

• Generating economic growth across the United States: Research activities promote job growth and encourage long-term economic development through innovation. It has been estimated that for every dollar awarded in biomedical research grants, more than $2 of additional business activity is created. Defense health research grants are awarded to universities and institutes in every state in the country.

In short, the well-executed and efficient programs within the defense health research programs demonstrate responsible government stewardship of taxpayer dollars and benefit current and former military service members, the general patient population, and our nation’s economy.

Perhaps most importantly, DoD’s innovative approaches to funding biomedical research have led to a number of significant breakthroughs and achievements, contributing to national security and the health and welfare of U.S. Armed Forces personnel and their dependents. Enclosed is a detailed white paper providing several examples. Continued federal funding will only build on these successes.

Lastly, we are concerned about reports that Congress may not complete the fiscal year 2018 appropriations process and instead attempt to pass a long-term continuing resolution. This approach would have devastating consequences for medical research, creating unnecessary instability and uncertainty in the grant solicitation, grant review, and grant making processes at DoD. This will also delay the ability of DoD to most effectively convene programmatic panels to identify and implement programmatic changes, effectively convene peer-review panels to provide thorough review of grant applications, and conduct appropriate negotiations to ultimately award FY18 grants.

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Asthma and Allergy Foundation of America  
Autism Speaks  
Beyond Celiac  
Bladder Cancer Advocacy Network  
Children’s Heart Foundation  
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Coalition for National Security Research (CNSR)  
Crohn’s & Colitis Foundation  
Cure HHT  
Debbie’s Dream Foundation: Curing Stomach Cancer  
debra of America  
Digestive Disease National Coalition  
Duke University  
Duke University School of Medicine  
Dystonia Medical Research Foundation  
Epilepsy Foundation  
Fight Colorectal Cancer  
FORCE: Facing Our Risk of Cancer Empowered  
Foundation to Eradicate Duchenne  
George Mason University  
GBS|CIDP Foundation International  
Global Health Technologies Coalition  
Hepatitis B Foundation  
Hepatitis Foundation International  
Indiana University
International Foundation for Functional Gastrointestinal Disorders
International Myeloma Foundation
Interstitial Cystitis Association
Johns Hopkins University
LAM Foundation
Littlest Tumor Foundation
Living Beyond Breast Cancer
Lung Cancer Alliance
Lupus Foundation of America
Lupus Research Alliance
Lymphoma Research Foundation
Malecare Cancer Support
The Marfan Foundation
Melanoma Research Foundation
The Michael J. Fox Foundation for Parkinson’s Research
Michigan State University
Muscular Dystrophy Association
National Alliance for Eye and Vision Research
National Autism Association
National Brain Tumor Society
National Kidney Foundation
National Multiple Sclerosis Society
National Pancreas Foundation
NephCure Kidney International
Neurofibromatosis Midwest
Neurofibromatosis Network
Ovarian Cancer Research Fund Alliance
Pancreatic Cancer Action Network
Parent Project Muscular Dystrophy (PPMD)
Penn State University
Phelan-McDermid Syndrome Foundation
Prostate Cancer Clinical Trials Consortium, LLC
Prostate Conditions Education Council
Pulmonary Hypertension Association
Research!America
Scleroderma Foundation
The Sergeant Sullivan Circle
Society of Gynecologic Oncology
Stony Brook University
Susan G. Komen
Texas NF Foundation  
Tuberous Sclerosis Alliance  
University of Central Florida  
University of Cincinnati  
University of Kansas  
University of New Mexico Health Sciences Center  
University of Pittsburgh  
University of Washington  
U.S. Hereditary Angioedema Association  
Us TOO International Prostate Cancer Education & Support  
Vanderbilt University  
Veterans for Common Sense  
The Veterans Health Council  
Vietnam Veterans of America  
Weill Cornell Medicine  
ZERO - The End of Prostate Cancer  

Enclosure  
cc: Members, House Appropriations Committee
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Duke University School of Medicine
Dystonia Medical Research Foundation
Epilepsy Foundation
Fight Colorectal Cancer
FORCE: Facing Our Risk of Cancer Empowered
Foundation to Eradicate Duchenne
George Mason University
GBS|CIDP Foundation International
Global Health Technologies Coalition
Hepatitis B Foundation
Hepatitis Foundation International
Indiana University
International Foundation for Functional Gastrointestinal Disorders
International Myeloma Foundation
Interstitial Cystitis Association
Johns Hopkins University
LAM Foundation
Littlest Tumor Foundation
Living Beyond Breast Cancer
Lung Cancer Alliance
Lupus Foundation of America
Lupus Research Alliance
Lymphoma Research Foundation
Malecare Cancer Support
The Marfan Foundation
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NephCure Kidney International
Neurofibromatosis Midwest
Neurofibromatosis Network
Ovarian Cancer Research Fund Alliance
Pancreatic Cancer Action Network
Parent Project Muscular Dystrophy (PPMD)
Penn State University
Phelan-McDermid Syndrome Foundation
Prostate Cancer Clinical Trials Consortium, LLC
Prostate Conditions Education Council
Pulmonary Hypertension Association
Research!America
Scleroderma Foundation
The Sergeant Sullivan Circle
Society of Gynecologic Oncology
Stony Brook University
Susan G. Komen
Texas NF Foundation
Tuberous Sclerosis Alliance
University of Central Florida
University of Cincinnati
University of Kansas
University of New Mexico Health Sciences Center
University of Pittsburgh
University of Washington
U.S. Hereditary Angioedema Association
Us TOO International Prostate Cancer Education & Support
Vanderbilt University
Veterans for Common Sense
The Veterans Health Council
Vietnam Veterans of America
Weill Cornell Medicine
ZERO - The End of Prostate Cancer

Enclosure
cc: Members, House Appropriations Committee
Defense Health Research Programs
Relevance to National Security and Military Families
June, 2017

- **ALS**: According to studies by the DoD, VA, NIH and Harvard University, people who have served in the military are approximately twice as likely to develop ALS as the general population\(^1\). Most recently, researchers found an increased risk of ALS among those who served in Iraq and Afghanistan\(^2\). The VA has recognized the connection between ALS and military service by establishing a presumption of service connection for ALS\(^3\). The VA presumes that ALS was incurred in or aggravated by service in the military. Moreover, the presumption applies to any veteran who served, from any branch of the military, regardless of where or when a veteran served (home or abroad, during a time of peace or conflict) and regardless of when they were diagnosed with the disease following discharge (e.g., 1 year after service or 50 years). The ALS Research Program is supporting translational research and has developed four potential treatments for the disease, for which an effective treatment currently does not exist.

- **Autism**: According to the Centers for Disease Control and Prevention, 1 in 68 children have an autism spectrum disorder (ASD)\(^4\). The Department of Defense reports that 18,452 active duty family members had a diagnosis of ASD at the end of fiscal year 2013.\(^5\) This reflects a 77% increase in ASD diagnoses in just four years from fiscal year 2009.\(^6\) Military families are affected substantially by the financial and emotional costs of raising a child with autism and this impact extends to the performance and readiness of service members and their units. It is well known that children with autism, if they receive prompt treatment and early intervention services, can improve their long-term functional prospects dramatically.\(^7\) Research supported by the Autism Research Program has addressed current needs such as difficulties accessing care associated with mobile military families\(^8\) and gastrointestinal (GI) disorders which are among the most common medical conditions associated with autism.\(^9\) Additional research will help to improve treatment and intervention directly serving the interests of service members and DoD families impacted by autism as well as the medical, educational, healthcare and service professionals who serve the needs of the autism community within and beyond.

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\(^3\) 38 CFR 3.318 – Presumptive service connection for amyotrophic lateral sclerosis.


• **Bladder Cancer:** Bladder cancer is the 5th most common cause of cancer in the United States, and the 4th most common cancer within the U.S. veteran population.\(^{10}\)\(^{11}\) Smoking is a leading risk factor associated with bladder cancer, but male sex, advancing age, and white race are also strong risk factors. Despite mounting evidence in the 1950s of the adverse health effects of smoking and tobacco use, the military continued to include cigarettes in rations until 1975.\(^{12}\) Smoking prevalence in the veteran population is reported to be 27% compared to 21% in the non-veteran population.\(^{13}\) It has also been estimated that the prevalence of smoking is 43% higher in the population treated by VA hospitals compared to age matched controls.\(^{14}\) From 1961 to 1971, approximately 1,000,000 gallons of Agent Blue, containing high levels of arsenic were sprayed over the southern region of Vietnam.\(^{15}\) Inorganic arsenic compounds have been linked to cancer of the bladder.\(^{16}\) In addition, from the 1950s through the 1980s, people serving or living at the U.S. Marine Corps Base Camp Lejeune, North Carolina, were potentially exposed to drinking water contaminated with industrial solvents, benzene, and other chemicals. This chemical exposure may have led to adverse health conditions, including bladder cancer.\(^{17}\)

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\(^{15}\) H.R.2519 - Victims of Agent Orange Relief Act of 2013113th Congress (2013-2014).


\(^{17}\) US Department of Veterans Affairs, July, 2015, CAMP LEJEUNE: PAST WATER CONTAMINATION, IB 10-449.
• **Bone Marrow Failure Disorder:** Myelodysplastic Syndrome (MDS) is a rare bone marrow failure disorder that increases the risk of developing AML, a fast-growing cancer of the blood. Exposure to benzene, historically used extensively by the military, has been well established as a risk factor for myeloid malignancy, and is significantly associated with development of MDS and AML. Both ground troops and onboard support personnel have been at risk for significant exposure to dioxin, benzene, and Agent Orange herbicide during the Vietnam war. More recently, veterans stationed at Camp Lejeune between 1953 and 1987 were found to have potential exposure to industrial solvents in well water, inclusive of benzene, as recognized by the VA. The Bone Marrow Failure Research Program supports critical research into disease etiology and therapy development pathways. Continued research into bone marrow failure etiology and molecular genomics is essential to saving lives.

• **Breast Cancer:** According to recent demographic reports, active duty females and female spouses under the care of the United States military health system total approximately 1.4 million women. Assuming normal risk of developing breast cancer across a woman’s lifetime (1 in 8), 175,000 cases of breast cancer are expected to be diagnosed within that population. Furthermore, a 2009 study suggested that active duty females have a higher incidence of breast cancer than the general population, which would increase the expected number of breast cancer cases. Therefore, breast cancer is a significant issue for the United States military health system. Additionally, military families are affected substantially by the financial and emotional costs of breast cancer and this impact extends to the performance and readiness of service members and their units. The Breast Cancer Research Program has invested in research to better understand how and why breast cancer is initiated, factors that increase risk, and more advanced ways to detect and treat this disease including innovative treatments for breast cancer that are both more effective and less toxic (e.g. sentinel lymph node biopsy, trastuzumab for HER2+ breast cancer, vaccines and immunotherapies for breast cancer, nanoparticle-based drug delivery systems).

- **Colorectal Cancer:** According to a study published in the June 2009 issue of Cancer Epidemiology, Biomarkers & Prevention, researchers found that colorectal cancer was one of the most common forms of cancer among active duty military personnel. Yet, screening rates among military personnel for colorectal cancer remain low. As published in the 2009 Humana Military’s Clinical Quality Report Card, only 58 percent of those in the military were up to date with screening in 2008. The Peer Reviewed Cancer Research Program (PRCRP) has supported research into treatments for colorectal cancer, including research into treatments that would block the growth of metastatic colorectal cancer. (CA093415\(^28\), CA111002\(^29\), CA100879\(^30\), CA100512P1\(^31\), CA093176\(^32\))

- **Crohn’s Disease and Ulcerative Colitis (Inflammatory Bowel Diseases):** The prevalence of Crohn’s Disease and Ulcerative Colitis (collectively known as inflammatory bowel diseases-IBD) increased by two to threefold among veterans from 1998 to 2009. Researchers found nearly 17,000 unique incident cases of Crohn’s Disease and over 26,000 cases of Ulcerative Colitis within the military population during this time. Due to the population studied, 94% of the cases were in men. In 2009, the age and gender standardized prevalence rate of Crohn’s Disease was 287 per 100,000 VA users and the prevalence rate for Ulcerative Colitis was 413 per 100,000 VA users.\(^33\) Despite having a large population study, much is yet to be known about etiology or cause of these diseases, therefore continued research in this area is necessary to advance knowledge about IBD.

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• **Gulf War Illness**: According to a 2014 update report of the Congressionally-mandated Research Advisory Committee on Gulf War Veterans’ Illnesses (RAC), “Scientific research [since 2008] . . . supports and further substantiates . . . that Gulf War illness is a serious physical disease, affecting at least 175,000 veterans of the 1990-1991 Gulf War, that resulted from hazardous exposures in the Gulf War theater.” Studies reviewed in the report found an elevated incidence of Lou Gehrig’s disease (ALS) among Gulf War veterans as well as significantly elevated rates of death due to brain cancer among those who were most exposed to the release of nerve gas by the destruction of the Khamisiyah Iraqi arms depot. In addition to improving the health of Gulf War veterans, important discoveries made by the GWIRP will also help protect current and future American servicemembers who are at risk of similar toxic exposures.

• **Hydrocephalus**: Hydrocephalus is a chronic neurological condition that affects over one million people in the US. Hydrocephalus has no cure and the only treatment option is brain surgery. Often thought of as a pediatric condition, children can be born with hydrocephalus or develop it after birth, with the premature baby population being at particular risk of post-hemorrhagic hydrocephalus as a result of a brain bleed. Hydrocephalus is the leading cause of brain surgery in children. However, anyone at any time can develop hydrocephalus as it can be caused by a traumatic brain injury, tumor, infection, or as part of the aging process for reasons which are still not understood. This makes hydrocephalus’ impact and reach within our military population deep and wide. Families can be affected if their children are born with or develop the condition. Active service members and veterans who have experienced traumatic brain injury are particularly vulnerable to developing hydrocephalus. Since 2000, more than 333,000 U.S. service members have sustained a traumatic brain injury. Over 35,000 are at risk of developing hydrocephalus due to the severity of the injury. The Department of Defense does not currently track the development of hydrocephalus, so, while Normal Pressure Hydrocephalus (NPH) affects elderly adults, it is not known if previous injury,

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35 Research Advisory Committee on Gulf War Veterans’ Illnesses, pp. 23-25.
36 Research Advisory Committee on Gulf War Veterans’ Illnesses, pp. 23-26.
37 Research Advisory Committee on Gulf War Veterans’ Illnesses, pp. 1; 4; 5; 13; 78; 83. And: Institute of Medicine, N. R. C., 2010. Gulf War and Health: Volume 8 - Health Effects of Serving in the Gulf War. The National Academies Press, Washington, DC, pp. 10; 260-64.
even mild injury, increases the risk of NPH. It is estimated that NPH affects over 700,000 seniors in the United States, including over 180,000 veterans.  

- **Kidney Cancer:** Kidney cancer affects military personnel and their dependents and veterans. The body insult that causes kidney cancer may occur during active service but may not appear until later in life therefore affecting veterans more frequently than their US civilian counterparts. In a 2012 study identifying cancer incidence among patients of the United States Veterans Affairs Healthcare System kidney cancer was the 6th leading cancer. Vietnam veterans exposed to Agent Orange have had kidney cancer. Exposure to ionizing radiation, chemicals and hazardous materials can cause kidney cancer. Smoking, hypertension and obesity are high kidney cancer risk factors. A cohort of about 210,000 U.S. veterans followed for 26 years was analyzed for a study examining the role of smoking in the development of renal cancer. The follow-up of these military veterans revealed 719 deaths from renal cancer, making this one of the largest studies of renal cancer and cigarette smoking. Current smokers had a 47 percent increase in risk for renal cancer relative to nonsmokers, and the relative risk correlated positively with the number of cigarettes smoked per day. These results were later confirmed by several independent studies showing that about one fifth to one third of renal cancer is associated with smoking. Cigarette smoking generates oxidative stress, which is implicated as one of the direct chemical factors in renal oncogenesis. Most recently, researchers from Oak Ridge National Laboratory demonstrated a near real-time generation of hydrogen peroxide by cigarette smoke. According to a 2014 report issued by the Centers for Disease Control and Prevention US Marines and their families stationed at Camp Lejeune, North Carolina have a 35% higher risk of contracting kidney cancer than their US counterparts due to contaminated drinking water.  

- **Leukemia/Lymphoma/Multiple Myeloma:** Many of the blood cancers are linked to chemical and radiologic exposure during deployment. Leukemia, non-Hodgkin Lymphoma (NHL), Hodgkin Lymphoma (HL), and multiple myeloma have all been connected to chemical weapons, or storage, ionizing radiation, herbicides, electromagnetic fields, jet fuel, organic materials, etc. The Selected Cancers Cooperative Study Group showed that veterans of the Vietnam War had a 50% increase of risk of HL as compared to subjects who had not served in Vietnam. Evidence associates an increased risk for NHL, HL, and chronic lymphocytic leukemia to Vietnam War service and exposure to herbicides such as Agent Orange.  

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47 2014 CDC Camp Lejeune Contaminated Drinking Water Report  
• **Lung Cancer**: Numerous studies over the years published by the Institute of Medicine, *Cancer*, Military Medicine, *Chest* and others have shown that lung cancer incidence and mortality rates, due to much higher smoking rates and exposures to known carcinogens during active duty, are an estimated 25% – 30% higher in the military than in civilian populations. Of growing concern is the lung cancer risk among ground troops deployed during the Gulf Wars whose exposures included asbestos, chromium, diesel exhaust, radon, crystalline silica, pesticides, pollutants and particulate matter from burn pits, oil well fires and the destruction of chemical weapons including sarin gas. Research focused on these veterans is urgently needed. Given lung cancer’s long latency period, and the fact that the average age of Gulf War veterans is now in the mid-fifties, research projects should incorporate CT screening as a platform.

• **Lupus**: Lupus is a debilitating autoimmune disease up to three times more common among African Americans, Hispanics and Native Americans and it affects over one-and-a-half million persons in the U.S. --90 percent of whom are women. The disease often strikes young women of childbearing age who experience symptoms such as intense fatigue and exhaustion, joint pains, cognitive and memory problems, and skin rashes. It can also manifest in kidney problems, premature heart disease, strokes or lung inflammation. Defense Department data show that women now make up a much greater share of our armed forces than they have at any time in U.S. history. Women account for almost 15 percent of active duty Service Members, almost 20 percent of Reserves and 15.5 percent of the National Guard. A recent Pew Research Center report found that the active-duty female force is racially diverse --nearly one-third (31%) of active-duty women are black (including black Hispanics). Twelve percent of women in the Armed Forces report their ethnicity as Hispanic, whether white or black. Our nation now has over 2 million women veterans, about 9 percent of the total veteran population, a figure expected to rise to 15 percent by 2035.  

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51 A Study of Cancer in the Military Beneficiary Population, Guarantor: Raymond Shelton Crawford III, MD MBA, Contributors: Raymond Shelton Crawford III, MD MBA; Julian Wu, MD MPH; Dae Park, MD; Galen Lane Barbour, MD; Military Medicine, Vol. 172, October 2007.


• **Melanoma:** A 2000 "Annals of Epidemiology" study comparing mortality among WWII veterans of the Pacific and European Theaters found that Pacific Theater Prisoner of War veterans had an estimated 3-fold higher risk of dying from melanoma than veterans of the European Theater, concluding that exposure to high levels of solar radiation in young adulthood is associated with a higher risk of melanoma mortality.\(^{57}\) Given this information, U.S. military personnel currently stationed in Iraq and Afghanistan, where the intensity of sun exposure is similar to that of the Pacific, have the potential for a long-term risk of melanoma. According to the American Cancer Society, the American Academy of Dermatology and the Melanoma Research Foundation, skin cancer is the most commonly diagnosed cancer in the United States. Melanoma, the deadliest type of skin cancer, kills an estimated 10,000 Americans each year. Furthermore, people of all ages, races and genders are at risk. Melanoma is the most common form of cancer for young adults 25-29, the second most common form of cancer for young people 15-29 and SEER data suggests that the majority of people diagnosed with melanoma are white men over the age of 50.\(^{58}\)\(^{59}\)\(^{60}\)

• **Multiple Sclerosis:** According to a 2003 study in the Annals of Neurology, 5,345 veterans that served in Vietnam and the first Gulf War were diagnosed with MS that was deemed "service-connected."\(^{61}\) The relative risk for developing MS also was significantly higher for this group of veterans than those who served in World War II and the Korean War.\(^{62}\) An advisory committee commissioned by the VA recently recommended further study into the potential link between combat service and the increased risk of developing MS.\(^{63}\) By studying this population, scientists might be able to understand the cause and triggers of MS and develop effective treatments.

• **Neurofibromatosis (NF):** NF research critically addresses areas of great clinical need directly affecting the health of our soldiers. The genetic information learned from NF research holds the key to understanding a number of health issues that affect the war fighter, as well as the general population, including cancer, bone fracture and repair, vascular disease, wound healing and nerve regeneration, deafness, behavioral and psychosocial issues, learning disabilities, muscle weakness, and pain. For example, NF often requires surgical removal of nerve tumors, which can lead to nerve paralysis and loss of function, similar to nerve damage sustained by the war fighter after injury.

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The Gulf War era multiple sclerosis cohort: age and incidence rates by race, sex and service.
Understanding how nerves and skin might be regenerated and functionally restored will have significant quality of life value for affected individuals. Current NF research aims to develop a rapid approach for taking a person’s skin stem cells and differentiating them into cell types that need replacing after injury. This work will advance skin regeneration research and elucidate the potential of skin derived stem cells to make other cell types such as nerve cells, to restore function after injury. In another example, orthopedists, NFologists and tissue engineers are collaborating to investigate innovative technologies that will improve the healing of challenging and recurring bone breaks in NF patients, research that directly benefits war fighters with major bone breakages. Therefore, due to the nature of the wounds and recovery that soldiers are enduring, NF research is of particular benefit to the military mission. Proposals include: NF080017, NF120087, NF110052 and NF110052.

- **Osteoarthritis (OA):** Current research suggests that stresses placed on joints during military training activities, increased rates of injury, and increased weight of military packs have led active duty soldiers and veterans to have twice the rate of Osteoarthritis (OA) when compared to non-military populations. In fact, OA is the leading cause of disability and medical discharge in active service members under the age of 40. Rheumatoid arthritis (RA) strikes at the peak one’s career (mid-late thirties/forties) and often leads to early retirement and disability. CDMRP research funding for OA and RA could help identify arthritis prior to the onset of symptoms. This research could help identify medical and physical interventions to prevent or minimize joint damage and slow or stop the arthritis disease process before joints are permanently damaged. Targeted research efforts would focus on examining genetic factors, ways to improve diagnosis, screening, and treatment options. (Proposals: 101035, 120839, 130776)

- **Ovarian Cancer:** In the 45 years since the War on Cancer was declared, ovarian cancer mortality rates have not significantly improved. According to the American Cancer Society, it is estimated that in 2017, more than 22,400 American women will be diagnosed with ovarian cancer, and approximately 14,080 will lose their lives to this terrible disease. Ovarian cancer is the fifth leading cause of cancer death in women. Currently, more than half of the women diagnosed with ovarian cancer will die within five years. Of the 850,000 female service members, wives of active duty military and adult daughters of active duty military, approximately 11,800 will be diagnosed with

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64 Elefteriou, Florent. Neurofibromin Function in Chondrocytes.  
65 Kim, Aerang. Phase I/II Trial of an Hsp90 Inhibitor in Combination with an mTOR Inhibitor for Patients with Refractory Malignant Peripheral Nerve Sheath Tumors.  
66 Plotkin, Scott. Phase 2 Study of Bevacizumab in Children and Young Adults With NF 2 and Progressive Vestibular Schwannomas.  
67 North, Kathryn. A Randomized Placebo-Controlled Study of Lovastatin in Children with Neurofibromatosis Type 1 (STARS)  
68 McKinley, Todd O. Mitochondrial Based-Treatments that Prevent Post-Traumatic Osteoarthritis in a Translational Large Animal Intraarticular Fracture Survival Model.  
69 Deane, Kevin D. Pathogenesis and Prediction of Future Rheumatoid Arthritis  
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ovarian cancer over the course of their lifetimes. Over a five-year period, nearly 2,600 members of our military or their families may be hospitalized for ovarian cancer or suspected ovarian cancer. The cost of ovarian cancer to our military is great, not only in terms of troop readiness, but also in terms of cancer care costs: treating these cases of ovarian cancer over these patients' lifetimes could cost TRICARE an estimated $971.2 million. TRICARE's potential costs to care for women with ovarian cancer could fund the Ovarian Cancer Research Program at the Department of Defense for nearly 50 years at its current funding level.

- **Pancreatic Cancer:** Research has shown that there is direct evidence for excessive risk of death from pancreatic cancer in some US veterans. Specifically, nurses serving in Vietnam had a 2 to 5-fold higher risk of pancreatic cancer death compared with non-deployed US military women. The reasons for this increase may be related to environmental exposures such chemical agents used in the field or in medical facilities, an association with predisposing medical conditions such as diabetes, and/or lifestyle propensities such as smoking, all which include known risk factors for pancreatic cancer. Further, the link between type 2 diabetes and pancreatic cancer is well-established and type 2 diabetes is recognized by the VA as an Agent Orange-associated presumptive disease. The Peer Reviewed Cancer Research Program has funded a variety of critical research areas since pancreatic cancer was first included in 2011, including investigations into biomarkers to detect pancreatic cancer early or follow response to therapy, targeting the oncogene KRAS, activating the immune system, taking advantage of metabolic differences between normal and malignant pancreas cells, and a variety of highly novel therapeutic approaches. Continued support for this research is critical not only for the potential risks for developing pancreatic cancer associated with military service, but also because pancreatic cancer is currently the nation’s third leading cause of cancer-related death and is predicted to surpass colon cancer to become second only to lung cancer by the year 2020.

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72 The lifetime risk of a women developing ovarian cancer is 1.4% according to the SEER Fact Sheet available here: http://seer.cancer.gov/statfacts/html/ovary.html
73 The average cost of frontline ovarian cancer therapy is $82,000, per the National Institutes of Health. http://costprojections.cancer.gov/annual.costs.html
77 Nyska A et al. Exocrine pancreatic pathology in female Harlan Sprague-Dawley rats after chronic treatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin and dioxin-like compounds. Environ Health Perspect.112:903–9, 2004
79 http://www.publichealth.va.gov/exposures/agentorange/conditions/index.asp
• **Parkinson’s research program**: Parkinson’s Disease (PD) environmental risk factors overlap common soldier occupational exposures such as traumatic brain injury and neurotoxic chemical exposures. The combination of brain injury and chemical exposure triple Parkinson’s risk.\(^1\) In 2012, the Department of Veterans’ Affairs (VA) made PD presumptive for TBI-connected with military service\(^2\) and secondary service connection for diagnosable illnesses associated with traumatic brain injury.\(^3\) The Neurotoxin Exposure Treatment (Parkinson’s) Research Program (NETPR) is funding studies in biomarkers of TBI and PD. Environmental and occupational chemical exposures, notably pesticides, increase the risk of PD in service members and has also been a focus of NETPR, identifying organochlorine compounds previously used in agriculture, environmental PCBs, and permethrin used in Army uniforms as risk factors for PD.\(^4\) Parkinson’s Disease Research, Education, and Clinical Centers (PADRECCs) were established within six leading VA centers to provide treatment to veterans with PD; research in these centers has benefited from NETPR program grants and provides transition between active duty members diagnosed with PD and their state-of-the-art continuity of care for PD in the VA. PD also shares neurological effects of concerns to soldiers such as disrupted sleep, depression, and cognitive impairment. All of these “dual use” aspects that are relevant to soldiers and to the PD community and have been a focus of NETPR.

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\(^1\) Ritz et al., Neurology 2012;79:2061-6.
\(^2\) 38 CFR Part 3 Department of Veterans Affairs.
\(^3\) *Federal Register* 2013;78:76196–209.
\(^4\) Tanner et al., *Alz Dementia* 2014;10:213-225.
- **Prostate Cancer**: Prostate cancer is the second deadliest cancer among American men, killing more than 26,000 men annually, and there are more than 1.5 million prostate cancer patients in the U.S. that depend on breakthroughs in research to continue their fight. Prostate cancer significantly impacts both active duty servicemen, veterans, and their families; in fact, active duty males are twice as likely to be diagnosed with prostate cancer as their civilian counterparts, with negative effects on their ability to serve. In addition, soldiers exposed to chemical agents such as Agent Orange in Vietnam are considered to be at increased risk of death from prostate cancer due to its association with high-grade disease in a population-based study of US Veterans. Research funded by the Prostate Cancer Research Program (PCRP) advances treatments; PCRP funding was responsible for accelerating the development of the two most impactful new treatments for advanced disease in the last four years, bringing them to patients faster than typical development of new drugs. Moreover, the program focuses on not only developing more effective therapeutics but also on improving diagnosis to reduce over treatment and accurately distinguish life-threatening disease from indolent tumors, which is likely to have its greatest impact on active duty servicemen who can be confidently monitored through active surveillance, rather than compromising their service to undergo treatment.

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Sleep: Insufficient sleep and sleep disorders affect the health of an estimated 70 million Americans across all demographic groups, including military personnel. Sleep disruption, especially insomnia, is a contributing risk factor to the onset and severity of major mental health problems such as depression, bipolar disorder, substance abuse, posttraumatic stress disorder, traumatic brain injury, and suicide. An increasingly detrimental condition affecting military troops is sleep-disordered breathing, including obstructive sleep apnea which results in excessive daytime somnolence, poor performance, increased frequency of road traffic accidents, and arterial hypertension. Studies show that 85% of 725 troops returning home from Afghanistan and Iraq had a sleep disorder and the most common was obstructive sleep apnea (51%). If left untreated, obstructive sleep apnea has significant negative impacts on health, including early mortality. By using continuous positive airway pressure (CPAP), a treatment used to combat sleep apnea, military personnel report reductions in pain and fatigue, and improvements in cognitive function. The high prevalence of sleep and circadian disturbances indicates an opportunity for research advances and informed public policy to reduce disease risk across a lifespan and improve the health of our active troops. It is important to accelerate scientific discovery of the relationship between mental health, overall health and sleep and circadian disorders, and strengthen cognitive function and military readiness through the improvement of sleep quality.

• **Tuberous Sclerosis Complex (TSCRP):** Research supported by the TSCRP is paving the way to finding cures and treatments for individuals with TSC as well as those with other neurological disorders like epilepsy and autism spectrum disorder (ASD). Research through TSCRP award W81XWH-12-1-0190 developed a mouse model for TSC, which in addition to its use for studying epilepsy and autism, is helping understand the consequences and potential treatment for post-traumatic brain injury (TBI) – a disorder of growing concern to the U.S. Armed Services. A more recent award, W81XWH-14-1-0061, is testing existing FDA-approved drugs for their ability to treat or prevent epilepsy by regulating the biochemical pathway shared between TSC and TBI. Many other TSCRP awards enabled these key studies by generating the knowledge about this shared biochemical pathway. Some of the awards that built this foundation of knowledge include DAMD17-03-1-0073, W81XWH-04-1-0309, W81XWH-06-1-015, W81XWH-09-1-0088, W81XWH-10-1-0861, W81XWH-13-1-0040.

• **Vision:** Vision, the sense most critical for optimal military performance in battlefield and support positions, is vulnerable to acute and chronic injury. Research to effectively treat vision trauma and TBI-related visual disorders can have long-term implications for an individual’s vision health, productivity, and quality of life for the remainder of military service and into civilian life. Traumatic eye injury from penetrating wounds and TBI-related visual disorders ranks second only to hearing loss as the most common injury among “active” military, accounting for upwards of 16 percent of all injuries in Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF). The VHA reports 202,000 OEF/OIF veterans with eye injuries since 2000, as well as that upwards of 75 percent of all TBI patients experience short- or long-term visual disorders (double vision, light sensitivity, inability to read print, and other cognitive impairments). A 2012 study using published data from 2000-2010 estimated that deployment-related eye injuries and blindness have cost the U.S. $2.3 billion a year, yielding a total of $25.1 billion, driven primarily by the present value of long-term benefits, lost wages, and family care.

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101 Bernardo, Sabatini. The Role of TSC1 in the Formation and Maintenance of Excitatory Synapses
102 McNeill, Helen. Genetic and Molecular Analysis of the Mechanisms by which TSC Regulates Neuronal Differentiation
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105 Sahin, Mustafa. Role of CTGF in White Matter Development in Tuberous Sclerosis