Dear Chairman Frelinghuysen and Ranking Member Visclosky:

As you begin work on the Fiscal Year 2017 (FY17) 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 FY16 budget process. 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), Veterans Administration (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. This disease-specific approach includes important medical research programs related to several forms of cancer (breast, blood, colorectal, kidney, melanoma, pancreatic, pediatric 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). Other 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). 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 orthopaedic 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.
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, programmatically 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 short white paper providing several examples. Continued federal funding will only build on these successes.

The undersigned respectfully request your support for FY 2017 funding of all programs within the defense health research programs.

Sincerely,

Action to Cure Kidney Cancer
Adult Congenital Heart Association
Alpha-1 Foundation
ALS Association
American Association of Clinical Urologists
American Association of Orthopaedic Surgeons
American Brain Tumor Association
American Cancer Society Cancer Action Network
American Congress of Obstetricians and Gynecologists
American Gastroenterological Association
American Psychological Association
American Society for Gastrointestinal Endoscopy
American Urological Association
Aplastic Anemia & MDS International Foundation
Asthma and Allergy Foundation of America
Autism Speaks
Bladder Cancer Advocacy Network (BCAN)
Children’s Tumor Foundation
Coalition for National Security Research (CNSR)
Colon Cancer Alliance
COPD Foundation
Crohn’s and Colitis Foundation of America
CureHHT
Debbie’s Dream Foundation: Curing Stomach Cancer
Digestive Disease National Coalition
Epilepsy Foundation
Fight Colorectal Cancer
FORCE: Facing Our Risk of Cancer Empowered
Foundation to Eradicate Duchenne
GBS/CIDP Foundation International
Hydrocephalus Association
Interstitial Cystitis Association
International Foundation for Functional Gastrointestinal Disorders
International Myeloma Foundation
Kidney Cancer Association
LAM Foundation
Littlest Tumor Foundation
Living Beyond Breast Cancer
Lung Cancer Alliance
Lupus Research Institute/Alliance for Lupus Research
Lymphoma Research Foundation
Malecare Cancer Support
Melanoma Research Foundation
Men’s Health Network
Muscular Dystrophy Association (MDA)
National Alliance for Eye and Vision Research
National Alliance of State Prostate Cancer Coalitions
National Autism Association
National Gulf War Resource Center
National Kidney Foundation
National LGBT Cancer Project
National Multiple Sclerosis Society
Neurofibromatosis Midwest
Neurofibromatosis Network
Ovarian Cancer Research Fund Alliance
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April 4, 2016
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Pancreatic Cancer Action Network
Parent Project Muscular Dystrophy (PPMD)
Parkinson's Action Network
Prostate Cancer Foundation
Prostate Conditions Education Council
Prostate Health Education Network (PHEN)
Pulmonary Hypertension Association
Research!America
Scleroderma Foundation
Sleep Research Society
Society for Women’s Health Research
Society of Gynecologic Oncology
Susan G. Komen
Texas Neurofibromatosis Foundation
Tuberous Sclerosis Alliance
Us TOO International Prostate Cancer Education and Support Network
Veterans for Common Sense
Veterans Health Council
Vietnam Veterans of America (VVA)
Women Against Prostate Cancer
ZERO-The End of Prostate Cancer

Enclosure
cc: Members, House Appropriations Committee
Defense Health Research Programs
Relevance to National Security and Military Families
April 4, 2016

- **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. Most recently, researchers found an increased risk of ALS among those who served in Iraq and Afghanistan. The VA has recognized the connection between ALS and military service by establishing a presumption of service connection for ALS. 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 (eg, 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). The Department of Defense reports that 18,452 active duty family members had a diagnosis of ASD at the end of fiscal year 2013. This reflects a 77% increase in ASD diagnoses in just four years from fiscal year 2009. 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. Research supported by the Autism Research Program has addressed current needs such as difficulties accessing care associated with mobile military families and gastrointestinal (GI) disorders which are among the most common medical conditions associated with autism. 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. 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. Smoking prevalence in the veteran population is reported to be 27% compared to 21% in the non-veteran population. 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. 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. Inorganic arsenic compounds have been linked to cancer of the bladder. 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.

**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).

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17 US Department of Veterans Affairs, July, 2015, CAMP LEJEUNE: PAST WATER CONTAMINATION, IB 10-449.
• **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. (CA09341521, CA11100222, CA10087923, CA100512P124, CA09317625)

• **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. 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.

- **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, 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.


28 Research Advisory Committee on Gulf War Veterans’ Illnesses, pp. 23-25.

29 Research Advisory Committee on Gulf War Veterans’ Illnesses, pp. 23-26.

30 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.


- **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.\(^{38}\) 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.\(^{39}\) 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.\(^{40}\)

- **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.\(^{41}\)

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\(^{40}\) 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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44 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.\(^{50}\) 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.\(^{51}\) 52 53

• **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."\(^{54}\) 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.\(^{55}\) 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.\(^{56}\) 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. 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

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The Gulf War era multiple sclerosis cohort: age and incidence rates by race, sex and service.
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, NF-ologists 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)

- **Pancreatic Cancer:** Research has shown that members of the military are at a higher risk for pancreatic cancer, which is the only major cancer with a five-year relative survival rate in the single digits, as a result of exposure to agents such as heavy metals, chlorinated hydrocarbons and DDT. A higher risk of pancreatic cancer is also suggested in populations exposed to other pesticides such as Agent Orange. Direct evidence for increased incidence of pancreatic cancer comes from a study published in the Journal of Occupational & Environmental Medicine that indicates that female Vietnam War military nurses, compared to female non-Vietnam War military nurses and to the general population, were significantly more likely to be diagnosed with pancreatic cancer. Research supported by the Department of Defense’s Peer Reviewed Cancer Research Program has included investigation of ways to diagnose pancreatic cancer early when it is most treatable. (CA140634, CA130578, CA130288, CA120412, CA110530).

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57 Elefteriou, Florent. Neurofibromin Function in Chondrocytes.
58 Kim, Aerang. Phase I/II Trial of an Hsp90 Inhibitor in Combination with an Inhibitor for Patients with Refractory Malignant Peripheral Nerve Sheath Tumors.
59 Plotkin, Scott. Phase 2 Study of Bevacizumab in Children and Young Adults With NF 2 and Progressive Vestibular Schwannomas.
60 North, Kathryn. A Randomized Placebo-Controlled Study of Lovastatin in Children with Neurofibromatosis Type 1 (STARS).
61 McKinley, Todd O. Mitochondrial Based-Treatments that Prevent Post-Traumatic Osteoarthritis in a Translational Large Animal Intraarticular Fracture Survival Model.
63 Hammond, Paula T. Cartilage-Penetrating Chondrogenic Nanoparticles for Early Posttraumatic Osteoarthritis Therapy.
64 Stanger, A Cell-Based Approach to Early Pancreatic Cancer Detection.
Other promising research includes work to discover the metabolic pathways that pancreatic cancers, but not normal cells, rely on for survival as a target for new pancreatic cancer treatments.\(^{69,70}\) This research is critical for the military population as well as the general American public because pancreatic cancer is currently the nation’s fourth leading cause of cancer-related death and is predicted to surpass colon and breast cancers to become the second leading cause by 2020.

- **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.\(^{71}\) In 2012, the Department of Veterans’ Affairs (VA) made PD presumptive for TBI-connected with military service\(^{72}\) and secondary service connection for diagnosable illnesses associated with traumatic brain injury.\(^{73}\) 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.\(^{74}\) 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.

- **Prostate Cancer:** Prostate cancer is the second deadliest cancer among American men, killing more than 26,000 men annually,\(^{75}\) 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,\(^{76}\) 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...

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\(^{65}\) Tuveson, The Early Detection of Pancreatic Cancer in the U.S. Military

\(^{66}\) Wolpin, Comprehensive Evaluation of Altered Systemic Metabolism and Pancreatic Cancer Risk

\(^{67}\) Nagrath, Integrated Microfluidic Magnetic CTC Sorter and Enumerator for Early Diagnosis and Management of Pancreatic Cancer

\(^{68}\) Solomon, Metabolomics Profiles and Pancreatic Cancer Risk

\(^{69}\) Lunt, Understanding the Warburg Effect and the Metabolic Requirements of Cancer Cells

\(^{70}\) Kimmelman, In Vivo Measurement of Oncogenic Kras-Dependent Glucose Metabolism in Mouse Models of Pancreatic Cancer

\(^{71}\) Ritz et al., Neurology 2012;79:2061-6.

\(^{72}\) 38 CFR Part 3 Department of Veterans Affairs.

\(^{73}\) Federal Register 2013;78:76196–209.

\(^{74}\) Tanner et al., Alz Dementia 2014;10:213-225.


high-grade disease in a population-based study of US Veterans.\textsuperscript{77} 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,\textsuperscript{78, 79} 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,\textsuperscript{80} which is likely to have its greatest impact on active duty servicemen who can be confidently monitored through active surveillance,\textsuperscript{81} rather than compromising their service to undergo treatment.

- **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.\textsuperscript{82-86} 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.\textsuperscript{87} 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.\textsuperscript{88} The high prevalence of sleep and circadian disturbances indicates an opportunity for research advances and informed public policy to


\textsuperscript{80} http://cdmrp.army.mil/pcrp/default.shtml


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-12-1-019089 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 DAMD17-03-1-007390, W81XWH-04-1-030991, W81XWH-06-1-01592, W81XWH-09-1-008893, W81XWH-10-1-086194, W81XWH-13-1-004095.

- **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 DOD/VA Vision Center of Excellence reports 186,555 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.

89 Wong, Michael. *The Role of Brain Inflammation in Epileptogenesis in TSC*
90 Gutmann, David. *Mouse Models of TSC-Related Epilepsy*
91 Bernardo, Sabatini. *The Role of TSC1 in the Formation and Maintenance of Excitatory Synapses*
92 McNeill, Helen. *Genetic and Molecular Analysis of the Mechanisms by which TSC Regulates Neuronal Differentiation*
93 Yoshii, Akira. *Studying Protein Synthesis-Dependent Synaptic Changes in Tuberous Sclerosis*
94 Manning, Brendan. *Defining the Therapeutic Implications of the Integrative Stress Response in TSC*
95 Sahin, Mustafa. *Role of CTGF in White Matter Development in Tuberous Sclerosis*
97 Hilber DJ, 2011, Armed Forces Surveillance Center MSMR Report