Impact Highlights

CDMRP Impact Highlights

U.S. Army Medical Research and Development Command
Department of Defense
U.S. Army Medical Research and Development Command
Congressionally Directed Medical Research Programs

Impact Highlights
June 2021
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INTRODUCTION

**Vision:** Transform healthcare for Service Members and the American public through innovative and impactful research

**Mission:** Responsibly manage collaborative research that discovers, develops, and delivers health care solutions for Service Members, Veterans, and the American public.

The Congressionally Directed Medical Research Programs (CDMRP), located within the U.S. Army Medical Research and Development Command and under the U.S. Army Futures Command, is a global funding organization that fosters novel approaches to congressionally targeted biomedical research areas in response to the expressed needs of its stakeholders – Service Members, Veterans, the American public, and Congress. CDMRP-managed programs are diverse but share the common goals of accelerating progress, advancing paradigm-shifting research, developing cutting-edge technologies, and identifying breakthroughs and solutions that will lead to cures, improved patient care, and enhanced quality of life.
CDMRP receives annual appropriations that are disease- or condition-specific, which allows flexibility to implement targeted investment strategies each year that are focused on areas of highest potential impact and highest priority needs of the patient and research communities. This is accomplished through close coordination and continual development of strategic and research partnerships with the scientific and clinical communities, industry, other federal and non-federal funding organizations, and consumers (patients, survivors, family members, and/or caregivers) — all of which are critical to enabling successful outcomes.

CDMRP maintains a passionate dedication to its mission and readily adapts to emerging priorities or congressional establishment of new programs or topics. Across all programs, CDMRP funds research to benefit people in the military healthcare system, to include military members, military retirees, family members, and other beneficiaries, as well as benefiting the civilian population.
Since the first program appropriation in 1992, CDMRP-funded research has significantly advanced knowledge, technologies, and products that are saving and improving lives:

- U.S. Food and Drug Administration (FDA)-approved drugs and therapeutic strategies
- Diagnostic and prognostic biomarkers/tests
- Novel approaches to prevention and treatment
- Imaging technologies for clinical use
- New standards of care and clinical practice
- Biorepositories with clinical samples and data

This book highlights some examples of the successes and impacts of CDMRP-funded research in fostering exploration of innovative ideas, opening new research avenues, developing key resources and technologies, and translating promising research into clinical care. Key partners and collaborators for each effort are listed in chronological order by award, with prime awardee(s) listed first. All currently active CDMRP programs are represented, with new Fiscal Year 2020 (FY20)-FY21 programs shown in Appendix A.
Lucie Bruijn, PhD, Amyotrophic Lateral Sclerosis Research Program (ALSRP) Programmatic Panel Member

“This is a particularly exciting time for drug discovery for ALS, with an increasing number of small and large biotech companies dedicating programs to the disease. Investment through the ALSRP is critical to provide the necessary support for academia and small biotech to drive their novel treatment approaches toward the clinic. In just a few years, with the support from this program, six very different treatment approaches progressed from early preclinical development into advanced development and/or clinical trials.”

MAJ Toni Grimes (U.S. Army, Ret.), Lupus Research Program (LRP) Consumer Peer Reviewer

“Serving on the LRP allowed me to continue doing what I have done my entire Army career, to serve my country. Through the LRP I was able to serve my lupus community and to have a voice as a lupus patient with regards to future innovative treatments, therapies, and research. It has been a true honor.”

Additional research accomplishment highlights for each CDMRP program can be found at:

https://cdmrp.army.mil/highlights/default

Highlights are available in individual program materials as well as the CDMRP Annual Report published each year:

https://cdmrp.army.mil/pubs/annreports/annual_reports

The CDMRP also hosts a searchable database which provides details on CDMRP-funded awards:

Vision: Improve the clinical outcomes of alcohol, opioid, and other substance use disorders

Mission: To explore integrated approaches to address alcohol and substance use disorders, and reduce the number of opioid and other substance use-related deaths, through multidisciplinary, team-based research efforts that translate basic knowledge into enhanced clinical pharmacological treatment protocols and enhanced quality of life for Service Members, Veterans, and the American public

Years Program Appropriated: FY10-FY19 and FY21

Total Appropriations: $48.1 million (M)

The Alcohol and Substance Abuse Disorders Research Program (ASADRP) aims to bring new medications to market for the treatment of alcohol and substance use disorders (ASUD) by conducting studies of new medications to treat ASUD, with a special emphasis on comorbidities of Traumatic Brain Injury (TBI) and Post-Traumatic Stress Disorder (PTSD) in populations of Service Members and Veterans. The program will use a translational approach (from animal models to humans) to understand the complex interaction of substance abuse with the now-common military stress comorbidities of PTSD and TBI.

Program goals include:

• New medications to treat Opioid Use Disorder (OUD) (preclinical)
• New medications to treat Alcohol Use Disorder (AUD) with co-morbid PTSD (clinical)
• New medications to treat OUD with co-morbid PTSD (clinical)
Anti-Fentanyl Vaccine and Buprenorphine Combination Therapy

**DESCRIPTION**
The vaccine being developed produces antibodies in the blood that attach to fentanyl. When fentanyl is ingested, this large antibody-fentanyl complex cannot get out of the bloodstream to enter the brain, heart, or other vulnerable organs to produce psychological effects, analgesia, or respiratory depression. Thus, these antibodies prevent both abuse of fentanyl and overdose.

**PARTNERS/COLLABORATORS**
University of Houston; Fina Biosolutions, LLC; Tulane University

**AWARD NUMBER:** W81XWH-18-2-0044 (Consortium Award)

**IMPACT:** Use of a fentanyl vaccine in high-risk populations could prevent the high rate of overdoses and deaths occurring with opioid use disorders. The vaccine also could block the effects of aerosolized fentanyl on active-duty soldiers in terrorist- or combat-related attacks.

*A visual presenting the mechanism of action of anti-fentanyl antibodies binding to fentanyl and preventing it from entering the brain from peripheral circulation (blood)*
PT150 – Cortisol Blocking Treatment

DESCRIPTION
PT150 is a glucocorticoid receptor antagonist that blocks the effects of cortisol, an endogenous stress hormone. The studies being conducted examine the efficacy, safety, and tolerability of this drug for PTSD and AUD dual diagnosis treatment. Researchers have successfully completed a phase 1, single center, alcohol interaction study and are now conducting a phase 1, drug-drug interaction study to assess pharmacokinetic (PK) interactions between ethanol and PT150. Successful completion of the PK study will enable researchers to conduct the proof of concept study.

PARTNERS/COLLABORATORS
University of California San Diego; Baylor College of Medicine; POP Test Oncology, LLC

AWARD NUMBER: W81XWH-18-2-0077 (Consortium Award)

IMPACT: Proven safe, effective treatments for PTSD alone, AUD alone, or co-occurring illness are severely limited. PT150 potentially could be safe and effective in improving PTSD and AUD symptoms.

BXCL 501

DESCRIPTION
This proof of concept study examines the use of BXCL501 (dexmedetomidine (DEX) on a sublingual film) as a potentially effective therapeutic for the treatment of patients with PTSD, especially those that are undergoing treatment for AUD. DEX exerts its effects by preventing release of the neurotransmitter norepinephrine, which is responsible for stress-related agitation and hyper-arousal. Because PTSD is associated with hyper-arousal and high sympathetic nervous system activity, BXCL501 has the potential to alleviate agitation that occurs in PTSD.

PARTNERS/COLLABORATORS
VA Connecticut Healthcare System, West Haven; BioXcel Therapeutics

AWARD NUMBER: W81XWH-18-2-0044 (Consortium Award)

IMPACT: BXCL501 could be a safe and effective treatment option for AUD and PTSD.
Kappa Opioid Receptor Antagonist

**DESCRIPTION**
Given their general ability to mitigate the effects of stress, there is substantial interest in the development of Kappa Opioid Receptor (KOR) antagonists for indications such as AUD and PTSD. The combination of buprenorphine and naltrexone yields a pharmacological net effect of a KOR antagonist. This proof of concept study will evaluate the efficacy and physiological effects of buprenorphine combined with naltrexone in the treatment of comorbid AUD and PTSD.

**PARTNERS/COLLABORATORS**
University of Alabama Birmingham School of Medicine; Yale School of Medicine; Alkermes

**AWARD NUMBER:**
W81XWH-18-2-0077 (Consortium Award)

**IMPACT:** KOR antagonists potentially could be safe and effective in improving PTSD and AUD symptoms.

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Lofexidine Combined with Buprenorphine

**DESCRIPTION**
Lofexidine is approved by the FDA for opioid withdrawal, while buprenorphine is a narcotic used to treat addiction. The overall objective of this proof of concept study is to determine if lofexidine as an adjunct to buprenorphine treatment improves symptoms of both OUD and PTSD.

**PARTNERS/COLLABORATORS**
Baylor College of Medicine; US World Meds

**AWARD NUMBER:**
W81XWH-18-2-0044 (Consortium Award)

**IMPACT:** This drug combination may offer an additional safe and effective treatment option for improving OUD and PTSD symptoms.
Vision: Improve treatment and find a cure for ALS

Mission: Fund innovative and impactful research to develop new treatments for ALS

Years Program Appropriated: FY07, FY09-FY21

Total Appropriations: $149.4M

The ALSRP is guided by a vision to improve treatment and find a cure for ALS. Through its award mechanisms and funding recommendations, the ALSRP specifically supports innovative and impactful research targeting development of new therapeutics for amyotrophic lateral sclerosis (ALS).
Combination of Riluzole + Elacridar

**DESCRIPTION**
The ALSRP funded the development of a combination therapy improving the action of an FDA-approved drug for ALS (riluzole). Using a mouse model of ALS, researchers established that when a protein membrane pump was blocked by the use of a known inhibiting drug, elacridar, the effectiveness of riluzole therapy was improved. Pump inhibition by chronic treatment with elacridar increased penetration of riluzole in the central nervous system, improved behavioral measures (including muscle function), and significantly extended survival of the mice. The ALSRP continued support of this combination approach under a separate award to an industrial partner to develop their own elacridar formulation, perform detailed PK, toxicology, and large-scale good laboratory practice compound manufacturing.

**PARTNERS/COLLABORATORS**
Izumi Biosciences, Inc.

**AWARD NUMBER:** W81XWH-16-1-0072

Copper Carrier CuATSM

**DESCRIPTION**
Use of the copper carrier CuATSM in a mouse model of ALS revealed that treated mice lived longer than untreated controls. CuATSM corrects the lack of copper ions in misfolded SOD1 proteins and may also help eliminate a chemical that interferes with mitochondrial function in ALS. The ALSRP funded the development of three novel CuATSM derivatives, all of which have low toxicity, are easily synthesized, and are effective at low dosages. The ALSRP-funded investigator has secured collaborative follow-on funding from the ALS Association and is now moving forward with submission of an Investigational New Drug (IND) and has plans to open a trial in the United States.

**PARTNERS/COLLABORATORS**
Oregon State University; Procypra Therapeutics

**AWARD NUMBER:** W81XWH-15-1-0289
CNM-Au8

DESCRIPTION
Both sporadic- and familial-ALS patients show disease hallmarks of mitochondrial dysfunction. An agent that could improve cellular bioenergetic metabolism while reducing oxidative stress could therefore be a promising disease-modifying therapeutic for ALS. CNM-Au8 is a suspension of catalytically active, clean-surfaced, faceted gold nanocrystals. It is administered orally, penetrates the blood-brain barrier, and has a good safety, tolerability, and toxicology profile. Researchers are working to validate a metabolic biomarker to identify a sub-population of patients who may respond optimally to treatment with CNM-Au8, which was one of the first treatments selected for the HEALEY ALS platform trial.

PARTNERS/COLLABORATORS
Clene Nanomedicine, Inc.

AWARD NUMBER: W81XWH-20-1-0166

Targeting microRNA miR-155

DESCRIPTION
miR-155 is a microRNA that promotes inflammation, and increased levels of miR-155 have been found in monocytes from ALS patient blood samples. Monocytes play a key role in ALS disease progression. Genetic manipulation of miR-155 in an ALS animal model was shown to delay disease onset and extend survival. Based on these findings, a therapeutic development company has invested in a therapeutic strategy to target miR-155 as a treatment for ALS.

PARTNERS/COLLABORATORS
Brigham and Women’s Hospital, Inc.; MiRagen Therapeutics

AWARD NUMBER: W81XWH-13-1-0181

IMPACT: Researchers are developing a bioenergetic clinical screening tool that aims to identify the sub-population of patients who may respond optimally to a treatment in the HEALEY ALS platform trial.

IMPACT: miR-155 has the potential to prolong survival of ALS patients and provide a biomarker that can be used to monitor overall disease progression.
Small Molecule Apilimod and Software DRVision

**DESCRIPTION**
Under an ALSRP-supported award, a chemical screen revealed Apilimod, an inhibitor of a protein called PIKFYVE, as a potentially potent and broadly efficacious way to eliminate toxic proteins that cause neurodegeneration in ALS. Based on these findings, and in conjunction with the company AcuraStem Inc., a novel PIKFYVE inhibitor is now advancing into ALS clinical trials. The ALSRP-supported work additionally developed analysis software, with partner DRVision Technologies, enabling automated detection of neuron number and rate of neurodegeneration during large-scale screens. This software is now moving toward commercialization.

**PARTNERS/COLLABORATORS**
University of Southern California Keck School of Medicine; AcuraStem Inc.; DRVision Technologies

**AWARD NUMBER:** W81XWH-15-1-0187

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Human Neural Progenitor Cells Expressing GDNF (CNS10-NPC-GDNF)

**DESCRIPTION**
The ALSRP funded preclinical studies to deliver the growth factor GDNF to motor neurons. Delivery of GDNF, through hNPCs, enhanced motor neuron function and extended survival in ALS animal models. These results, as well as additional results outside of the ALSRP, contributed to a California Institute of Regenerative Medicine grant moving this approach into clinical trials in patients (NCT02943850).

**PARTNERS/COLLABORATORS**
Cedars-Sinai Medical Center; California Institute of Regenerative Medicine

**AWARD NUMBER:** W81XWH-14-1-0189
FDA-Approved Neuroleptic Drug Pimozide

DESCRIPTION
The ALSRP funded large-scale screens of thousands of FDA-approved drugs to identify chemical modifiers of TDP-43 in preclinical models of ALS. A class of neuroleptics was identified, with pimozide being the most potent compound, as confirmed in all models tested. A national clinical trial has started in Canada (funded by ALS Canada and Brain Canada) to determine the potential for pimozide as a therapeutic (NCT03272503).

PARTNERS/COLLABORATORS
University of Montreal

AWARD NUMBER: W81XWH-11-1-0573

IMPACT: Extending on the findings funded by ALSRP, the Canadian team found that Pimozide may be able to prevent the progression of ALS.

Anti-CD40L Antibody AT-1501

DESCRIPTION
Evidence suggests that some aspects of disease onset and progression in ALS are regulated by immune cells. The ALSRP funded pharmacokinetic and toxicology studies using a novel antibody that is designed to block the protein activity of CD40L, a key player in immune response activation. These preclinical studies supported IND-enabling pharmacokinetics and toxicology studies of the humanized anti-CD40L antibody (AT-1501), which showed significant therapeutic benefit in an ALS mouse model, as evidenced by prolonged weight maintenance, delayed onset of neurological disease, and extended survival. Results led to testing AT-1501 in human clinical trials by Anelixis Therapeutics, Inc., and in 2020 the FDA granted AT-1501 orphan drug designation.

PARTNERS/COLLABORATORS
ALS Therapy Development Institute; Anelixis Therapeutics, Inc.

AWARD NUMBER: W81XWH-17-1-0057

IMPACT: If the ongoing clinical trials are successful, AT-1501 will become a new treatment option to slow disease progression and extend lives in people living with ALS.
**Apo-H-Ferritin**

**DESCRIPTION**
Iron accumulation can induce oxidative stress and that oxidative stress, along with iron dysregulation, has been implicated in the pathogenesis of ALS. Researchers worked to determine if infusion of a protein that can bind and remove iron in a natural way (apo-h-ferritin) is a potential treatment for ALS. Infusion of apo-h-ferritin at the time of motor disease onset was shown to extend lifespan in several ALS animal models. Development of this strategy is being further supported by the ALS Association, and the researchers are working with a medical device company to develop an implantable device that can deliver the apo-h-ferritin solution directly into the spinal lumbar space.

**PARTNERS/COLLABORATORS**
Pennsylvania State University, Milton S. Hershey Medical Center

**AWARD NUMBER:** W81XWH-11-1-0733

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**RASRx1902**

**DESCRIPTION**
RASRx1902 is an investigational oral drug that has been shown to reduce inflammation and oxidative stress, improve cognitive function, and stimulate muscle regeneration in Duchenne muscular dystrophy (DMD). Since these factors are known to be involved in ALS, the ALSRP supported investigations re-purposing this compound to decrease neurological deficits and increase lifespan of ALS models. In 2017, the FDA granted orphan drug designation to RASRx1902, clearing its path to potential therapeutic use.

**PARTNERS/COLLABORATORS**
The University of Arizona Health Sciences Center for Innovation in Brain Science

**AWARD NUMBER:** W81XWH-19-1-0471

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**IMPACT:** Apo-h-ferritin therapy is a promising treatment option that could extend the life and, importantly, improve quality of life of ALS patients by preserving motor function.

**IMPACT:** Successful development of RASRx1902 has the potential to improve the treatment, quality of life, and long-term outlook for individuals affected by ALS.
Vision: Improve the lives of individuals with autism spectrum disorders now

Mission: Promote innovative research that advances the understanding of autism spectrum disorders and leads to improved outcomes for Service Members, their families, and the American public

Years Program Appropriated: FY07-FY21

Total Appropriations: $119.4M

The ARP’s mission is to promote innovative research that advances the understanding of Autism Spectrum Disorders (ASD) and leads to improved outcomes for Service Members, their families, and the American public. The ARP developed its overall strategic goals, which include: (1) understand causes, mechanisms, and signs of ASD, (2) advance effective treatments and interventions for autism, (3) address the needs of persons with autism into adulthood, and (4) support those caring for the autism community.
Cognitive Enhancement Therapy for Adults with ASD

DESCRIPTION
Cognitive Enhancement Therapy (CET) has been successful in helping people with schizophrenia improve cognitive development and social functioning. Only a few interventions currently exist for the adult population, none of which effectively targets both the social and non-social cognitive impairments that can influence major domains of functioning, including employment. CET was found to be highly efficacious in enhancing neurocognitive function, specifically attention and processing speed in ASD adults. These improvements demonstrated a substantial effect on employability in these adults. The investigators have been funded by the National Institutes of Mental Health to conduct a large-scale clinical trial to evaluate the use of CET in adults with ASD.

PARTNERS/COLLABORATORS
University of Pittsburgh

AWARD NUMBERS: W81XWH-11-1-0665, NIMH R01 MH106450

IMPACT: Once the NIH pivotal trial is completed, CET could become a reimbursable and standardized therapy for adults with ASD.
Google Glass with Empowered Brain

**DESCRIPTION**
Empowered Brain is an augmented reality and virtual reality software technology that is aimed at improving the symptoms of social interaction disorders often seen in those with ASD. With Empowered Brain, individuals look through Google Glass, which incorporates virtual reality displays to provide users with experiences that will help them cope with real-life situations. Empowered Brain technology proved both feasible and efficacious in improving symptoms of ASD, including social withdrawal, irritability, and hyperactivity in students with ASD. Educators who have incorporated the technology in their classroom reported that students’ attention was significantly increased and there was improved development of student-teacher relationships. The research team is currently working with one of the largest public school districts in Massachusetts to implement the technology in their job placement effort.

**PARTNERS/COLLABORATORS**
Brain Power LLC

**AWARD NUMBER:** W81XWH-17-1-0449

**IMPACT:** The Empowered Brain technology has already been implemented in classrooms to improve the social and emotional behavior of students with ASD.
Project SEARCH with ASD Supports for Adult Military Dependent with ASD

DESCRIPTION
Project SEARCH plus ASD Supports (PS+ASD) is an employment-based training program for improving social communication, behavior, and employment outcomes for transition-aged youth with ASD. The training support system consists of intensive applied behavioral analysis, assistance from an on-site behavior and autism specialist, and staff training in ASD. The training program works with young adults with ASD from military families who are in their last year of high school; the students are immersed in large community businesses with real-world work environments. Participants from the PS+ASD program have improved independence, social responsiveness, self-management, work skills, and quality of life. Over 76% of the internship participants gained competitive integrated employment.

PARTNERS/COLLABORATORS
Virginia Commonwealth University

AWARD NUMBER: W81XWH-16-1-0707

IMPACT: The PS+ASD program was found to be extremely successful for helping young adults with ASD in obtaining employment and transitioning into independence.
ImPACT Online Program

**DESCRIPTION**
Although parent training is considered as an essential component of early intervention programs for children with ASD, many families have difficulty in accessing such training programs. Web-based distance learning programs have great potential for increasing access to families. This project developed a highly innovative, web-based, distance learning program called Improving Parents as Communication Teachers (ImPACT). ImPACT uses effective adult learning tools to help parents learn the intervention techniques and to integrate them into their daily interactions with their child. Results showed that internet-based instruction is a feasible method for training parents of children with ASD in evidence-based intervention strategies. The project received follow-on funding from HRSA for an efficacy study.

**PARTNERS/COLLABORATORS**
Michigan State University

**AWARD NUMBER:** W81XWH-10-1-0586

**IMPACT:** This type of online training could allow greater dissemination of interventions to underserved populations. The ImPACT program has now been adapted to ImPACT for Toddlers, a program to coach parents and caregivers of 12- to 24-month-olds (http://www.project-impact.org).
MAXout for Social-Communication

DESCRIPTION
Individuals with ASD exhibit social-communication impairments that impede their daily living. This project aimed to develop an outpatient comprehensive psychosocial treatment (MAXout) and evaluate its efficacy on improving ASD symptoms and social-communicative function of 7- to 12-year-olds with ASD in a randomized controlled trial. The MAXout intervention is an 18-week treatment program targeting social and social-communication skills, face-emotion recognition, nonliteral language skills, and interest expansion. The results showed that MAXout has significantly reduced ASD symptoms and improved social skills and behavior symptoms. These treatment effects were well maintained at post-treatment follow-up.

PARTNERS/COLLABORATORS
Canisius College

AWARD NUMBER: W81XWH-15-1-0195

IMPACT: The MAXout treatment manual will be disseminated freely to the public.
Vision: To understand and cure bone marrow failure diseases

Mission: To encourage and support innovative research that is committed to advancing the understanding and treatment of inherited and acquired bone marrow failure diseases, thereby improving the health of affected Service Members, Veterans, and the general public, with the ultimate goals of prevention and cure

Years Program Appropriated: FY08-FY21
Total Appropriations: $49.05M

The Bone Marrow Failure Research Program (BMFRP) encourages and supports innovative research that is committed to advancing the understanding and treatment of inherited and acquired bone marrow failure (BMF) diseases, thereby improving the health of affected Service Members, Veterans, and the general public, with the ultimate goals of prevention and cure. The pathology of BMF is complex. It is complicated by the diverse syndromes that contribute to it, which vary in etiology, age of onset, symptoms, and severity. There are many unanswered BMF research questions; thus, the strategy of the BMFRP is to retain a broad set of research priorities. Current emphasis is placed on projects that improve our understanding of the causes and progression of BMF diseases and those that discover effective BMF treatments and cures.
H3B-8800

**DESCRIPTION**
H3B-8800 is an orally available small molecule that binds to a complex of seven proteins responsible for mRNA processing that is commonly mutated in Myelodysplastic Syndromes (MDS), Acute Myeloid Leukemia (AML), and Chronic Myelomonocytic Leukemia (CMML). The BMFRP supported preclinical mouse model studies of H3B-8800 and related molecules that displayed preferential killing of cancer cells harboring relevant mutations. H3B-8800 has since been evaluated in a phase 1 clinical trial (NCT02841540), demonstrating safety, even with prolonged dosing, for patients with MDS, AML, and CMML.

**PARTNERS/COLLABORATORS**
Sloan Kettering Institute for Cancer Research; Fred Hutchinson Cancer Research

**AWARD NUMBER:** W81XWH-16-1-0059

GSK3326595

**DESCRIPTION**
GSK3326595 is a small molecule inhibitor of protein methyltransferase 5 (PRMT5). The BMFRP supported preclinical investigations in which it was observed that inhibition of PRMT5 reduced RNA processing fidelity in cancer cells with spliceosomal mutations, which resulted in preferential cell killing. These findings led GlaxoSmithKline to launch a phase 1/2 clinical trial of GSK3326595 for the treatment of MDS and AML that is currently recruiting participants (NCT03614728).

**PARTNERS/COLLABORATORS**
Sloan Kettering Institute for Cancer Research; Fred Hutchinson Cancer Research

**AWARD NUMBER:** W81XWH-16-1-0059
Dendritic Cell Ligands Mediate T Cells Activity

DESCRIPTION
Hematopoietic stem and progenitor cells (HSPCs) are a critical component of bone marrow responsible for the production of blood cells. The development of some bone marrow failure disorders can arise when T cells of the immune system attack HSPCs, depleting their population and limiting the production of new blood. In mechanistic studies supported by the BMFRP, it was observed that dendritic cell expression of the Notch ligand, Dll4, mediated T cell response. Targeting of Dll4 with blocking antibodies was observed to reverse the contributions of inflammatory T cells to BMF diseases such as aplastic anemia and graft vs host diseases.

PARTNERS/COLLABORATORS
Temple University

AWARD NUMBER: W81XWH-11-1-0294

Metformin Therapy for Fanconi Anemia

DESCRIPTION
Metformin is an orally administered FDA-approved therapy for type 2 diabetes. The BMFRP funded studies that showed the drug increased blood production and reduced cancer formation in animal models of Fanconi Anemia, suggesting that it could potentially be repurposed to treat the disease. Based on these findings, Boston Children’s Hospital initiated a pilot phase 2 clinical trial (NCT03398824) to evaluate hematologic response, as well as safety, tolerability, and biologic effects.

PARTNERS/COLLABORATORS
Oregon Health and Science University, Portland

AWARD NUMBER: W81XWH-16-1-0300

IMPACT: Metformin, an FDA-approved diabetes therapeutic, has the potential to be repurposed for improved care/treatment of Fanconi Anemia.
**DESCRIPTION**

HSPCs are an important part of the bone marrow that differentiates to produce blood cells in a process known as hematopoiesis. To sustain an appropriate population, these cells must also expand and replicate. The stem cell niche, a special compartment of the bone marrow where HSPCs conduct this process of self-renewal, was identified as an immune privilege site in bone marrow where regulatory T cells are immune-suppressive and shield HSPCs from immune rejection. This finding could pave the way for allogeneic transplant in unconditioned hosts and benefit a larger patient pool for bone marrow transplant, ultimately leading to better treatment of bone marrow disorders.

**PARTNERS/COLLABORATORS**
Massachusetts General Hospital

**AWARD NUMBER:** W81XWH-10-1-0217
**Vision:** A world without breast cancer

**Mission:** To end breast cancer for Service Members, Veterans, and the general public by funding innovative, high-impact research through a partnership of scientists and consumers

**Years Program Appropriated:** FY92-FY21

**Total Appropriations:** $3.94 billion (B)

The Breast Cancer Research Program’s (BCRP) mission is to end breast cancer for Service Members, Veterans, and the general public by funding innovative, high-impact research through a partnership of scientists and consumers. The BCRP recognizes that many overarching questions remain unanswered in breast cancer, and funding must be invested in critical areas of research to make breakthroughs that will save lives and lead to eradication of this disease. To meet this urgent need, the BCRP requires all applications to address overarching challenges that focus on the goals of primary prevention and risk, identifying what drives breast cancer progression, revolutionizing treatment regimens, and improving prognosis by preventing recurrence and eliminating mortality associated with metastasis.
**DESCRIPTION**
Herceptin (trastuzumab) is a monoclonal antibody that targets the human epidermal growth factor receptor 2 (HER2). HER2-positive breast cancer accounts for approximately 25% of all breast cancers. The BCRP was instrumental in supporting the preliminary studies needed to test the efficacy of Herceptin, which later led to clinical trials and ultimately, FDA approval.

**PARTNERS/COLLABORATORS**
University of California, Los Angeles

**AWARD NUMBER:** DAMD17-94-J-4118

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“I am alive today because of a research grant funded by the DOD BCRP to Dr. Dennis Slamon. That groundbreaking research led to the development of my personal miracle drug: Herceptin.”

Beth Emery, BCRP Consumer Reviewer, National Breast Cancer Coalition Team Leader

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**IMPACT:** Herceptin revolutionized breast cancer treatment and the field of targeted therapeutics and is now part of standard-of-care treatment regimens for HER2+ early-stage and metastatic breast cancers.

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**DESCRIPTION**
Adjuvant tamoxifen is the first-line treatment for ER+ breast cancer in premenopausal women. BCRP funds supported initiation of the phase 3 ATLAS (Adjuvant Tamoxifen Longer Against Shorter) clinical trial which showed that the risk of recurrence or death from breast cancer was reduced in women who took tamoxifen for 10 years, compared to those who took it for 5 years (the previous standard of care).

**PARTNERS/COLLABORATORS**
University of Oxford

**AWARD NUMBER:** DAMD17-94-J-4422

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**IMPACT:** The American Society of Clinical Oncology published new guidelines on adjuvant hormonal therapy that recommended all women diagnosed with hormone receptor-positive (HR+) breast cancer be offered the option of taking hormonal therapy for 10 years.
**Cyclin-Dependent Kinase (CDK) Inhibitors – Ibrance®, Verzenio®, Kisqali®**

**DESCRIPTION**
Ibrance (palbociclib), Verzenio (abemaciclib), and Kisqali (ribociclib) are drugs that inhibit the cyclin-dependent kinases, which play a key role in the uncontrolled proliferation of cancer cells. The BCRP funded preliminary laboratory studies that provided support for subsequent clinical trials combining Ibrance with letrozole. BCRP-funded preclinical studies also contributed to development of other CDK inhibitors, including Verzenio and Kisqali.

“The same month the CDK4/6 inhibitor [ademaciclib] got approval, I was diagnosed with metastatic breast cancer. Words can’t express the gratitude I have of living each day.”

Patti Kellerhouse, BCRP Consumer Reviewer

**PARTNERS/COLLABORATORS**
University of California, Los Angeles

**AWARD NUMBER:** W81XWH-11-1-0104

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**Prone Radiotherapy Treatment to Reduce Harmful Radiation to the Heart and Lung**

**DESCRIPTION**
With BCRP support, clinical trials were conducted to assess the efficacy of an accelerated, hypofractionated whole-breast radiation therapy designed to minimize the length of radiotherapy required after partial mastectomy in patients with ductal carcinoma in situ (DCIS). In this method, patients are treated on a specially designed table in the prone position rather than in the supine position, greatly reducing unnecessary radiation exposure of the heart and lungs.

**PARTNERS/COLLABORATORS**
New York University School of Medicine

**AWARD NUMBER:** DAMD17-01-1-0345

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**IMPACT:** Ibrance, Verzenio, and Kisqali are currently approved by the FDA for the treatment of metastatic HR+, HER2-negative breast cancer.

**IMPACT:** Prone radiotherapy is poised to become a standard choice in breast radiotherapy. Current clinical trials and long-term follow-up will continue to examine this radiotherapy approach for efficacy and toxicity.
Sentinel Lymph Node (SLN) Biopsy

DESCRIPTION
The previous standard for detecting breast cancer invasion into the lymph nodes was to remove the majority of axillary lymph nodes and search for cancer cells. In a significant proportion of women, this causes lymphedema of the arm, a condition that compromises functionality and quality of life. In SLN biopsy, lymph node removal is limited to only the first few nodes that receive lymph drainage from the breast. The BCRP provided funding for multicenter clinical trials to validate lymph node mapping and SLN biopsy as an accurate method to predict the presence of disease in the axillary lymph nodes.

PARTNERS/COLLABORATORS
East Carolina University; University of South Florida

AWARD NUMBERS: DAMD17-98-1-8079, DAMD17-00-1-0239, DAMD17-97-1-7209

Molecular Breast Imaging

DESCRIPTION
Molecular breast imaging (MBI) is a nuclear medicine technique that uses high-resolution gamma cameras to detect the functional uptake of a radiotracer in the breast. Following a Mayo Clinic study that demonstrated MBI to be more sensitive than conventional mammograms for detecting breast cancer in women with dense breast tissue, the BCRP funded work to evaluate the concordance of MBI with magnetic resonance imaging (MRI) of the breast, to investigate the effects of fluctuating hormonal levels on the appearance of MBI, and to develop important quantitative analysis software for MBI.

PARTNERS/COLLABORATORS
Mayo Clinic

AWARD NUMBER: W81XWH-07-1-0548
Digital Mammography and Digital Breast Tomosynthesis

**DESCRIPTION**
Digital mammography allows for an expanded detection range of X-ray signals than standard film mammography. A BCRP-supported study demonstrated that digital mammography is superior to film mammography in detecting breast cancer in women with dense breast tissue, leading to a change in clinical practice. The BCRP also supported the development and clinical evaluation of digital breast tomosynthesis, a tool that offers an additional 3D view to capture images for improved sensitivity.

**PARTNERS/COLLABORATORS**
University of Iowa; Massachusetts General Hospital

**AWARD NUMBERS:** DAMD17-99-1-9001, DAMD17-98-1-8309

**IMPACT:**
Digital mammography is now used in clinical practice, and a tomosynthesis system is FDA-approved and commercialized.
**BRCA2 617delT Mutation**

**DESCRIPTION**
Breast cancer and ovarian cancer risk is greater in individuals with mutations in the BRCA1 and BRCA2 tumor suppressor genes. The likelihood of BRCA1 or BRCA2 mutations is higher in certain populations, including individuals of Ashkenazi Jewish descent. BCRP funding contributed to the discovery of the BRCA2 617delT mutation, one of the three founder BRCA1/2 mutations that occur in Ashkenazi Jews.

**PARTNERS/COLLABORATORS**
University of Utah

**AWARD NUMBER:** DAMD17-94-J-4260

**IMPACT:** The BRCA2 617delT mutation is now part of a commercialized test for BRCA1/BRC2 gene mutations in this risk group.

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**OncoVue®**

**DESCRIPTION**
Risk association studies funded by the BCRP formed the foundation for a breast cancer risk assessment test. Single nucleotide polymorphisms (SNPs) are DNA sequence variations that occur when a single nucleotide (A, T, C, or G) in the genome sequence is altered. OncoVue is the first genetic-based breast cancer risk test that incorporates a woman’s SNPs with her personal history to estimate her risk for breast cancer.

**PARTNERS/COLLABORATORS**
Oklahoma Medical Research Foundation

**AWARD NUMBER:** DAMD17-01-1-0358

**IMPACT:** The OncoVue, which is commercially available, can identify high-risk patients and enable clinicians to individualize breast cancer screening and monitoring.
Breast Cancer Index™ for Predicting Disease Recurrence

DESCRIPTION
Women with ER+ breast cancer have an increased risk of relapse many years after their initial diagnosis. To identify women with an increased risk of disease recurrence, research was conducted with BCRP support to validate biomarkers that correlate with relapse-free survival and tumor grade. Ultimately, this led to a risk assessment test termed the Breast Cancer Index (BCI).

PARTNERS/COLLABORATORS
Massachusetts General Hospital

AWARD NUMBERS: W81XWH-04-1-0606, W81XWH-10-1-0444

IMPACT: The BCI test, which is now commercially available, provides a quantitative assessment of the likelihood of recurrence and benefit from extended endocrine therapy.

PTEN Gene

DESCRIPTION
BCRP funding contributed to the original discovery of the PTEN (phosphatase and tensin homolog) gene. In normal cells, PTEN functions as a tumor suppressor protein that helps regulate cell division and growth. PTEN is one of the most frequently mutated genes in several cancers, and PTEN mutations have been shown to be predictive of aggressive cancer. PTEN mutations also occur in a group of genetic syndromes that are characterized by malignant and benign tumors.

PARTNERS/COLLABORATORS
Cold Spring Harbor Laboratory

AWARD NUMBER: DAMD17-94-J-4247

IMPACT: A PTEN test is commercially available to confirm mutations in this gene for clinical and prenatal diagnoses and identification of at-risk family members.
PALB2 Gene Mutations

DESCRIPTION
BCRP funding contributed to the discovery of PALB2, a BRCA2 binding protein. PALB2 and BRCA2 work together to mend broken strands of DNA, which helps to maintain the rate of cell growth. While BRCA1 and BRCA2 gene mutations are high-risk factors for breast cancer, these mutations do not account for all familial breast cancers. Identification of mutations in the PALB2 gene indicates an approximate two-fold increase in breast cancer susceptibility due to its inability to interact with BRCA2.

PARTNERS/COLLABORATORS
Dana-Farber Cancer Institute

AWARD NUMBER: DAMD17-02-1-0360

IMPACT: A commercialized PALB2 genetic test is available for those with familial breast cancer.
Vision: Improving the medical readiness of Service Members, as well as quality of life and level of function of all Americans, with or at risk for developing chronic pain

Mission: To support and promote innovative, high-impact research to prevent the development and improve the management of chronic pain

Years Program Appropriated: FY19-FY21

Total Appropriations: $40M

Chronic pain management is a major public health concern for civilian and military populations, affecting millions in the U.S. at an estimated annual cost in personal and health system expenditures of $560-$635 billion. The impact of the problem is magnified in light of the current opioid crisis, which has been exacerbated by use of addictive narcotics to manage chronic pain. Chronic pain is defined as a pain that occurs on at least half the days for 6 months or more and which can be caused by issues including, but not limited to: combat- and training-related physical or mental stress and trauma, migraines and chronic headaches, traumatic brain injury, arthritis, muscular-skeletal conditions, neurological disease, tick- and vector-borne disease, other insect-transmitted or tropical disease, and cancer. The Chronic Pain Management Research Program (CPMRP) supports research in the fields of: pain chronification, the development of novel non-opioid therapies, and the implementation and comparative effectiveness of evidence-based efficacious interventions to manage chronic pain.
Psychologically Informed Physical Therapy (PiPT)

DESCRIPTION
PiPT is a treatment modality in which physical therapists have been trained to identify and address psychological factors that increase the likelihood of disability in patients. The feasibility of using PiPT to reduce disabilities related to musculoskeletal disorders (MSD) has been demonstrated in pilot studies conducted onboard a U.S. Navy aircraft carrier. The CPMRP is supporting a hybrid effectiveness-implementation study to identify optimal conditions to use PiPT in shore-based healthcare settings for active-duty Service Members and measure its effectiveness in reducing MSD-related chronicity when compared to standard-of-care physical therapy.

PARTNERS/COLLABORATORS
New York University School of Medicine; Naval Medical Center Portsmouth

AWARD NUMBER: W81XWH-20-2-0036

IMPACT: The study may pave the way for PiPT implementation in military treatment facilities and healthcare settings, providing improved care and facilitating return to Service.
Brain-Penetrant P2X4 Receptor Antibody Fragment Therapies

**DESCRIPTION**
P2X4 is a fast-acting receptor that is activated and upregulated in response to nerve injury. Preclinical evaluation of P2X4 receptor-targeting antibody fragments has displayed their efficacy as analgesics and in the reduction of anxiety-related behaviors associated with chronic pain. The CPMRP is funding studies designed to optimize P2X4 receptor therapies along with preclinical evaluation of the lead candidate for safety, toxicity, biodistribution, and pharmacokinetics to facilitate translation to clinical evaluation.

**PARTNERS/COLLABORATORS**
University of New Mexico Health Science Center

**AWARD NUMBER:** W81XWH-20-1-0930

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Mechanism of Osteoarthritis Pain via a Tissue Chip Model System

**DESCRIPTION**
The CPMRP is supporting an effort to improve the tissue chip microJoint, a model system of the knee joint comprised of cartilage, bone, synovium, and fat pad, by introducing neural cells. Mechanical stimulation of the updated model system will be used to replicate the onset and progression of osteoarthritis (OA). Intracellular signaling and the remodeling of the tissue and sensory neurons will be monitored to identify biomarkers associated with the transition from acute to chronic pain. Once identified, the mediators responsible for chronic pain development can be targeted to prevent the development of OA.

**PARTNERS/COLLABORATORS**
University of Pittsburgh

**AWARD NUMBER:** W81XWH-20-1-0902

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**IMPACT:** Study results could lead to a potential therapeutic for chronic pain and pain-related anxiety.

**IMPACT:** The development of an advanced system that can model the conditions contributing to the development of OA may help identify potential therapeutic targets for treatment.
NIH-DOD-VA Interagency Collaboration

DESCRIPTION
The CPMRP leverages existing interagency connections that were established as part of the ongoing NIH-DOD-U.S. Department of Veterans Affairs (VA) Pain Management Collaboratory (PMC). Representatives from the PMC-sponsoring agencies, funded investigators, and supporting working groups and committees have been incorporated into the CPMRP Programmatic Panel to remain informed of different initiatives throughout the government that address pain management. The CPMRP team manages four pragmatic clinical trials funded through the PMC by the Joint Program Committees and actively participates in PMC meetings. The CPMRP also plans to participate in future inter-governmental funding opportunities and programs as they develop, to support the next round of studies that provides medical solutions to our Service Members, Veterans, and the American public.

PARTNERS/COLLABORATORS
NIH National Center for Complementary and Integrative Health; VA; Defense and Veterans Center for Integrative Pain Management; University of Texas Health, San Antonio; Brooke Army Medical Center

AWARD NUMBER: N/A
The Combat Readiness–Medical Research Program (CRRP) was established in FY19 to pursue military-relevant advanced technology and therapeutic research related to forward-deployable solutions that can promptly address life-threatening injuries, medical threats, and treatments for Service Members in battlefield settings. The congressional language for the CRRP encompasses research that would enable the Warfighter to better respond to serious injury and mitigate the long-term effects of battlefield trauma in rural and austere environments, as well as solutions that can translate to prolonged prehospital civilian trauma care in situations of mass casualty events and/or extended disruption of communications in dense urban or subterranean environments. CRRP Topic Areas vary each fiscal year in response to congressional direction.
ClotChip,™ a Field-Deployable Dielectric Coagulometer for Point-of-Care Assessment of Trauma-Induced Coagulopathy

DESCRIPTION
ClotChip is a sensor device that can be used to rapidly assess a patient’s bleeding risk by measuring clotting ability following injury. This funded effort seeks to evaluate performance of the current commercial-ready ClotChip device under environmental conditions similar to various military environments (extreme temperature, high vibration, etc.), as well as develop and perform initial validation of a ruggedized prototype that would be suitable for use closer to the point of injury and in extreme fielding conditions. This work complements the strategic research goals and investments of the Combat Casualty Care Research Program (CCCRP).

PARTNERS/COLLABORATORS
Case Western Reserve University; XaTek, Inc.; Naval Medical Center Portsmouth

AWARD NUMBER: W81XWH-20-C-0120

IMPACT: Early detection of blood clotting problems in injured patients in both combat and civilian trauma settings may improve trauma care by helping clinicians make earlier decisions on the best types of blood products needed, thus potentially increasing survivability.
Combat-Ready Exposure Device (CRED) for Detection of Heavy Metals

DESCRIPTION
CRED is a portable device for the detection of lead and other heavy metals in human blood and tissue. This research effort is focused on refining and validating the CRED prototype in order to combine validated metrics for human-absorbed heavy metal dose with portability for monitoring both acute and chronic heavy metal exposures in field settings and military training and combat environments (e.g., from ammunition and munitions, burn pits, and particulate matter from improvised explosive devices). This project is synergistic with the Military Operational Medicine Research Program’s (MOMRP’s) efforts relating to detecting, monitoring, and assessing environmental and occupational exposure to toxic contaminants.

PARTNERS/COLLABORATORS
Henry M. Jackson Foundation; U.S. Army Research Institute for Environmental Medicine; Harvard University T.H. Chan School of Public Health

AWARD NUMBER: W81XWH-20-2-0037

IMPACT: A wearable sensor to detect and monitor exposures to toxic levels of heavy metals in the body could lessen short- and long-term neurological and physiological effects, as well as improve military performance and force readiness.
Transcranial Ultrasound Brain Imaging (TRUBI) Instrument for Point-of-Care Assessment of Brain Hemorrhage

DESCRIPTION
TRUBI technology uses a proprietary ultrasound method to detect bleeding in the brain. This research project aims to build a second generation of the TRUBI device for rapid and precise 3D-imaging (3D-TRUBI) of bleed location, extent, and shape. All components of 3D-TRUBI will be carried in a ruggedized container that meets military specifications for use at the point-of-injury on the battlefield and during transportation, where standard computed tomography (CT) is not available. This project aligns with the CCCRP and U.S. Army Medical Materiel Development Activity’s efforts to develop fieldable, non-invasive technologies for traumatic brain injury assessment.

PARTNERS/COLLABORATORS
Tessonics Medical Systems; Wayne State University

AWARD NUMBER: W81XWH-20-1-0852

IMPACT: Early detection of bleeding in the brain at the point of injury, before the patient reaches a hospital, could enable rapid and life-saving treatment, thus improving long-term outcomes and limiting trauma-associated death.
Vision: To preserve and improve the function and quality of life, and to extend the life span of all individuals with Duchenne

Mission: To better characterize Duchenne pathophysiology, support discovery and development of therapeutics, related devices and tools, as well as to promote their rigorous preclinical and clinical testing for the benefit of military beneficiaries and the general public.

Years Program Appropriated: FY11-FY21
Total Appropriations: $49.6M

The initial research programs for Duchenne muscular dystrophy and muscle diseases began in 2003 and were institution-based at Children’s National Medical Center and the University of Pittsburgh. The success of these early programs during the mid- to late-2000s led to initiation of the Duchenne Muscular Dystrophy Research Program (DMDRP). The DMDRP acknowledges there are a broad range of unanswered questions that are critical to treating DMD patients, improving their quality of life, and developing a cure. To make its biggest impact for the DMD research field and patient communities, the DMDRP focuses its funding on developing or improving treatments and clinical trial readiness. To support these priorities, all applications are required to address challenges that focus on development of safe and effective macromolecular and cellular therapies, assessment of clinical trial tools and outcome measures, preclinical translational research to support therapeutic development, or research to improve clinical care and quality of life.
Exondys 51® (Eteplirsen) and Viltepso (Vitolarsen)

DESCRIPTION
DMD is a genetic disease characterized by progressive muscle weakness and degeneration of skeletal and cardiac muscles. There is no cure for DMD, and young men with this disease rarely live beyond their early 30s. DMD is caused by mutations in the dystrophin gene that lead to an absence of dystrophin in muscle cells. One approach to treat DMD is to induce dystrophin production by skipping over the mutation(s) in the genetic code (exon skipping), which can lead to production of a truncated form of dystrophin that is functional. Expression of a functional form of dystrophin will provide clinical benefit by helping to maintain muscle function. The DMDRP supported preclinical studies optimizing sequences for exon 51- and 53-skipping drugs, proof-of-concept studies in large animal models, and GLP toxicology studies. The continued development of exon 51- and 53-skipping drugs by industry, the federal government, and non-government organizations led to accelerated FDA approval of Exondys 51 and Viltepso.

PARTNERS/COLLABORATORS
Children’s National Medical Center (Muscle Research Consortium; Cooperative International Neuromuscular Research Group)

AWARD NUMBERS: W81XWH-09-1-0599, W81XWH-09-1-0215, W81XWH-11-1-0419

IMPACT: These exon-skipping drugs are currently available as potential treatments for the over 20% of patients with DMD who have a mutation amenable to exon 51 skipping (13%) or exon 53 skipping (8%).
Vamorolone

DESCRIPTION
The current standard of care (SOC) for DMD is to use anti-inflammatory corticosteroids to prolong muscle function, but they drive significant adverse side effects. The DMDRP supported preclinical studies on the development, safety, and efficacy evaluation of a non-hormonal steroid drug, VBP15, now called Vamorolone, which demonstrated decreased muscle inflammation and reduced side effects observed with other corticosteroid-based treatments. Completion of a phase 2a study in boys with DMD demonstrated efficacy similar to corticosteroids and safety outcomes and indicated a benign safety profile.

PARTNERS/COLLABORATORS
Children’s National Medical Center

AWARD NUMBERS: W81XWH-05-1-0616, W81XWH-09-1-0218, W81-XWH-11-1-0754

IMPACT: Vamorolone is now in clinical testing in an FDA/European Medicines Agency registration study that, if successful, will lead to a new drug application soon and a new SOC to prolong muscle function in DMD.
Micro-Dystrophin Gene Therapy

DESCRIPTION
The anti-inflammatory corticosteroids currently used to prolong muscle function in DMD have significant adverse side effects, and muscle function is only prolonged temporarily. Efforts to develop long-term treatments and even a cure are focused on correcting the genetic mutations in the dystrophin gene that cause the disease. A very promising treatment approach is gene therapy using a micro-dystrophin gene that produces functional dystrophin. The DMDRP supported independent preclinical studies on adeno-associated virus (AAV) vector optimization, production, and delivery methods for gene therapy that demonstrated improved cardiorespiratory function and persistent micro-dystrophin expression in large animal models for at least 2 years. The combined results from these two studies led to a collaboration with Solid Biosciences for a clinical trial evaluating micro-dystrophin gene transfer (SGT-001) in adolescents and children with DMD.

PARTNERS/COLLABORATORS
University of Florida; University of Missouri; Texas A&M University

AWARD NUMBERS: W81XWH-13-1-0283, W81XWH-14-1-0302

IMPACT: This gene therapy approach, if successful, will offer a treatment for maintaining muscle function long-term and improving the quality of life for individuals with DMD.
**Vision:** A time when post-traumatic epilepsy can be prevented or optimally managed

**Mission:** To understand the mechanisms of post-traumatic epilepsy and associated comorbidities to improve quality of life, especially in Service Members, Veterans, and caregivers

**Years Program Appropriated:** FY15-FY21

**Total Appropriations:** $61.5M

The Epilepsy Research Program (ERP) was initiated in 2015 to develop an understanding of the magnitude of post-traumatic epilepsy (PTE) within the military and to expand research into the basic mechanisms by which traumatic brain injury (TBI) produces epilepsy. The ERP’s goal is a world in which PTE can be prevented or optimally managed. Its strategy consists of four Focus Areas to include (1) innovations in PTE research, (2) identifying markers or mechanisms of PTE via preclinical models, (3) studies of the evolution of PTE, and (4) epidemiology.
ANX005

DESCRIPTION
ANX005 is a monoclonal antibody designed to inhibit the complement protein, C1q. C1q is involved in neuroinflammation. ERP-funded researchers discovered that C1q expression increased in a key part of the brain called the corticothalamic circuit (CTC) after TBI. The CTC is thought to be involved in PTE. Blocking C1q counteracted most of these outcomes, suggesting that C1q is a disease modifier in PTE and a potential therapy. Research is currently in animals only.

PARTNERS/COLLABORATORS
J. David Gladstone Institutes

AWARD NUMBER: W81XWH-16-1-0576

Sodium Butyrate

DESCRIPTION
Histone deacetylases (HDAC) are proteins that control gene expression. In TBI, these proteins drastically increase in number. This study evaluated whether sodium butyrate could inhibit HDAC function. Sodium butyrate not only inhibited HDAC function, but also decreased events associated with PTE. Research is currently in animals only.

PARTNERS/COLLABORATORS
Texas A&M Health Sciences Center, College of Medicine and Center for Epigenetics

AWARD NUMBER: W81XWH-16-1-0660
**2-Deoxyglucose**

**DESCRIPTION**
Brain metabolism after TBI drastically increases. Its major fuel is glucose, which is broken down by a process known as glycolysis. Inhibitors of glycolysis were tested to see if they could modulate brain metabolism and subsequently prevent the development of PTE. 2-Deoxyglucose was shown to prevent cortical hyperexcitability after TBI, which is a potential key step in the development of PTE. Research is currently in animals only.

**PARTNERS/COLLABORATORS**
Tufts University School of Medicine; University of Virginia School of Medicine; Massachusetts General Hospital

**AWARD NUMBER:** W81XWH-17-1-0531

**IMPACT:** Study results of glycolysis inhibitors could lead to potential therapy for PTE or even the prevention of PTE after injury.

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**Medication Use in Military Populations for Post-Traumatic Epilepsy**

**DESCRIPTION**
Epidemiological data is needed in order to better understand patient management for PTE. The ERP is supporting a rare effort to compile this data, which will provide an understanding of other common co-occurring factors and conditions involved in PTE patients. This could lead to customized and improved patient care for individuals with PTE.

**PARTNERS/COLLABORATORS**
Western Institute for Biomedical Research; University of Texas Health Science Center at San Antonio; Hunter Holmes McGuire VA Medical Center (VAMC)

**AWARD NUMBER:** W81XWH-18-1-0247

**IMPACT:** Understanding how PTE patient care is currently managed will help us improve future patient care. This study will reveal disease-specific mortality and reveal comorbidities in post-9/11 Veterans.
Large Animal Models of Post-Traumatic Epilepsy

DESCRIPTION
During the time between TBI and the development of PTE, the brain undergoes changes that make it prone to seizures, a process known as epileptogenesis. The most common models rely on rodents. While these models replicate some of the hallmarks of PTE, they may not adequately model the complex focal and diffuse brain injuries typically seen in PTE patients. The swine brain more closely resembles human neuroanatomy. The work is showing some novel brain circuitry alterations, electrophysiological markers, and blood biomarkers that will lead to a much deeper understanding of the fundamental mechanisms of epileptogenesis.

PARTNERS/COLLABORATORS
The University of Pennsylvania; CURE Epilepsy; Department of Neuropathology, Queen Elizabeth University Hospital

Vision: Improved health and lives of Veterans who have Gulf War Illness

Mission: Fund Gulf War Illness research that expeditiously identifies effective treatments and accelerates their clinical application, improves definition and diagnosis, and results in better understanding of pathobiology and symptoms of disease

Years Program Appropriated: FY06, FY08-FY21
Total Appropriations: $236M

The population of Veterans affected by Gulf War Illness (GWI) is a subset of the nearly 700,000 U.S. Warfighters who served during the 1990-1991 Gulf War. Studies indicate that approximately 25%-32% of Gulf War Veterans continue to experience multiple, diverse symptoms not explained by established medical diagnoses or standard laboratory tests. The Gulf War Illness Research Program (GWIRP) prioritizes innovative, competitively peer-reviewed research to develop and accelerate clinical application of treatments for the complex of GWI symptoms and their underlying causes. The identification of objective markers for improved definition, diagnosis, and therapeutic efficacy is also a program Focus Area. The GWIRP vision is to improve the health and lives of affected Veterans and their families.
Coenzyme Q10 (CoQ10) for Gulf War Illness

DESCRIPTION
The antioxidant CoQ10’s mechanism of action in treating GWI is unknown, but researchers have suggested both remediation of mitochondrial dysfunction and suppression of inflammation. The GWIRP funded a phase 3 double-blind, placebo-controlled trial of different doses of Ubiquinone (the oxidized form of CoQ10) in 225 Veterans with GWI. This study will validate an initial GWIRP-funded, double-blind placebo-controlled crossover pilot trial and complements a double-blind, placebo-controlled, four-site trial of Ubiquinol (the reduced form of CoQ10) funded by the VA Office of Research and Development. The results of these studies together should shed light on the relative merits of treatment with Ubiquinol versus Ubiquinone as well as defining the most effective dose range.

PARTNERS/COLLABORATORS
University of California San Diego; Miami VA Healthcare System

AWARD NUMBERS: W81XWH-07-1-0667, W81XWH-20-1-0523, VA 5I01CX001480

IMPACT: Because of its current status as a dietary supplement and a known, broad safety margin, CoQ10 has the potential for universal safe and inexpensive treatment for Veterans with GWI.
Gulf War Illness Clinical Trial Consortium (GWICTIC)

DESCRIPTION
The GWICTIC brings together expertise of clinical and preclinical GWI researchers from academia and the VA to implement early phase clinical trials of interventions. Therapeutic targets include neuro-inflammation and homeostatic regulatory networks previously identified biological pathways associated with GWI. In addition, the GWICTIC comprises a foundation of scalable infrastructure and management to facilitate the implementation of future trials.

PARTNERS/COLLABORATORS
Nova Southeastern University/Miami VAMC; RTI International; Boston University; New Jersey War-Related Illness and Injury Study Center (WRIISC); Palo Alto WRIISC; Weill Cornell Medical College; Rochester Hospital

AWARD NUMBER: W81XWH-18-2-0062

IMPACT: Within the next few years, the GWICTIC will complete four multisite clinical trials for the treatment of GWI. Other clinical trial researchers outside of the GWICTIC can leverage the organizational structure and resources of this consortium to enhance and improve their own studies.
Repository for Gulf War Illness Biomaterials and Data

**DESCRIPTION**

The Boston Biorepository, Recruitment, and Integrative Network (BBRAIN) is a biorepository network that provides a centralized holding and cataloging of retrospective and prospective biological samples, specimens, and data related to human GWI research studies. This repository expands an earlier GWIRP research consortium effort that banked large numbers of specimens and developed large datasets. Using the BBRAIN, researchers can compare biomarkers with medical features of GWI, including corresponding cognitive outcomes, brain imaging, demographics, health symptom surveys, and study outcomes.

**PARTNERS/COLLABORATORS**

Boston University Medical Campus; Miami VAMC/NOVA Southeastern University; Bronx VAMC; San Francisco VAMC

**AWARD NUMBER:** W81XWH-18-1-0549

**IMPACT:** There is currently no other open source for GWI biomaterials and data available to extramural researchers. Through the BBRAIN, any researcher can request specimens or data for their own research purposes and can employ the BBRAIN data resources to compare biomarkers with medical features of GWI and study outcomes.
Etanercept Plus Mifepristone for Gulf War Illness (Sub-Study of the GWICTIC)

DESCRIPTION
Researchers have shown dysregulation of homeostatic regulatory networks, particularly the hypothalamic–pituitary–adrenal (HPA) axis, in Veterans with GWI. It is thought that stepwise inhibition of tumor necrosis factor-alpha signaling with Etanercept, followed later by glucocorticoid receptor antagonism using Mifepristone, will shift the homeostatic signaling network into a normal regulatory pattern. An initial GWIRP-funded pilot study using low doses of Etanercept in 20 subjects demonstrated good safety but only moderate efficacy. A follow-on study tests an additional two-site phase 1 study using higher doses of Etanercept for longer durations, followed by a larger five-site phase 2 study in more than 105 subjects using doses and durations found to be safe.

PARTNERS/COLLABORATORS
Nova Southeastern University/Miami VAMC; RTI International; Boston University; New Jersey WRIISC; Palo Alto WRIISC; Weill Cornell Medical College; Rochester Hospital

AWARD NUMBERS: W81XWH-13-2-0085, W81XWH-18-2-0062

IMPACT: The Etanercept plus Mifepristone treatment protocol uses FDA-approved drugs and has the potential for rapid translation as a treatment for GWI.
Neuronavigation-Guided Transcranial Magnetic Stimulation (NG-rTMS) for GWI-Related Headaches and Pain (GWI-HAP)

**DESCRIPTION**
NG-rTMS is currently an FDA-approved treatment for major depression and migraine. In a GWIRP-funded pilot trial in 40 Veterans with GWI, repetitive NG-rTMS applied to the left motor cortex (LMC) was shown to provide significant relief of muscle pain, concentration difficulties, and fatigue as well as trends for improvement in joint pain and headache. A follow-on dual-blind sham treatment-controlled phase 2 trial of NG-rTMS will employ 150 subjects with GWI-HAP to look for improvements in several GWI symptom domains. This study complements a randomized, double-blind assessment of rTMS in 150 Veterans with GWI-HAP and moderate-severe depression funded by the VA Office of Research and Development.

**PARTNERS/COLLABORATORS**
Veterans Medical Research Foundation of San Diego; VA Palo Alto Health Care; Atlanta VAMC

**AWARD NUMBERS:** W81XWH-16-1-0754, W81XWH-19-1-0691; VA (pending)

**IMPACT:** NG-rTMS is a low-risk, non-invasive, and FDA-approved therapy that could immediately be translated to clinical treatment of Veterans experiencing GWI-HAP. The treatment has already been found to be effective against the frequently reported GWI symptoms of generalized pain, fatigue, and difficulty concentrating.
Central Nervous System (CNS) Antibodies as Diagnostic Markers of Gulf War Illness

DESCRIPTION
The central theory of this product is that an initial chemical insult during deployment in the 1990-1991 Persian Gulf War (such as exposure to organophosphate nerve toxins) caused loss of cell and blood-brain barrier integrity, allowing proteins of the CNS to enter the circulation. This, in turn resulted in formation of autoantibodies to these CNS proteins. Researchers have been developing methods for detecting these circulating CNS protein autoantibodies in blood, plasma, serum, and saliva. In a GWIRP-funded pilot study, samples from GWI cases were analyzed and differences in levels of circulating antibodies to several CNS proteins were found. In a follow-on study, these findings were expanded and validated in 100 additional GWI cases. Levels of antibody markers are being correlated with brain volumetric data and microstructural alterations to further validate potential use as GWI diagnostic biomarkers.

PARTNERS/COLLABORATORS
Duke University; Boston University


IMPACT: Objective markers such as these can provide a strong foundation for an inductive definition and diagnosis of GWI.
Anthony Hardie
GWIRP Programmatic Panel Member and Consumer

“I’m grateful for the members of Congress that have stood by Gulf War Veterans, support which has never wavered. I’m grateful for the leadership within the Department of Defense that helps to make this program happen and helps to ensure that this program is indeed finding and funding the best research aimed at finding treatments and cures for Gulf War Illness.”

Col Todd S. Desgrosseilliers (U.S. Marine Corps, Ret.)
Hearing Restoration Research Program (HRRP) Programmatic Panel and Consumer

“Almost every man and woman who served our country suffers from some hearing loss or other hearing-related challenge. It’s an ongoing battle that we face for the rest of our lives. As a disabled Veteran who suffers from hearing loss and vertigo, I cannot overstate the importance of the HRRP. This program holds the potential to mitigate the impact of this widespread health issue and thereby greatly improve the quality of life for our nation’s Veterans. It’s an honor and a privilege to continue to serve our nation as a part of the effort to significantly improve the lives of our Service Members and Veterans.”
**Vision:** Improve the operational performance/effectiveness, medical readiness, and quality of life of Service Members and Veterans with auditory system injuries

**Mission:** Advance the science of hearing restoration by delivering groundbreaking research and solutions that remove barriers to the successful treatment of auditory system injury

**Years Program Appropriated:** FY17-FY21

**Total Appropriations:** $50M

The HRRP pursues the treatment of auditory system injuries and the restoration of hearing. Currently, no drug has been approved by the FDA to treat hearing loss associated with sensory, neural, synaptic, or central auditory dysfunction. Significant progress has been made in the understanding of hearing loss and regeneration mechanisms in animal models. However, the unique anatomical features of the inner ear severely hinder the clinical validation of preclinical findings, the translation of preclinical findings into clinical applications, and precision diagnostics that allow patients to be matched to appropriate interventions and outcome measurements. The HRRP challenges the science community to design innovative studies to overcome the major obstacles in clinical translation and precision diagnostics, as well as to advance the diagnosis of acute auditory system injury in austere or remote environments.
Miniature μOCT Intracochlear Imaging Probe

DESCRIPTION
The lack of capability to examine cochlear pathology at the cellular level severely hinders efforts to understand, diagnose, and develop treatment for sensorineural hearing loss, one of the most common war-induced injuries among American military personnel. With 1-micrometer resolution, the miniature μOCT intracochlear imaging probe can resolve intracochlear cells and auditory nerve fibers and reveal cochlear microstructure. Its successful development will make a breakthrough in the diagnosis of cellular-level cochlear pathology, enabling precision medicine in the treatment of sensorineural hearing loss.

PARTNERS/COLLABORATORS
Massachusetts Eye and Ear Infirmary, Harvard Medical School

AWARD NUMBER: W81XWH-20-1-0855

IMPACT: Developing a key technology, the miniature intracochlear imaging probe will revolutionize the diagnosis and treatment of sensorineural hearing loss.

μOCT image of nerve fiber bundles traversing the tunnel of Corti and space of Nuel to innervate outer hair cells (500 μm × 500 μm).

(a) Volumetric reconstruction of maximum-projected μOCT image stack, depicting bundles of nerve fibers traversing the organ of Corti towards the outer hair cell region. The schematic in the top right-hand corner shows the orientation of the virtual sectioning plane. Scale = 150 μm. (b) Schematic representation of the microanatomy in the top panel, with bundles of nerve fibers (NF) crossing the tunnel of Corti (TC) and/or the space of Nuel (SN). OPC = outer pillar cells. Scale = 150 μm. (c) For reference, a confocal laser scanning microscopy image of the guinea pig organ of Corti. Rhodamine phalloidin (red) marks outer and inner pillar cells (OPC and IPC, respectively), Hoechst stain (blue) marks cell nuclei, and neurofilament-H (green) marks neuronal fibers. Scale = 50 μm.

Figure: Iyer, J. S. et al. Micro-optical coherence tomography of the mammalian cochlea. Sci. Rep. 6, 33288; doi: 10.1038/srep33288 (2016).
Cell Reprogramming in the Mature Mammalian Inner Ear

**DESCRIPTION**
This proof-of-principle research establishes the potential of “reprogramming” as a strategy to make new auditory cells in the adult mammalian inner ear, which normally lack the capacity to divide or regenerate. It demonstrated that robust proliferation of diverse adult cochlear sensory epithelial cell types (purple), regeneration of hair cells (green), and connection with neurons (red) could be induced by co-activation of two genes, an exciting result that was published in the prominent journal Nature Communication.

**PARTNERS/COLLABORATORS**
Massachusetts Eye and Ear Infirmary, Harvard Medical School

**AWARD NUMBER:** W81XWH-18-1-0331

**IMPACT:** This significant advancement in research has the potential and novel strategy to regenerate auditory hair cells in adult mammals, which may ultimately lead to new hearing restoration therapies.

3-D Stem Cells Niche

**DESCRIPTION**
The artificial 3-D stem cells niche was shown to enhance the survival and neuronal differentiation of transplanted otic neuronal progenitors. It is a significant progress toward the goal of regenerating neuronal cells in the inner ear with a cell transplantation approach. This exciting result was published in 2020 and also supported the filing of a provisional patent.

**PARTNERS/COLLABORATORS**
Northwestern University; Indiana University

**AWARD NUMBER:** W81XWH-18-1-0752

**IMPACT:** This development of a key technology toward the regeneration of neuronal cells in the inner ear could ultimately lead to new hearing restoration therapies.
Automated Brain-Behavior Listening Assessment

DESCRIPTION
The automated brain-behavior assessment of listening is intended for use by non-specialists with minimal training to classify auditory fitness-to-duty in austere environments. Its successful development will significantly expand diagnosis capability beyond current auditory tests using pure tone audiometry.

PARTNERS/COLLABORATORS
University of California, Davis

AWARD NUMBER: W81XWH-20-1-0485

Statins

DESCRIPTION
Recent research suggested that statins, a class of readily available drugs commonly used to treat high cholesterol, are protective against hearing threshold increases and cochlear structure damage in two animal models. Ongoing efforts aim to identify the most effective oral statin to protect against noise-induced hearing loss and cochlear damage and to investigate its effect, either alone or in combination with oral steroids, in both an animal model and in a pilot, first-in-kind clinical trial with human patients.

PARTNERS/COLLABORATORS
Northwestern University

AWARD NUMBER: W81XWH-20-1-0484
Vision: Move military-relevant medical solutions forward in the acquisition life-cycle to meet the needs of Service Members and other military health system beneficiaries

Mission: Accelerate research and development projects that have the potential to close high-priority Department of Defense medical capability gaps

Years Program Appropriated: FY12-FY21

Total Appropriations: $530M

The Joint Warfighter Medical Research Program’s (JWMRP) mission is to augment and accelerate research and development projects that have the potential to close high-priority DOD and Service medical capability gaps and move military-relevant medical solutions forward in the acquisition life-cycle. To achieve this, the JWMRP requires that applications are a continuation of either congressionally directed or core prior-year medical research or advanced product development efforts that are close to achieving their objectives and transitioning promising advancements from the laboratory toward the clinic for the benefit of our Service Members, other Military Health System beneficiaries, and the American public. Applications are linked to one of the Joint Program Committee scientific domains (Medical Simulation and Information Sciences, Military Infectious Diseases, Military Operational Medicine, Combat Casualty Care, Radiation Health Effects, or Clinical and Rehabilitative Medicine).
Riluzole

DESCRIPTION
Riluzole can be used as a neuroprotective therapy for acute spinal cord injury (SCI) that can be orally administered on the battlefield or at an accident site. DOD-funded clinical trial data suggest that treatment with Riluzole has a beneficial effect on motor, sensory, functional, and quality of life outcomes of patients with traumatic acute SCI as compared to placebo.

PARTNERS/COLLABORATORS
Christopher & Dana Reeve Foundation; Houston Methodist Hospital; University of Miami; Toronto Western Hospital; University of Texas Health Science Center; University of Maryland; Thomas Jefferson University; University of Houston Pharmacology Center

AWARD NUMBER: W81XWH-16-C-0031

IMPACT: In a landscape where there are no demonstrated effective treatments for either acute or chronic spinal cord injury, this project fills a critical gap toward improving care.

Sufentanil Nanotab®

DESCRIPTION
Sufentanil is a microtablet for non-invasive sublingual delivery of a high therapeutic index opioid for the treatment of acute pain. The non-invasive sublingual tablet formulation is more portable than larger morphine syringes, and it eliminates the risk of local and systemic infection or accidental needle sticks and provides even drug uptake into the muscles, which improves pain relief in patient care. AcelRx awarded Federal Supply Schedule contract through VA National Acquisition Center on March 4, 2019.

PARTNERS/COLLABORATORS
AcelRx Pharmaceuticals, Inc.

AWARD NUMBER: W81XWH-15-C-0046

IMPACT: This microtablet for sublingual delivery provides a more portable, easier to administer, and more effective pain relief option – particularly important for battlefield and trauma care applications.
TAK-214 Vaccine for Norovirus Gastroenteritis

**DESCRIPTION**
Human norovirus is the major cause of infectious acute gastroenteritis (AGE) throughout the world, accounting for 90% of all non-bacterial incidents of AGE disease, and with more than 21 million cases annually in the U.S. JWRMP funds advanced this vaccine candidate along the regulatory pathway for FDA licensure.

**PARTNERS/COLLABORATORS**
Takeda Vaccines (formerly Ligocyte)

**AWARD NUMBER:** W81XWH-15-C-0063

**IMPACT:** This vaccine has the potential to prevent millions of cases of norovirus each year in both military and public settings.

J-PRO Osteoarthritis Therapeutic

**DESCRIPTION**
J-PRO is an injectable lyophilized extracellular matrix that is mixed with the patient’s blood as a point-of-care therapeutic for post-traumatic OA. This therapeutic restores articular cartilage after joint injury and prevents the development of OA, thus maximizing joint function.

**PARTNERS/COLLABORATORS**
Massachusetts General Hospital; Boston Children’s Hospital; Rhode Island Hospital

**AWARD NUMBERS:**
W81XWH-17-2-0016
W81XWH-15-C-0052
W81XWH-16-C-0043
W81XWH-16-C-0172

**IMPACT:** Among the military population, acute knee injuries comprise 5% of the reported injuries, and post-traumatic OA is a primary source of disability. This injectable therapeutic can enhance the opportunity to return to duty and improve injured Service Members’ quality of life.
Autologous Bone Marrow Mononuclear Cells (BMMNCS) for Treatment of Severe TBI

**DESCRIPTION**
An infusion of cells harvested and isolated from a patient’s own bone marrow may be able to control brain swelling after TBI. DOD-funded clinical trial data suggest that bone marrow-derived cells improve neurocognitive and functional outcomes, as well as brain structure after severe TBI in adults.

**PARTNERS/COLLABORATORS**
The University of Texas Health Science Center at Houston; Memorial Hermann-Texas Medical Center; Houston Methodist Research Institute; Parkland Hospital; University of Texas Southwestern Medical Center; University of Texas Health Evelyn H. Griffin Stem Cell Therapeutics Research Laboratory

**AWARD NUMBERS:** W81XWH-16-C-0040; prior funding under TBIPHRP W81XWH-11-1-0460

Pudendal Nerve Stimulator (PSTIM)

**DESCRIPTION**
The PSTIM is an implantable pudendal (pelvic) nerve stimulator to repair bladder dysfunction resulting from some SCIs and eliminate the need for daily catheterization. Currently, there is no medication that can treat both incontinence and the ability of the bladder to empty completely after SCI.

**PARTNERS/COLLABORATORS**
University of Pittsburgh; InCube Labs

**AWARD NUMBERS:** W81XWH-15-C-0066; prior funding under SCIRP W81XWH-11-1-0819
SPRINT® Peripheral Nerve Stimulation (PNS) System

DESCRIPTION
The PNS system is designed to improve functional outcomes by alleviating residual limb pain and phantom limb pain in major lower limb amputees. This product provides a non-drug solution for managing post-amputation pain, which can lead to disability, reduced quality of life, frustration, and depression, factors that can impact function even more than the actual loss of a limb.

PARTNERS/COLLABORATORS
SPR Therapeutics; Northwestern University; University of California San Diego; University of Texas Health Science Center at San Antonio; James A. Haley Veteran’s Hospital; Otrimed Clinical Research Center; Duke University; Better Health Clinical Research; MedVadis (Boston PainCare)

AWARD NUMBERS: W81XWH-17-C-0019; additional funding from PRORP W81XWH-12-2-0132, PRORP W81XWH-18-1-0799, and PRMRP W81XWH-18-1-0800

IMPACT: JWMRP funds advanced this device along the pathway for 510(k) clearance. This project importantly addresses a significant healthcare need for non-narcotic pain relief in patient care.

Novel Adhesive Hydrogel for Ocular Trauma Intervention

DESCRIPTION
This thermoresponsive reversibly attachable hydrogel patch would temporarily seal penetrating injuries to the eye. Penetrating eye injuries left untreated for more than 24 hours can lead to retinal detachment and permanent vision loss, so this temporary solution is critical in austere environments where casualties may not be able to receive surgical intervention for days.

PARTNERS/COLLABORATORS
University of Southern California; Walter Reed Ophthalmology

AWARD NUMBERS: W81XWH-16-C-0086; prior funding under VRP W81XWH-12-1-0314

IMPACT: This intervention can improve vision outcomes for combat casualties, improve return to duty time, and increase quality of life for our Veteran population.
**Intracranial Pressure Assessment and Screening System (IPASS)**

**DESCRIPTION**
The IPASS is a compact, portable monitor for non-invasive measurement of intracranial pressure to assess impairments following TBI. This device eliminates the need for invasive neurosurgical procedures by using sensors placed on the forehead, earlobe, and/or fingertip and allows medics and clinicians to reliably monitor TBI patients across the spectrum of en-route care and facilities-based treatment.

**PARTNERS/COLLABORATORS**
Vivonics, Inc.; University of Miami; Johns Hopkins University School of Medicine; University of Pittsburgh; Baylor College of Medicine; Rhode Island Hospital; Tufts Medical Center; Beth Israel Deaconess Hospital

**AWARD NUMBERS:** W81XWH-17-C-0006; additional funding under W81XWH-13-0187 and W81XWH-15-9-0001

**IMPACT:** This system provides the capability to triage casualties with closed-head brain injuries much closer to the time of the trauma, enabling rapid treatment to preclude further injury, thus improving patient care.

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**Transfusion Prediction Algorithm**

**DESCRIPTION**
This is a vital sign input-based decision support tool to differentiate, at the early stages of care during transport, the casualties who require immediate and/or large-scale blood transfusion immediately upon hospital arrival. This robust, user-friendly, reliable software application can be embedded in patient care monitors that are already widely in use on the battlefield and civilian care. JWMRP funds augmented a 5-year effort to deliver a hospital/center-based, wireless, real-time vital signs data collection system by enabling the building of this transfusion prediction algorithm.

**PARTNERS/COLLABORATORS**
University of Maryland, Baltimore; U.S. Army Institute of Surgical Research; Telemedicine and Advanced Technology Research Center

**AWARD NUMBER:** W81XWH-16-R-0003

**IMPACT:** This initiative directly impacts clinical practices related to the use of blood in trauma patients on the battlefield and in civilian care and mitigates the risk of death from traumatic bleeding.
Vision: To eliminate kidney cancer through collaboration and discovery

Mission: To promote rigorous, innovative, high-impact research in kidney cancer for the benefit of Service Members, Veterans, and the American public

Years Program Appropriated: FY17-FY21
Total Appropriations: $135M

Since its inception in FY17, the Peer Reviewed Kidney Cancer Research Program (KCRP) has rapidly become a leader in the drive to eliminate kidney cancer by fostering clinical collaborations and promoting innovative high-impact research. To focus the program’s investment priorities, the KCRP established four strategic goals:

- Increase understanding of the biology of kidney cancer
  - Encourage innovative ideas with high impact

- Develop novel therapeutic strategies for the treatment of kidney cancer
  - Identify new targets
  - Develop pharmacological, immunological, and genetic interventions
  - Optimize prognostic or predictive markers to assist with therapeutic decision-making
  - Repurpose existing and currently approved drugs

- Improve patient care for kidney cancer
  - Integrate bench research with bedside care and emphasize translational research
  - Invest in early career kidney cancer physicians – next generation
  - Facilitate multi-site, collaborative clinical research development and clinical trials
  - Eliminate disparities in populations with an unequal burden of kidney cancer

- Grow integration of bench research with bedside care – translational research
  - Invest in next generation kidney cancer physicians and scientists
  - Facilitate multi-site, collaborative clinical research development and clinical trials
  - Encourage experts inside and outside kidney cancer to apply knowledge for advancements
  - Foster collaborations that cross translational, disciplinary, and institutional boundaries
Kidney Cancer Research Consortium (KCRC)

DESCRIPTION
The KCRP awarded a Consortium Development Award (CDA) followed by a Clinical Consortium Award to establish and support a geographically dispersed KCRC composed of a coordinating center and three clinical trial sites. The KCRC will open trials for patients with all types of renal cell carcinoma, including rarer forms like medullary, papillary, and chromophobe renal cell carcinomas. The ultimate goal is discovery of more specific treatment approaches, driven by an improved understanding of renal cell carcinoma biology and therapies that are targeted to the right patient subpopulations.

PARTNERS/COLLABORATORS
M.D. Anderson Cancer Center; University of Texas, Southwestern Medical Center at Dallas; University of Pennsylvania; Beth Israel Deaconess Medical Center


IMPACT: To achieve improved kidney cancer patient outcomes, this award established a multi-site network of exceptional institutions and investigators who can rapidly execute kidney cancer trials that would otherwise be difficult to complete at any single center.
**Academy of Kidney Cancer Investigators (AKCI)**

**DESCRIPTION**
The AKCI brings together an Academy Dean with a cadre of early career investigators in a unique, interactive virtual academy to develop a network of early-career researchers who are committed to careers as kidney cancer experts and accelerating advances in kidney cancer treatment. The overarching goal of the AKCI is to develop successful, highly productive kidney cancer researchers in a collaborative research and career development environment.

**PARTNERS/COLLABORATORS**
Vanderbilt University Medical Center; Dana-Farber Cancer Institute; Dartmouth College; Cleveland Clinic Foundation

**AWARD NUMBERS:** W81XWH-20-2-0046, W81XWH-20-1-0882, W81XWH-20-1-0778, W81XWH-20-1-0804

**IMPACT:** This virtual academy provides new opportunities for collaboration across kidney cancer disciplines and is expected to synergize with the KCRP’s other signature effort, the KCRC, to accelerate translation of research for improved patient outcomes.

**Prognostic Biomarker to Detect Recurrent Kidney Cancer**

**DESCRIPTION**
The goal of this project is to develop and validate cell-free methylated DNA (cfmeDNA, DNA found freely circulating in the blood) as a prognostic biomarker to predict recurrent renal cell carcinoma (RCC) following kidney removal. Samples are being analyzed from two randomized controlled clinical trials that compared the effectiveness of targeted therapy versus placebo in patients with advanced high-risk RCC treated with surgery. The advantages of cfmeDNA as a biomarker are (1) it is a simple, non-invasive way to detect cancer cells and (2) it allows identification of tumor tissue origin.

**PARTNERS/COLLABORATORS**
Dana Farber Cancer Institute

**AWARD NUMBER:** W81XWH-19-1-0553

**IMPACT:** Identification of a possible new biomarker to accurately predict RCC recurrence following kidney removal may transform clinical care by allowing clinicians to identify patients who will benefit from additional therapy.
Preventing Therapeutic Resistance in Kidney Cancer

DESCRIPTION
One class of front-line therapy for patients with metastatic renal cell carcinoma (mRCC) targets tumor-associated new blood vessel growth in order to starve tumor cells of oxygen and nutrients carried by the bloodstream. Therapies that inhibit this blood vessel growth have shown promise to extend the lives of patients with mRCC, although most eventually fail due to therapeutic resistance. Once treatment ends, the resistant tumor cells emerge from their dormant state, and tumor growth and metastasis ensue. This work describes how RCC tumors become resistant to therapies by inhibiting growth of new blood vessels and “starving” the tumor and suggests that adding a second therapy that prohibits tumor cells from entering a dormant state may prevent tumor resistance and metastasis.

PARTNERS/COLLABORATORS
Health Research Inc., Roswell Park Division

AWARD NUMBER: W81XWH-14-1-0210 (PRCRP-funded award under the kidney cancer Topic Area)
Silk as a Scaffold to Model the Tumor Microenvironment

DESCRIPTION
This KCRP-funded project establishes a synthetic tumor microenvironment to model clear cell renal cell carcinoma (ccRCC) in an effort to better understand the role that tumor stromal cells play in disease progression. The team is developing an assay that mimics the extracellular matrix scaffolding “structure” to determine the complex interactions and influences that tumor-associated fibroblasts have on tumor aggressiveness. Use of the silk-based growth conditions that can mimic ccRCC in patients provides a robust system for detailed cellular and genetic analyses to better understand disease development, progression, and potential therapeutic targets.

PARTNERS/COLLABORATORS
The Rogosin Institute, Inc.

AWARD NUMBER: W81XWH-18-1-0620

Validation of silk scaffolding for ccRCC cell coculture with fibroblasts.
(A) Strategy for seeding cells into silk scaffolds: fluorescently labeled fibroblasts and tumor cells were mixed at 1:10 ratio, added to scaffolds, centrifuged into scaffolds, and cultured for 3 days before visualization.
(B) Confocal micrograph of representative scaffolded tumor cells and fibroblasts from 6 replicates. The silk material is autofluorescent in the DAPI channel (blue).
(C) Example of human ccRCC with tumor cells stained for cytokeratin 18 (green) and PDGFRB-expressing stromal cells (red). Tumor cell clusters and stromal cell arrangement are similar between the scaffolded cells and the tumor.

IMPACT: Better understanding of disease progression via a new model allows for rapid and large-scale evaluation of novel therapeutics and the study of therapeutic resistance in ccRCC and potentially other cancers as well.
C74–Tumor Cell Growth Inhibitor

DESCRIPTION
Higher expression of the protein profilin-1 (Pfn-1) in ccRCC tumors has been linked to advanced disease and poor patient outcomes. The research team conducted studies to understand the role of Pfn-1 in promoting tumor aggressiveness. This funding resulted in the development of a small molecule C74 that can bind to Pfn-1 and interfere with the pro-tumor activity of Pfn-1. The study also showed the C74 molecule was able to limit tumor cell growth in a preclinical proof of concept study. Next steps include continued improvements in the formulation and delivery of the C74 molecule as well as derivative forms of this inhibitor.

PARTNERS/COLLABORATORS
University of Pittsburgh

AWARD NUMBER: W81XWH-19-1-0768

IMPACT: This study could potentially provide a new tool to slow or prevent metastasis for the vast majority of ccRCC patients with more advanced disease.

C74 inhibits kidney tumor growth in vivo. Mice bearing subcutaneous RENCA tumors, a mouse model of ccRCC, were treated daily with either control (DMSO) or the Pfn-1/Actin inhibitor C74. After 20 days, C74-treated tumors were found to be significantly smaller in size (C) and in weight (D), indicating a reduction in tumor aggressiveness.

Vision: To eradicate deaths and suffering from lung cancer to better the health and welfare of Service Members, Veterans, and the American public

Mission: Support and integrate research from multiple disciplines for risk assessment, prevention, early detection, diagnosis, and treatment for the control and cure of lung cancer

Years Program Appropriated: FY09-FY21
Total Appropriations: $175.5M

The Lung Cancer Research Program’s (LCRP’s) mission is to eradicate deaths and suffering from lung cancer to better the health and welfare of Service Members, Veterans, and the American public by supporting and integrating research from multiple disciplines for risk assessment, prevention, early detection, diagnosis, and treatment for the control and cure of lung cancer. The LCRP recognizes that there are a broad range of unanswered research questions in lung cancer; therefore, LCRP’s strategic priorities seek to address an important gap in the funding of lung cancer research—specifically, the seeding of new and innovative ideas that, once proven, can proceed forward for further translational development and clinical trial testing under the auspices of other funding agencies, as well as the LCRP.
Detection of Early Lung Cancer Among Military Personnel (DECAMP) Clinical Consortium

DESCRIPTION
Initiated by the LCRP, the DECAMP consortium is a multidisciplinary and translational research program established to develop and validate biomarkers that could be used to improve the early detection of lung cancer among military personnel, military family members, and Veterans believed to be at high risk. Consortium members include seven Veterans Administration Hospitals, three Military Treatment Facilities, and two academic hospitals. DECAMP clinical research seeks to establish non-invasive clinical biomarkers (1) to clarify the results of low-dose CT scans of patients where initial clinical findings are indeterminate for lung cancer, and (2) to screen and identify individuals at highest risk for developing lung cancer. The DECAMP consortium secured subsequent funding through industry and other federal agency partnerships, which is ensuring the consortium continues beyond the original LCRP investment.

PARTNERS/COLLABORATORS
Boston University Medical Campus; VA Tennessee Valley Healthcare System; University of California Los Angeles; Brown University; M.D. Anderson Cancer Center; Boston University Medical Campus; Naval Medical Center San Diego; Walter Reed National Military Medical Center; Naval Medical Center Portsmouth; Brooke Army Medical Center*

AWARD NUMBER: W81XWH-11-2-0161

* Initial partner, currently no longer participating
Overcoming Apoptotic Defects in Therapy-Resistant Lung Cancers

DESCRIPTION
Lung cancers are frequently driven by specific oncogenes that offer unique opportunities to develop targeted therapies. Unfortunately, targeted therapies often have variable success rates owing to the heterogeneous nature of the tumors, and responsive tumors often develop resistance to therapy. LCRP-funded work evaluated the role that a pro-cell death (apoptosis) gene, BIM, plays as both a predictor of potential therapeutic success and as a therapy itself. Results demonstrated that defective apoptosis is a key mediator of resistance to tyrosine kinase inhibitor-targeted therapies. This work led to an NCI-supported clinical trial (NCT02520778) evaluating Navitoclax in combination with Osimertinib in metastatic EGFR-positive lung cancer patients.

PARTNERS/COLLABORATORS
Massachusetts General Hospital

AWARD NUMBERS: W81XWH-13-1-0226, W81XWH-13-1-0227

IMPACT: Researchers identified novel cell-signaling targets involved in cancer development, which led to testing of new therapeutics with the potential to improve care options for lung cancer patients.

Novel KRAS G12C Inhibitors for Lung Cancer

DESCRIPTION
Mutations in the KRAS gene are responsible for driving many forms of solid tumors, although not all mutations promote tumorigenesis in the same manner. LCRP funds supported the development and characterization of two novel classes of KRAS binding compounds that demonstrated enhanced anti-proliferative and pro-cell death effects, as well as methods to evaluate their binding to KRAS. In lung cancer, KRAS G12C is the predominant mutation. Targeting of G12C mutant KRAS is currently the focus of several human clinical trials, and at least two draw their lead compound design directly from this LCRP-funded and published work.

PARTNERS/COLLABORATORS
University of Texas, Southwestern Medical Center at Dallas

AWARD NUMBER: W81XWH-16-1-0106

IMPACT: This more specific, mutant-targeting therapy may provide unique benefit and potentially improve treatment for lung cancer patients.
Novel Combination Therapy for Inoperable Lung Cancer

DESCRIPTION
The LCRP provided funding for a phase 1 clinical trial of TECENTRIQ® (atezolizumab, an immunotherapy that blocks PD-L1) in combination with standard of care stereotactic body radiotherapy (SBRT) in patients with early stage, inoperable, non-small cell lung cancer (NSCLC). Patients enrolled in this first-of-its-kind phase 1 study demonstrated no disease progression or dose-limiting toxicity while on the study. Additionally, several patients in the small cohort experienced a partial regression of their primary tumors. These exciting data led to the NCI-supported, ongoing phase 3 clinical trial (NCT04214262) to examine the benefit of adding atezolizumab to SBRT for NSCLC patients with inoperable stage I-IIA tumors.

PARTNERS/COLLABORATORS
University of California, Davis; Genetech

AWARD NUMBER: W81XWH-15-2-0063

Impact: This combination therapy will potentially address inadequate treatment strategies for the nearly 20% of patients diagnosed with early stage NSCLC who are not candidates for surgical or chemotherapeutic intervention.

Rigosertib: A Novel NSCLC Therapy

DESCRIPTION
K-RAS is a known driver of NSCLC, but efforts to target the molecule therapeutically have proven challenging. The LCRP funded preclinical studies of novel small molecules that mimic and prevent an important binding function of RAS and can thus block signaling leading to progression of NSCLC. Rigosertib (RGS) is an orally available RAS mimetic that exhibits efficacy as a lung tumor growth inhibitor in mice. Additional work demonstrated that RGS may synergize with conventional immune checkpoint inhibitor therapies to reduce total lung tumor burden in mouse models. Based on these results, an Icahn School of Medicine at Mount Sinai-supported clinical trial (NCT04263090) launched to evaluate RGS in combination with immune checkpoint inhibition.

PARTNERS/COLLABORATORS
Icahn School of Medicine at Mount Sinai

AWARD NUMBER: W81XWH-17-1-0207

Impact: Successful results from preclinical studies supported clinical testing for RGS as a novel and potentially more effective therapeutic to improve treatment options for NSCLC patients.
Mesothelin-Targeting CAR T Cells

DESCRIPTION
Lung adenocarcinoma patients whose tumors exhibit KRAS mutations typically respond poorly to adjuvant chemotherapy. The LCRP funded work to establish mesothelin, a tumor-associated protein, as a biomarker of aggressive, therapy-resistant disease. Additional work supported by the award developed mesothelin as a bona fide target for genetically engineered chimeric antigen receptor T (CAR T) cells. These CAR T cells were shown to infiltrate lung tumors and selectively kill mesothelin-expressing cancer cells in multiple preclinical mouse models. These results supported the opening of a Memorial Sloan Kettering Cancer Center-sponsored clinical trial (NCT02414269) to determine the safety of mesothelin-targeting CAR T cells, as well as effectiveness in combination with the immune checkpoint inhibitor, pembrolizumab, in patients with malignant pleural disease.

PARTNERS/COLLABORATORS
Sloan Kettering Institute for Cancer Research

AWARD NUMBER: W81XWH-12-1-0230

IMPACT: Mesothelin-targeting CAR T cells provide a novel therapeutic approach with the potential to improve treatment options for patients with aggressive, therapy-resistant lung adenocarcinoma.
Lung Cancer Biospecimen Resource Network (LCBRN)

DESCRIPTION
The LCRP established the first national lung cancer biospecimen resource unattached to a clinical trial, the LCBRN, with the intent to further basic, translational, and clinical research in the understanding, diagnosis, and treatment of lung cancer. Over its active life, the LCBRN collected, annotated, stored, and distributed human lung cancer biospecimens and follow-up clinical data from 763 patients in a manner that embraced the highest ethical standards for human subjects research. The LCBRN participated in the Cancer Moonshot Program’s APOLLO (Applied Proteogenomics Organizational Learning and Outcomes) Consortium, a tri-agency effort between the DOD, the VA, and the NCI. All LCBRN samples are now managed through the NIH’s Cooperative Human Tissue Network (http://lungbio.sites.virginia.edu).

PARTNERS/COLLABORATORS
University of Virginia; Washington University in St. Louis; Medical University of South Carolina

AWARD NUMBER: W81XWH-10-1-0818

IMPACT: LCBRN-supplied tissue samples have been used to evaluate gene mutation and expression signatures associated with lung cancer recurrence and then to test these molecular changes as prognostic markers for use in clinical decision-making. The LCBRN is a valuable tool for discovery, development, and testing aimed at providing novel approaches to treatment and overall better care for lung cancer patients.
LUPUS RESEARCH PROGRAM

**Vision:** To cure lupus through partnership of scientists, clinicians, and consumers

**Mission:** Fund research to understand, prevent, and diagnose lupus and to improve treatments and quality of life of patients, including Service Members, Veterans, and beneficiaries

**Years Program Appropriated:** FY17-FY21

**Total Appropriations:** $35M

The LRP’s mission is to fund research to understand, prevent, and diagnose lupus and to improve treatments and quality of life of patients, including Service Members, Veterans, and beneficiaries. Lupus is a heterogeneous autoimmune disease that is difficult to diagnose and treat. It can take months or years for an individual to be diagnosed, and treatment options are limited. Long-term use of current lupus treatments can result in serious side effects, including kidney problems, liver damage, and increased risk of infection. Priorities of the program include advancing the understanding of subsets of lupus patients to improve appropriate treatment of these patients, gaining insight into the disease mechanisms and heterogeneity, and improving patients’ quality of life by predicting and preventing lupus flares.
Utility of a Functioning Report for Lupus Patients and Their Providers

DESCRIPTION
Systemic lupus erythematosus (SLE) is a chronic, heterogeneous autoimmune disease that causes inflammation in numerous tissues within the body. This research aims to improve recognition of the issue of functional impairment in SLE patients and facilitate discussion around it. The research team developed an app that 60 SLE patients used for assessments of physical and cognitive functioning. The app-generated reports gave the results from self-reports and physician-guided exams using color and number scales. The reports included sections rating a patient’s ease of performing everyday activities, their concern for falling, and their mobility, including walking speed, balance, and ease of leaving the house.

PARTNERS/COLLABORATORS
Emory University

AWARD NUMBER: W81XWH-18-1-0619

Targeting IRF5 Hyperactivation in SLE as a Driver of Disease Risk and Pathogenesis

DESCRIPTION
Although the specific causes of SLE remain unclear, genetic risk factors and environmental stressors have been identified that are known to contribute to the disease. Previous research has suggested that there is a genetic association between SLE and certain genetic variants of interferon regulatory factor 5 (IRF5), a protein that controls inflammatory and immune responses. This project builds upon previous work to investigate whether IRF5 hyper-activation is a driver of SLE onset and severity and whether or not its inhibition will mediate protective effects in a spontaneous murine lupus model.

PARTNERS/COLLABORATORS
The Feinstein Institute for Medical Research

AWARD NUMBER: W81XWH-18-1-0674
Improving the Rationale for Treatment Choices in a Heterogeneous Disease

DESCRIPTION

Lupus is different in each patient, so the treatments and responses will also depend on understanding each patient. This project compares the immune patterns of responders vs non-responders to the lupus treatment methotrexate. Using clinical trial data to create a database, investigators are able to tease out differences in how various combinations of individual and overlapping treatments impact the patient’s immune system.

Understanding how these specific immune expressions correlate to treatments within a large cohort of lupus patients will allow researchers to find commonalities and create subsets within the heterogeneous population.

PARTNERS/COLLABORATORS

Oklahoma Medical Research Foundation

AWARD NUMBER: W81XWH-18-1-0693

IMPACT: Positive results of this type of research may create new opportunities for care providers to optimize treatment regimens to the specific immune markers expressed in individual patients for improved therapeutic benefit. Additionally, integrating “precision medicine” in lupus clinical trials by understanding the phenotypic subtypes of individuals with lupus would result in better clinical trials.
Therapeutic Targeting of Senescent Cells in Lupus

DESCRIPTION
Senescent cells, or cells that have stopped dividing, are increased in SLE target tissue and contribute to organ dysfunction, disease activity, and poor long-term prognosis. Senolytic drugs can selectively eliminate senescent cells' rejuvenating tissues, improving organ function and promoting better disease management. The Principal Investigator (PI) documented that bone marrow cells from lupus patients are a mixture of senescent and non-senescent cells; and senolytic drugs, in particular FOXO4-DRI, are able to selectively induce cell death in the senescent cells. They have also documented a marker of senescent cells in kidneys of lupus-prone mice. These findings suggest that use of senolytic drugs in lupus may selectively eliminate senescent cells in kidneys and improve renal function.

PARTNERS/COLLABORATORS
University of Rochester

AWARD NUMBER: W81XWH-18-1-0704

IMPACT: Rejuvenation of the reparative processes in tissues by eliminating senescent cells using senolytic drugs has already been achieved in vivo in animal models of aging. The results from this project support continued research and potential for using senolytic drugs to treat lupus.
Vision: Prevent melanoma initiation and progression

Mission: Promote earlier interventions to enhance mission readiness and diminish melanoma burden on Service Members, Veterans, and the American public

Years Program Appropriated: FY19-FY21
Total Appropriations: $60M

Active-duty Service Members are at risk of developing the deadliest form of skin cancer, melanoma, due to prolonged sun exposure. Studies suggest exposure to high levels of solar radiation in young adulthood is associated with a higher risk of melanoma mortality. According to the DOD Office of the Deputy Assistant Secretary of Defense for Military Community and Family Policy, 45% of the active-duty force is 25 years or younger in age, and 92% are less than 40 years of age. In response, Congress appropriated funds to establish an individual stand-alone program, the Melanoma Research Program (MRP).

The MRP challenges the research community to redefine the concept of prevention to effect a cure. The traditional view of prevention is the use of sunscreen/blockers to protect melanocytes from UV radiation. The MRP tasks the research community to redefine prevention to include the entire melanomagenesis process. This is critical in rare subtypes of melanoma where sunscreen blockers are not applicable. Rare melanoma variants may not be initiated by exposure to UV radiation. The MRP looks to shift the paradigm of prevention by investing in research focused on eliminating the progression of this deadly disease.
Developing Artificial Intelligence (AI) and Teledermatopathology Techniques

DESCRIPTION
This study analyzes dermatopathologists’ viewing behaviors to improve melanoma diagnosis using AI/machine learning. A dermatopathologist at Puget Sound VA Hospital will lead the effort to establish a VA consultation network and a digital catalog of specimens. Viewing behaviors will be documented to support human-computer interface with AI/machine learning. The goal is a better understanding of human dermatopathologists’ viewing behaviors and how they influence the diagnosis. This will assist the team in future designs of AI/machine learning tools to supplement human-led diagnosis and improve diagnostic tools.

PARTNERS/COLLABORATORS
University of California at Los Angeles; University of Washington; Puget Sound VA Hospital

AWARD NUMBERS: W81XWH-20-1-0797, W81XWH-20-1-0798

IMPACT: The results of this study may lead to better diagnostic platforms for cutaneous (skin) melanoma and will benefit the 1.9 million U.S. military personnel deployed to areas of high UV radiation.
Quisinostat for Uveal Melanoma Treatment

DESCRIPTION
UM is a rare form of melanoma that develops from melanocytes in the eye (within the uvea, which contains the iris, ciliary body, and choroid). The genetics and immune cell infiltration of UM is significantly different from cutaneous melanoma and as a result, the therapeutics approved to treat cutaneous melanoma have not been successful in treating UM. Germline mutations in the BAP1 tumor suppressor are strongly associated with a predisposition to UM. MRP-funded research discovered the therapeutic efficacy of quisinostat in treating BAP1-mutant cancers using mouse xenograft models of UM. Quisinostat was demonstrated to significantly reduce tumor growth in BAP-1 mutant UM tumors, thus identifying a potential new therapeutic to prevent the progression of UM.

“I believe being part of a group with top medical clinicians and researchers evaluating proposals that might be the key to ending this and other melanoma and rare cancers is an opportunity unlike any other, and it is a chance to turn an unfortunate diagnosis into a cause for good. It’s a chance to give a person I’ll probably never meet, who receives similar news, a more hopeful future. It’s a rare occasion when you can have a lasting impact on humanity, and I’m thankful I’ve been able to be a part of it.”
Jon Davis, Air Force Veteran, Uveal Melanoma Survivor

PARTNERS/COLLABORATORS
University of Miami Miller School of Medicine

AWARD NUMBER: W81XWH-15-1-0578
**Biomarkers of Cutaneous Melanoma (CM) Recurrence**

**DESCRIPTION**
Approximately 90% of patients with stage I or stage II CM can be cured with surgical removal of the tumor, but those who recur have poor long-term outcomes. Many patients at the time of surgery undergo lymph node dissection or sentinel lymph node biopsy, a procedure to assess whether the primary tumor has spread to the lymphatic system. The goal of this project is to extract information from the SLN biopsy to identify patients at high risk for tumor recurrence, hence a poorer prognosis. B cell status in the SLN may predict prognosis and long-term outcomes. This study will potentially innovate how we identify and define biomarkers predictive of recurrence.

**PARTNERS/COLLABORATORS**
Duke University

**AWARD NUMBER:** W81XWH-20-1-0808

**IMPACT:** The ability to detect biomarkers of CM recurrence in SLNs may help identify early-stage melanoma patients who are most at risk for recurrence and therefore more intensive initial treatment that will potentially improve outcomes.

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**Overcoming Drug Resistance in Aggressive Melanoma**

**DESCRIPTION**
A paradigm shift for the treatment of aggressive melanoma occurred with the emergence of combined BRAF plus MEK inhibitors (BRAFi+MEKi); however, acquired resistance to these mitogen-activated protein kinase inhibitors (MAPKi) limits long-term patient survival and therefore remains an urgent clinical problem. This project investigated the cellular responses to drug withdrawal in MAPKi-resistant melanoma and identified novel therapeutic approaches for enhanced sequential/rotational therapy. Results demonstrated that treatment of MEKi-resistant melanoma cells with vemurafenib, a type I RAF inhibitor, induced tumor regression by promoting cell death in the predominant MAPKi-addiction phenotype.

**PARTNERS/COLLABORATORS**
University of California, Los Angeles

**AWARD NUMBER:** W81XWH-16-1-0290

**IMPACT:** This significant research advance provides a better understanding of the mechanisms of MAPKi addiction and identifies new potential therapeutic options for controlling MAPKi resistance.
The Military Burn Research Program (MBRP) envisions a medical community that is ready to support the burn-injured Warfighter through the delivery of the best burn care. The ability of health practitioners to provide top-notch care to military Service Members facilitates the goal of improving health and performance outcomes among those who sustain burn injuries while serving the nation. The MBRP seeks to identify and address current and ongoing gaps in burn trauma care through funding of military-focused clinical and translational research. The MBRP funds innovative and impactful research through all phases of the health care continuum, with an emphasis on the immediate treatment of complex, multiply injured burn casualties.
Amicidin-α Surgical Gel and Amicidin-β Solution

**DESCRIPTION**

Susceptibility to infection after burn, traumatic injuries, or surgery remains a problem for patients, threatening to negatively impact health outcomes and potentially lead to drug-resistant bacterial infections. Generated by the A-BLOCKS™ (antimicrobial block copolymers) technology platform, Amicidin-α surgical gel and Amicidin-β solution are innovative, synthetic biomaterials purpose-built for direct application to tissues exposed by surgery or trauma. They are designed with the key qualities of broad microbicidal activity, ease of application, and safety. The MBRP supported early product development efforts for Amicidin-α and Amicidin-β and successfully advanced both products toward clinical use, with additional funding obtained through the Peer Reviewed Medical Research Program and the National Institute of Allergy and Infectious Diseases (NIAID) Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X).

**PARTNERS/COLLABORATORS**

Amicrobe, Inc.; University of Cincinnati

**AWARD NUMBER:** W81XWH-15-2-0065

**IMPACT:** Amicidin-α and Amicidin-β represent a novel class of antimicrobials with the potential to prevent and treat life-threatening wound infections in both military and civilian clinical settings.
**Phases of Illness Paradigm (POIP) Checklist**

**DESCRIPTION**
Clinical care of patients within the burn intensive care unit is complex and challenging, particularly in the face of new technologies, new knowledge, and the diversity of perspectives on clinical best practices. Checklists may help to ensure clinicians adhere to local protocols, best practices, clinical practice guidelines, and specific care bundles. The MBRP funded the refinement, validation, and implementation of the POIP Checklist. This checklist-centric healthcare model promises to enable healthcare teams to better focus care priorities and to more reliably provide key elements of patient care. This pilot project validated the POIP by measuring changes in clinician understanding of the patient’s condition and plan of care, such as their perceptions of communication, teamwork, quality of life, and cognitive workload. Use of the POIP checklist decreased certain aspects of cognitive workload for nurses and physicians and improved the consistency of clinician perception of the patient’s condition.

**PARTNERS/COLLABORATORS**
The Geneva Foundation; U.S. Army Institute of Surgical Research

**AWARD NUMBER:** W81XWH-13-2-0011

**IMPACT:** The POIP checklist may help clinicians better assess patient condition, thus providing more appropriate and timely treatment, potentially improving patient outcomes.
Acute Burn Resuscitation Prospective Multicenter Observational Trial (ABRUPT)

DESCRIPTION
Military personnel who sustain severe burn injuries in the line of duty face prolonged convalescence and may never return to duty. One way to reduce mortality and improve outcomes is to provide optimized fluid resuscitation in the crucial hours immediately after burn injury. The ABRUPT examined the effect of albumin during the first 48 hours after burn injury and whether it results in fewer edema-related adverse effects and complications. The results of this study suggest that adding albumin has the potential to reduce fluids required for patients with massive burns and informed the design of a follow-on clinical trial funded by the Combat Casualty Care Research Program that compares crystalloid use versus albumin use for acute burn resuscitation.

PARTNERS/COLLABORATORS
American Burn Association; University of California, Davis

AWARD NUMBER: W81XWH-16-2-0048
Oral Fluid Resuscitation for Burn Injuries

DESCRIPTION
While large, severe burns are survivable, patients often experience adverse effects such as systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction (MOD) due to the loss of plasma (the liquid portion of the blood) in the bloodstream. These complications significantly increase the risk of death or worsened outcomes and require large—but carefully delivered—volumes of fluid to replace what has been lost. There is a need to develop a comprehensive burn resuscitation strategy that involves minimal intervention. This study demonstrated that fluids delivered directly into the stomach may be a viable option for resuscitation of burn patients when intravascular (IV) access cannot be obtained or IV fluids are in limited supply, such as in austere environments with limited resources. The results of this study led to the researchers obtaining funding for a clinical trial examining the use of oral rehydration solutions to reduce the need for IV fluids.

PARTNERS/COLLABORATORS
The Geneva Foundation; U.S. Army Institute of Surgical Research

AWARD NUMBER: W81XWH-16-2-0041

IMPACT: This hydration method may offer a viable option for burn resuscitation in a prolonged field care situation, in the aftermath of natural disasters, or anywhere resources may be limited. This study facilitated the development of a clinical protocol for the use of oral fluid as an adjunctive treatment in the care of burn patients.
Revised Goniometry for Measuring Burn Scar Contracture

DESCRIPTION
Permanent shortening of muscle, tendon, and skin as a result of burn scarring all too frequently plagues burn survivors in terms of range of motion (ROM) limitations and ability to perform activities of daily living. Goniometry (GM) is the most commonly and widely used assessment method to measure patient ROM and subsequent severity of burn scar contracture in burn populations. While standard GM is described as a reliable method of functional measurement, the validity has not been established, especially as related to functional patient outcomes. This study critically assessed standard GM as compared to a new paradigm of revised GM. The study findings suggest that standard GM underestimates the clinical impairment for individuals whose motion is limited by scars and that revised GM is a more appropriate measure of motion limitation for patients with burn scars. The researchers developed a freely distributed mobile application and also won the Best American Burn Association Clinical Research Award in 2019.

PARTNERS/COLLABORATORS
The Geneva Foundation; U.S. Army Institute of Surgical Research

AWARD NUMBER: W81XWH-14-2-0148

IMPACT: Revised goniometry provides a more accurate projection of recovery time as well as degree of recovery after burn injury. This capability helps define a patient’s response to treatment and influence the development or modification of a patient’s plan of care related to functional recovery.
Granexin® Gel

DESCRIPTION
A major unmet need in the treatment of war-related thermal burn casualties is the prevention of the progression of partial-thickness burns to full-thickness burns (burn conversion). Burn conversion represents a critical pathophysiological determinant of morbidity and clinical outcomes, as wound area and depth correlate with risk of infection, requirement for invasive surgical procedures (e.g., excision and skin grafting), wound contracture, and severe scarring, all of which translate to aesthetic and functional sequelae that impact quality of life. The researchers bioengineered a cell-permeable peptide-therapeutic (aCT1) that targets immunomodulation, wound healing, inflammation, and scarring. Granexin, a safe, stable, topical gel formulation of aCT1, has previously been advanced for indications in acute and chronic dermal wounds. The MBRP funded studies to evaluate the use of Granexin gel in improving the healing of second-degree thermal burns as well as accelerating healing, mitigating scar formation, and preventing burn conversion in deep second-degree burns.

PARTNERS/COLLABORATORS
The Geneva Foundation; U.S. Army Institute of Surgical Research

AWARD NUMBERS: W81XWH-16-1-0716 (preclinical), W81XWH-20-2-0005 (clinical)

IMPACT: Granexin offers the potential for use across multiple levels of care and may reduce the need for skin grafting, simplify wound care regimens, and improve aesthetic and functional outcomes.
SSG James West  
MBRP Programmatic Panel Member and Consumer

“Burns are one of the most devastating injuries. Disfigurement, chronic pain, and the constant medical procedures can lead to depression, then suicidal ideation which Service Members/Veterans are more likely to act on. Knowing that we can not only save lives, but also provide a better quality of life after injury is why I will continue to serve the burn community.”

Tina Rosenthal, MSRP Consumer Peer Reviewer

“The MS community is vast: patients, clinicians, caregivers, foundations, volunteers, physical therapists, MSRP, etc. Before a cure is found we need to push forward with research for innovative treatments and continue supporting programs that disrupt isolation and despair. Efforts to change the course of the disease are somewhat effective, but as with all patients with a chronic disease, I hope there will be more and better interventions for MS sooner rather than later. CDMRP is helping to drive this innovation.”
**Vision:** To prevent, cure, reverse, or slow the progression, and lessen the personal and societal impact of multiple sclerosis

**Mission:** To support pioneering concepts and high-impact research relevant to the prevention, etiology, pathogenesis, assessment, treatment, and ultimate cure of multiple sclerosis for the benefit of Service Members, Veterans, and the American public

**Years Program Appropriated:** FY09-FY21

**Total Appropriations:** $93.1M

**Multiple Sclerosis (MS)** is a chronic immune-mediated disease that causes damage to the central nervous system and affects nearly 1 million individuals in the United States. It has a higher incidence in U.S. Armed Forces personnel than in the general population. MS is characterized by the demyelination of axons due to the immune system incorrectly attacking healthy tissues in the CNS. Symptoms of MS vary widely in type and severity and may include pain, fatigue, depression, anxiety, loss of bladder control, impaired mobility, and cognitive, motor, visual, or sexual dysfunction. Currently, there is no cure for MS. Since its inception, the Multiple Sclerosis Research Program (MSRP) has supported innovative and impactful research that addresses fundamental issues and gaps in MS.
Online Toolkit for Self-Management of MS Symptoms

DESCRIPTION
This project developed and validated My MS Toolkit (www.mymstoolkit.com), a web-based self-management intervention for people with MS. Individuals with MS frequently have multiple co-occurring symptoms, and self-management interventions have been shown to be effective and have the potential to improve behavioral health via remote delivery. This toolkit provides evidence-based education, guidance, and skills-building exercises for people with MS and their support community. Pilot study participants completed pre-treatment outcome measures followed by 12 weeks of intervention and post-treatment outcome measures. As a result, 30% of participants showed clinically significant improvements, while 60% of participants reported feeling “moderately better” and noticed a “slight change” in their physical and emotional symptoms.

PARTNERS/COLLABORATORS
University of Michigan

AWARD NUMBER: W81XWH-17-1-0367
Foot and Hand Tapping Tool to Track Progressive MS

DESCRIPTION
This project developed a tool to assess sensorimotor function and used it to diagnose and track progressive MS. There is a critical need to quantify disability progression in a targeted way to treat MS and slow its progression; however, many mobility assessments are limited by poor psychometric properties. Investigators studied rapid hand and foot tapping using inertial sensors in relapsing remitting MS (RRMS) and progressive MS (PMS) patients and compared them to controls. They observed that the ability to tap hand and foot simultaneously is reduced in both MS groups compared to controls, while foot tapping was reduced only in the PMS group.

PARTNERS/COLLABORATORS
University of Massachusetts

AWARD NUMBER: W81XWH-16-1-0351

IMPACT: This work advanced the current knowledge of the sensorimotor function changes in people with progressive MS. The foot- and hand-tapping tool can potentially be used to identify and track disease progression in MS patients.

Experimental setup. (A) Participants wore inertial sensors on the dorsum of the hand, wrapped around the 2nd to 5th metacarpal bones. (B) Foot sensors were placed on the dorsum of the foot.
Clinical Trial of Oral L-Histidine to Treat MS Fatigue

DESCRIPTION
This project examined the efficacy of L-histidine in the treatment for MS fatigue, one of the most disabling symptoms of MS. Compelling evidence suggests that levels of brain histamine may be low in patients experiencing fatigue. There is no effective way to elevate brain histamine due to restrictions at the blood-brain barrier. However, L-histidine, the precursor amino acid of histamine has, like all amino acids, free access to the brain. The investigators optimized and validated the best dose of L-histidine that can be tolerated while elevating the histamine levels in the brain. Treatment of MS patients with the optimum L-histidine dosage resulted in 31%-83% improvement compared to baseline assessments, as measured using the Modified Fatigue Impact Score. This improvement was dose-dependent.

PARTNERS/COLLABORATORS
University of Miami

AWARD NUMBER: W81XWH-16-1-0462

IMPACT: This study could potentially lead to a new class of drugs for the treatment of fatigue in MS patients.
Anti-Inflammatory Drug to Reduce MS Disease Activity

DESCRIPTION
This preclinical study assessed and validated an anti-inflammatory drug, angiotensin 1-7 (A[1-7]) to treat MS symptoms and inflammation. While several disease modifying drugs are available to treat RRMS, none of them offers neuroprotection. The renin-angiotensin-system (RAS) is a peptide hormone system that regulates blood pressure and water balance and exists as a balance between two distinct axes, which counter-regulate with each other; a blood vessel-constricting, pro-inflammatory axis (pathological axis) and a blood vessel-dilating, anti-inflammatory axis (protective axis). There is evidence that the pro-inflammatory axis of RAS is upregulated in the CNS of MS patients, while the anti-inflammatory axis is decreased. This study assessed whether treatment with A(1-7), one component of the anti-inflammatory axis, will attenuate disease severity and neurodegeneration in an animal model of MS. A(1-7) treatment caused a dose-dependent reduction in clinical disease severity and progression, including reduced spinal cord lesions, attenuated axon loss, and improved symptoms of grip, weakness, ataxia, and paralysis.

PARTNERS/COLLABORATORS
Southern California University, Keck School of Medicine

AWARD NUMBER: W81XWH-14-1-0523

IMPACT: Since A(1-7) is already being tested (through phase 2 and phase 3) in humans for other diseases, it may serve as a therapeutic intervention for people with MS and other neurodegenerative disorders.
Quantitative MRI Methods for Cognitive Impairment in MS Patients

DESCRIPTION
This project developed and deployed a set of quantitative MRI methods to characterize the cognitive impairment in MS patients. Many MS patients suffer from cognitive impairment at some point in their disease course; however, characterization of cognitive changes has been difficult to quantify. Conventional imaging is not accurate in detecting gray matter changes seen in MS patients. To overcome this challenge, this study developed methods that are based on 7T MRI, which has more than twice the strength of many conventional MRI units and has the potential to detect these gray matter changes. Using these quantitative MRI methods, this study was able to quantify myelin loss, protein or peptide changes, neurotransmitter deficiencies, and functional impairment in the gray matter of MS patients.

PARTNERS/COLLABORATORS
Vanderbilt University Medical Center

AWARD NUMBER: W81XWH-13-1-0073
Novel Functional MRI (fMRI) Methods for Pediatric MS Patients

DESCRIPTION
This project developed and validated novel functional MRI methods to detect changes in the brain of pediatric MS patients. Children with MS suffer from memory deficits, language impairment, and/or poor visual-motor performance. The sequence of these events is unpredictable, making treatment challenging. By measuring brain structural changes prior to the occurrence of symptoms, clinicians may be able to treat patients earlier. This study was able to identify specific regions in the brain that are associated with language, memory, and motor tasks and showed differences between normal and MS pediatric brains. These differences were correlated with changes seen in neurocognitive examinations. In addition, these new fMRI techniques have been used to improve pre-surgical planning in pediatric patients who must undergo surgery to resect tumors, atrial-venous malformations, and epileptic centers, in order to spare them from post-operative impairment in brain functions located near the surgical site.

PARTNERS/COLLABORATORS
Boston Children’s Hospital

AWARD NUMBER: W81XWH-13-1-0464

IMPACT: The novel fMRI methods could detect brain changes in pediatric MS patients early and therefore allow treatment prior to the development of symptoms. Moreover, it could optimize brain surgery outcomes in pediatric patients.
Jeffery Cohen, M.D., MSRP Programmatic Panel Member

“Multiple sclerosis is the most common non-traumatic cause of neurological disability in young adults. The CDMRP MS Research Program is addressing several unmet needs in MS, including strategies to promote repair of central nervous system tissue damage, symptomatic therapies, and approaches to restore function.”

Tracy Wirtanen, NFRP Consumer Peer Reviewer

“Having a child with NF has changed my and my family’s entire lives; we live with a lot of uncertainty. However, we decided to be part of the solution by creating the Littlest Tumor Foundation, which advocates for research in NF, but also by serving on the peer review panel for the NFRP. Being a part of such a well-run program that is a crucial part of moving us toward a treatment for NF has made me even more passionate about the NFRP and is a highlight in my life.”
Vision: Decrease the clinical impact of neurofibromatosis

Mission: Promote research directed toward the understanding, diagnosis, and treatment of NF1, NF2, and schwannomatosis to enhance the quality of life for persons with these disorders that impact Service Members, Veterans, and the general public

Years Program Appropriated: FY96-FY21
Total Appropriations: $382.9M

The NFRP seeks to support innovative, high-impact research that will foster new directions for and address neglected issues in NF research. It will also sponsor multidisciplinary and multi-institutional collaborations that will bring new perspectives to the field, promote translational and clinical studies to move promising ideas from bench to bedside, and develop a balanced portfolio of meritorious research. To address the near- and long-term gaps and needs of the NF community of researchers, clinicians, and consumers, the NFRP has established four goals: (1) fostering basic and exploratory research to increase understanding of the underlying causes of NF1, NF2, and schwannomatosis, which is vital to identifying potential therapeutics, (2) facilitating rapid testing of potential therapeutics by supporting the transition of findings in basic research through preclinical studies and clinical testing of promising interventions, (3) increasing research capacity by supporting development of vital research resources which enable investigators, and (4) encouraging research in areas of critical interest to NF patients.
MEK Inhibitors: From Bench to Bedside

DESCRIPTION
Neurofibromatosis is a rare disease and as such, the time from bench to bedside in identifying potential therapeutics to delivery in patients is measured in decades. The NFRP has been instrumental in moving the field of NF research from understanding the basic biology of the disorder to identifying potential therapeutics and testing in clinical trials. Multiple studies from the NFRP on MEK inhibitors and their potential as a therapeutic provided the foundations of preclinical studies and eventually, clinical trials. In 2020, a MEK inhibitor, Koselugo (selumetinib) by AstraZeneca and Merck became the first FDA-approved drug for treatment of NF. This major milestone in NF research was possible because of collaborative efforts among multiple private and federal funding groups.

PARTNERS/COLLABORATORS
Neurofibromatosis Therapeutic Acceleration Program; National Institutes of Health (NIH); Children’s Tumor Foundation (CTF)

AWARD NUMBERS: W81XWH-17-1-0695, W81XWH-17-2-0037, plus 9 historical NFRP awards

IMPACT: This first NF therapeutic offers the hope that the collaboration between funders and the dedication of patients and scientists will lead to treatments.
Novel Light Therapy for Optic Glioma

DESCRIPTION
This award supported the investigation of light exposure as a potential therapeutic tool for NF1-related optic gliomas. Six-week-old transgenic NF1 mice reared in the dark until 12 weeks of age, then exposed to a normal light cycle for 4 weeks, showed no signs of optic tumor formation. This study identified a window of opportunity for NF1-related optic glioma initiation and uncovered the potential for interventions such as modulating light exposure using glasses as a means to reduce or eliminate optic glioma development. In addition, these findings provided a foundation to investigate potential drug targets that could inhibit neuronal activity of retinal ganglion cells. As a result, a second award was funded to interrogate the molecular mechanisms of retinal ganglion cell neuronal activity and investigate the possibility of drug intervention for the prevention of optic glioma.

PARTNERS/COLLABORATORS
The Leland Stanford Junior University


IMPACT: This study identified the potential for using light exclusion as a therapy to reduce or eliminate the development of optic gliomas from birth.
Neurofibromatosis Clinical Trials Consortium (NFCTC)

**DESCRIPTION**

The NFCTC was established to develop and perform phase 1 and 2 clinical trials for the management and treatment of NF complications in children and adults. Over the years, the NFCTC has brought together preeminent institutions and investigators and expanded to 25 sites. To date, the NFCTC has led or collaborated on 15 clinical trials focused on several manifestations of NF.

For more information, visit https://cdmrp.army.mil/nfrp/consortium/nfrpctc.

**PARTNERS/COLLABORATORS**

University of Alabama at Birmingham; Boston/Harvard Center for NF and Allied Disorders; Children’s Hospital at Westmead, University of Sydney; Children’s Hospital of Los Angeles; Children’s National Medical Center; Children’s Hospital of Philadelphia/University of Pennsylvania; Cincinnati Children’s Hospital Medical Center; Indiana University; Mayo Clinic; National Cancer Institute; New York University Medical Center; University of Chicago; University of Texas Southwestern; University of Utah; Washington University; Ann & Robert H. Lurie Children’s Hospital of Chicago; Children’s Healthcare of Atlanta/Emory University; Johns Hopkins Hospital; Massachusetts General Hospital; Dana Farber Cancer Institute; Memorial Sloan Kettering Cancer Center; Royal Children’s Hospital/Children’s Research Institute; Texas Scottish Rite Hospital; University of California, Los Angeles; University of Minnesota

**AWARD NUMBERS:** W81XWH-12-1-0155, W81XWH-17-2-0037, plus 11 historical NFRP awards. Additional funds provided by the University of Alabama at Birmingham, National Cancer Institute, CTF, Array Biopharma, Pfizer, Exelixis, Genentech, Novartis, Medtronic, and private donors

**IMPACT:** The NFCTC leveraged the power of collaboration to bring together the expertise required to strategically plan, prioritize, and execute multi-institutional clinical trials, which would otherwise not be possible.
Targeted Research into NF Specific Area of Emphasis Pain

DESCRIPTION
The NFRP has worked to bring awareness and focus research funding into pain, a major clinical manifestation of neurofibromatosis. NF patients have reported pain as one of the symptoms that most affects their quality of life. Primary treatment is usually surgery to resect painful tumors, but it often does not help patients’ pain and may make it worse. Pain medication has not been shown to be highly effective in relieving NF pain, either. NFRP-funded research is helping examine the relationship between the known genetic drivers of NF and pain receptors, signaling, and processing. It has been shown that the presence and intensity of pain does not always correlate with the number, location, and size of NF tumors. NFRP-funded studies are investigating why some types of NF tumors are more likely to become painful than others and are working to reveal the mechanisms behind pain specifically caused by neurofibromatosis.

PARTNERS/COLLABORATORS
House Research Institute; Oregon Health and Science University; University of California, Los Angeles; Yale University; and other key collaborators


IMPACT: Primary treatments for neurofibromatosis-related pain (surgical resection of tumors, pain medication) have not been shown to be highly effective. Research into how NF pain develops and persists is revealing possible novel therapeutic targets that could greatly improve NF patients’ quality of life.
NFRP Research Resources

DESCRIPTION
The NFRP has been critical to the progress made in NF research since the program was initiated by creating vital research resources that were lacking and needed by investigators to study neurofibromatosis. To date, over 105 resources have been developed and shared with the NF community. The collection of resources is publicized on the CDMRP website to encourage collaboration and provide access to the tools necessary to conduct NF research. This collection includes 5 drosophila models, 19 mouse models, 1 rat model, 17 methods, 6 antibodies, 16 cell and molecular methods, 19 cell lines, 3 zebrafish models, 1 yeast strain, and 17 databases and data sets.

PARTNERS/COLLABORATORS
Various

AWARD NUMBERS: 84 NFRP awards, total of $76.7M in funding

IMPACT: The NFRP-developed resources have been widely shared with the research community to facilitate research and collaborations to further scientific advances and knowledge that will ultimately lead to better care for NF patients.

https://cdmrp.army.mil/nfrp/resources/nfrpresources
Vision: To eliminate Parkinson’s disease through neurotoxin exposure and treatment-related research in partnership with scientists and consumers

Mission: Support Parkinson’s research investigating the underlying biologic mechanisms and therapeutic interventions of neuro-degenerative effects caused by deployment, environmental, and occupational exposures in Service Members and Veterans

Years Program Appropriated: FY97-FY21
Total Appropriations: $484.8M

The Neurotoxin Exposure Treatment Parkinson’s Program (NETP) invests in neurotoxin exposure and treatment-related Parkinson’s research to make progress toward eliminating the disease. The NETP strategy is to invest in research areas that will have the greatest impact. Currently, the NETP Focus Areas are:

• Basic biology and clinical implications of non-motor symptoms that could lead to the development of new treatments for Parkinson’s disease (PD) following neurotoxin exposure;
• Environmental exposures and gene–environment interactions at prodromal or manifest PD;
• Circuitry and synaptic mechanisms of PD, dopamine refractory motor symptoms, and treatment-associated dystonia that could lead to development of new treatments in patients;
• Understanding of disease heterogeneity to enable precision medicine approaches to PD treatments, including comparisons between neurotoxin exposures and other forms of Parkinson’s disease; and
• Research into military service-related risk factors such as deployment, environmental, and occupational exposures, which is critical for past, present, and future Service Members who may be affected by PD.
Parkinson’s Associated Risk Syndrome (PARS) Study

**DESCRIPTION**
This study is using a screening process to identify individuals at risk for Parkinson’s disease before motor symptoms are presented. This is based on the premise that there are years of neurodegeneration before motor symptoms occur. The screening strategy sequentially tested for reduced ability to smell (hyposmia), and deficient dopamine transporter (DAT) imaging, then clinically followed patients and repeated DAT imaging every 2 years. Six years into the study, 67% of patients with abnormal DAT imaging converted to a clinical diagnosis of PD. This study demonstrated that individuals at risk for PD without symptoms can be identified.

**PARTNERS/COLLABORATORS**
Institute for Neurodegenerative Disorders

**AWARD NUMBERS:** W81XWH-06-1-0678, W81XWH-12-1-0030, W81XWH-16-1-0214

**IMPACT:** The PARS study was a key advancement that opened the door to researching early stages of PD as well as treatments to slow or stop neurodegeneration. It also paved the way for future work, including the Parkinson’s Progression Marker Initiative.

Characterization of Intracellular Signaling Pathways Activated by Nerve Agents

**DESCRIPTION**
This study identified intervention points in the cholinergic system that are affected by organophosphate-type chemical agents and further identified candidate therapeutics for such exposures. Some of the earliest epidemiological studies indicate agricultural chemicals as risk factors for PD; thus, this study provided an initial point for identifying pathways associated with risks for neurodegeneration and the subpopulations most at risk for development of neurodegenerative conditions.

**PARTNERS/COLLABORATORS**
Intra-Cellular Therapies, Inc.

**AWARD NUMBER:** DAMD17-03-2-0019

**IMPACT:** This study identified signaling pathways activated by nerve agents to help develop new treatments for neurotoxin exposure.
The Parkinson’s Registry Investigation of Diagnosis and Etiology (PRIDE) Study

DESCRIPTION
The PRIDE Study, a case control analysis, identified residential exposure to environmental toxicants associated with increased risk for PD. This study examined the risk for development of PD from commonly used environmental chemicals such as insecticides, organophosphates, herbicides, organochlorines, fungicides, and fumigants. The geographic locations of over 3,000 PD patients in a California state-mandated PD registry were correlated with California Public Health data, with dates and extent of application at specific sites for 22 commonly used environmental chemicals. The population-based ascertainment of PD in Santa Clara County, California indicated significantly increased risk of PD associated with residential exposure to specific compounds in several classes of commonly used environmental chemicals.

PARTNERS/COLLABORATORS
University of California, San Francisco

AWARD NUMBER: W81XWH-13-1-0054

IMPACT: The PRIDE Study’s findings on residential exposure (i.e., simply living near an area where the agents are used) show an increased risk of developing PD; therefore, they have public health significance. These findings also provide a basis for studies on mechanisms of PD pathogenesis and potential identification of therapeutic intervention points.
The Role of SATB1 in Neuronal Plasticity

**DESCRIPTION**
Mechanisms associated with the loss of dopaminergic neurons in the Substantia nigra area of the brain, which leads to development of Parkinson’s disease, are not well known. Prior DOD-funded work identified several master regulators of dopaminergic neuron survival, of which the most important was the protein SATB1. This project investigated the mechanisms by which SATB1 may prevent eventual loss of dopaminergic neurons and identified potential intervention points for development.

**PARTNERS/COLLABORATORS**
Rockefeller University

**AWARD NUMBERS:** W81XWH-18-1-0467, W81XWH-12-1-0039

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Neuroprotective Effects of Carnosine in a Mouse Model of Parkinson’s Disease

**DESCRIPTION**
This study was intended to determine the neuroprotective potential and mechanisms of carnosine for prevention and treatment of PD. Brain section stereology demonstrated that Thy1-aSyn mice (a model for PD) treated intranasally with carnosine had fewer cellular signs of PD and improved motor responses compared to control animals.

**PARTNERS/COLLABORATORS**
University of Cincinnati

**AWARD NUMBER:** W81XWH-17-1-0699
Vision: The highest possible quality of life for our injured Service Members and beneficiaries through the advancement of knowledge in orthotics- and prosthetics-related research

Mission: Advance orthotic and prosthetic research to optimize evidence-based care and clinical outcomes for military-relevant neuromusculoskeletal injury

Years Program Appropriated: FY14–FY21
Total Appropriations: $90M

Loss of limb or limb functionality is one of the most debilitating injuries suffered by U.S. military personnel, Veterans, and civilians. Recent advancements in commercially available orthotics and prosthetics have dramatically improved device capability; however, there remains an urgent need for outcomes data to inform patients, clinicians, caregivers, and policymakers. The Orthotics and Prosthetics Outcomes Research Program (OPORP) supports research on outcomes-based best practices through analysis of prosthetic and/or orthotic device options that are currently available to advance device prescription, treatment, rehabilitation, and prevention of secondary health effects.
New Clinical Balance Test for Lower Limb Prosthesis Users

DESCRIPTION
Researchers have developed a new clinical balance test for lower limb prosthesis users, the Narrowing-Beam Walking Test (NBWT), which discriminates fallers and non-fallers with greater accuracy than existing tests in lower limb prosthesis users. This was accomplished by administering the test and four contemporary performance-based balance tests to 60 lower-limb prosthesis users. The NBWT proved to be a better predictor of future falls at 6 months. The test is now being used in a number of clinical, industry, and academic centers and is helping to ensure that balance impairments are diagnosed early and that individuals receive timely treatment before they experience falls and incur secondary injuries.

PARTNERS/COLLABORATORS
University of Illinois at Chicago; University of Washington

AWARD NUMBER: W81XWH-17-1-0547

IMPACT: Through early and more accurate assessment of balance, clinicians will be able to minimize fall risk and subsequent re-injury, which will help Service Members return to active duty and Veterans or civilians reintegrate into their communities where they can safely engage in physical activities that improve their quality of life.

Narrowing-Beam Walking Test. Participants walk along four progressively narrower beam segments with their arms crossed over their chest. If participants move their arms or step off the beam the trial is ended and the distance walked to that point is recorded. Height of each segment is 3.8 cm.
Personalized Mobility Interventions Using Smart Sensor Resources for Lower Limb Prostheses Users

DESCRIPTION
Identifying sensitive, quantitative measures that predict real-world mobility and social interactions will enable clinicians to provide optimal, cost-effective care in the context of the individual’s personal goals – including a return to active duty and deployment. This research project is using smartphone sensors, together with sensors on the prosthesis, to continuously gather multi-modal information on real-world mobility, including how many steps are taken with the prosthesis; whether the individual walks outside of their home; if they can negotiate stairs, curbs, or ramps; where they go and how they get there – outside of the clinic. Combining data on actual prosthesis use in the home and community with standard in-clinic outcome measures and participant-reported measures will provide a comprehensive picture of prosthesis use.

PARTNERS/COLLABORATORS
Shirley Ryan Ability Lab; Walter Reed National Military Medical Center; Minneapolis VA; University of Notre Dame

IMPACT: More effective use of a prosthesis would improve quality of life, reduce secondary injuries, maintain physical and psychological health, and reduce healthcare costs.

AWARD NUMBER: W81XWH-18-2-0057
**Needs, Preferences, and Functional Abilities of Veterans and Service Members with Upper Limb Amputation**

**DESCRIPTION**
Abandonment of a prosthesis is a significant problem for upper limb amputees, and it comes at a significant cost to the DOD and VA alike. This project provided comprehensive cross-sectional and longitudinal data on function, needs, preferences, and satisfaction of Veterans and Service Members with major upper limb amputation and found that amputees who do not use a prosthesis report more difficulty in activities, greater overall disability, and lower physical function compared to amputees who use any type of active prosthesis. Additionally, those who do not use a prosthesis are more likely to need help with activities of daily living (ADLs) compared to those who use a body-powered prosthesis.

**PARTNERS/COLLABORATORS**
Ocean State Research Institute/Providence VAMC; University of Massachusetts Medical School; University of South Florida; Center for the Intrepid; FDA; Tampa VA Research & Education Foundation/Tampa VAMC; North Florida Foundation for Research & Education/Gainesville VA; McGuire Research Institute/Richmond VAMC; Seattle Institute for Biomedical & Clinical Research/VA Puget Sound Healthcare System

**AWARD NUMBER:** W81XWH-16-2-0065

**IMPACT:** Findings demonstrated the value of active prostheses in improving quality of life and highlighted the clinical imperative to encourage prosthesis use by addressing factors such as early prosthetic training to improve satisfaction with devices and reduce abandonment.
A Novel Prosthetic Foot Designed to Maximize Functional Abilities, Health Outcomes, and Quality of Life in People with Transtibial Amputation

DESCRIPTION
Lower limb amputation significantly increases the energy required for walking, lowers endurance, and restricts participation in desired vocational and avocational activities. This study systematically evaluated lower limb prosthesis users’ functional ability as well as perceived health outcomes in both the modified running-specific foot and conventional energy-storing foot use. Users perceived improved mobility and balance, reduced fatigue, and fewer activity restrictions based on community-based measures using the crossover feet. Additionally laboratory-based findings generally suggested that the crossover feet perform equivalently to the traditional energy-storing feet when used for walking.

PARTNERS/COLLABORATORS
University of Washington

AWARD NUMBER: W81XWH-15-1-0458

IMPACT: Results indicate crossover feet may be a promising prosthetic alternative to traditional energy-storing feet for Service Members, Veterans, and civilians with transtibial amputation who engage in a range of mobility activities.
Sergeant Adam Kisielewski (U.S. Marine Corps, Ret.)
OPORP Programmatic Panel Member and Consumer

“After being wounded during combat operations and living with multiple limb amputations, I can personally attest to the physical challenges of our severely injured Warfighters. The Orthotics and Prosthetics Outcomes Research Program funds some of the most relevant research aimed to improve the quality of life for those suffering from extremity trauma and ultimately helps our injured Service Members restore a greater level of independence. I am very proud to serve on the OPORP Programmatic Panel and help my peers overcome some of the physical challenges their injuries have presented.”

Molly A. Brewer, DVM, MD, MS
OCRP Programmatic Panel Member

“The DOD OCRP is one of the largest ovarian cancer research funders... We are funding new research to better understand ovarian cancer, to improve treatment, to reduce side effects and most importantly to train the next generation of ovarian cancer researchers.”
**Vision:** To eliminate ovarian cancer

**Mission:** To support patient-centered research to prevent, detect, treat, and cure ovarian cancer to enhance the health and well-being of Service Members, Veterans, retirees, their family members, and all women impacted by this disease

**Years Program Appropriated:** FY97-FY21

**Total Appropriations:** $406.45M

Ovarian cancer is the fifth leading cause of cancer-related death in women and the deadliest of gynecologic cancers. The Ovarian Cancer Research Program (OCRP) was established in 1997 to define and address the critical research gaps facing the ovarian cancer community. The Strategic Plan of the OCRP identifies the high-impact research goals, which are most important to its stakeholders, while providing a framework that is adaptable to changes in the medical research environment to address those goals.

As the second-leading funder of ovarian cancer research in the United States, the OCRP has transformed the landscape of ovarian cancer to the benefit of patients everywhere by funding high-impact, cutting-edge research, which eventually developed a number of diagnostics, therapeutics, and preventive measures. Besides the scientific advancement, OCRP is also instrumental in developing a unique strategy to identify and foster talented young investigators who are committed to studying this disease.
BRCAness Profile Identifies Tumors More Sensitive to Chemotherapy

DESCRIPTION
A BRCAness 60-gene expression profile which tracks the mechanisms that cause defective homologous recombination was evaluated for its ability to identify tumors with a BRCAness phenotype and predict chemotherapy sensitivity. The BRCAness profile was determined to correlate with platinum sensitivity and survival in patients with sporadic disease. This profile also revealed that the HSP90 inhibitor, 17-AAG, enhances sensitivity of non-BRCA1/2 (Breast Cancer susceptibility genes 1 and 2) mutated ovarian cancer cells to poly (ADP-ribose) polymerase (PARP) inhibitors. Patients with homologous recombinant proficient ovarian cancer do not respond well to PARP inhibitor and platinum chemotherapy. The BRCAness profile identifies BRCA-like tumors deficient in homologous recombination and more sensitive to platinum and PARP inhibitors.

PARTNERS/COLLABORATORS
Dana-Farber Cancer Institute

AWARD NUMBER: W81XWH-10-1-0585
OTTA-SPOT Gene Expression Signature as a Prognostic for Overall Survival

DESCRIPTION
Twenty different studies provided tumor samples from 4,071 women diagnosed with ovarian cancer to develop a prognostic signature for ovarian cancer overall survival. The expression levels of 276 genes were associated with overall survival, and the best performing prognostic signature, the Ovarian Tumor Tissue Analysis consortium - Stratified Prognosis of Ovarian Tumours (OTTA-SPOT), included 101 genes enriched in pathways with treatment implications. The OTTA-SPOT signature was shown to perform substantially better than age and stage alone for prognosis of both 2- and 5-year overall survival in women with high-grade serous ovarian cancer.

PARTNERS/COLLABORATORS
University of Melbourne; Cedars-Sinai Medical Center; and 120 collaborators, including the Australian Ovarian Cancer Study and numerous national and international institutions

AWARD NUMBERS: W81XWH-12-1-0104, W81XWH-17-1-0144

IMPACT: There are no well-established gene expression signatures associated with prognosis for ovarian cancer patients. The OTTA-SPOT provides a robust prognostic signature for high-grade serous ovarian cancer that can be used to stratify patients and identify those in need of alternative treatments. It may also indicate targets for therapeutic approaches.
A Diagnostic to Identify Ovarian Cancer Patients Likely to Respond to PARP Inhibitor Treatment

DESCRIPTION
Researchers confirmed the accuracy of the companion diagnostic, CDxBRCA, in detecting the presence of mutations in the BRCA1 and BRCA2 genes and genomic loss of heterozygosity in tumor tissue samples from patients with ovarian cancer. This was done by the sequencing analysis of samples from the Assessment of Rucaparib in Ovarian Cancer: phase 2 (ARIEL2) clinical trial.

PARTNERS/COLLABORATORS
University of Washington; Foundation Medicine

AWARD NUMBER: W81XWH-13-1-0484

IMPACT: PARP inhibitors, including rucaparib, have differential activity in ovarian cancer patients depending on their BRCA mutations and loss of heterozygosity. CDxBRCA is an FDA-approved companion diagnostic that can identify ovarian cancer patients likely to respond to PARP inhibitor treatment.
Predicting Treatment Response to Rucaparib in Ovarian Cancer

DESCRIPTION
BRCA gene mutations and homologous recombination deficiencies were examined as clinical predictors of a patient’s response to PARP inhibitor treatment. Samples from the Assessment of Rucaparib in Ovarian Cancer: phase 2 (ARIEL2) clinical trial, which tested cancer patients’ responsiveness to treatment with the PARP inhibitor rucaparib, were sequenced and the results helped establish the relationship between homologous recombination status of the tumors and outcome of PARP inhibitor treatment. These results revealed that ovarian cancer patients with BRCA1 or BRCA2 mutations and loss of heterozygosity were most likely to respond to rucaparib treatment.

PARTNERS/COLLABORATORS
University of Washington; Mayo Clinic; Clovis Oncology

AWARD NUMBERS: W81XWH-13-1-0484, W81XWH-13-1-0485

IMPACT: These results predict which women are most likely to benefit from treatment with a PARP inhibitor (rucaparib) and supported the FDA-accelerated approval for oral therapy rucaparib. This therapy is currently used to treat Service Members.
673A Drug-Targeting Cancer Stem-Like Cells

DESCRIPTION
Ovarian cancer recurrence is due to a small population of chemotherapy-resistant cancer cells known as cancer stem-like cells. Therapeutics targeting cancer stem-like cells should improve patient response to therapy and reduce ovarian cancer reoccurrence. A novel aldehyde dehydrogenase inhibitor drug, 673A, was found to specifically target the cancer stem-like cells. In a mouse model of ovarian cancer, combined treatment with 673A and chemotherapy resulted in significantly greater survival rates. A follow-on NIH Award began in June 2017 to further optimize the drug.

PARTNERS/COLLABORATORS
University of Michigan; University of Pittsburgh; UPMC Hillman Cancer Center; Magee-Women’s Research Institute

AWARD NUMBER: W81XWH-14-1-0166

Clinical Predictors for PARP Inhibitor Therapy

DESCRIPTION
PARP inhibitors are effective treatment options for ovarian cancer patients with mutations in BRCA1 or BRCA2; however, there is no optimal test that predicts which patients with BRCA-wildtype (no BRCA gene mutations) ovarian cancer will respond to PARP inhibitor therapy. A new clinical test is being developed using whole genome sequencing to look for gene mutation and alteration patterns beyond BRCA 1 and BRCA 2 that lead to specific DNA repair process deficiencies and may be more predictive of PARP inhibitor response.

PARTNERS/COLLABORATORS
University of Washington; Clovis Oncology; University of Cambridge

AWARD NUMBER: W81XWH-17-1-0070

IMPACT: This research established early development of an effective treatment for recurrent ovarian cancer that has the potential to improve mortality rates for ovarian cancer patients.

IMPACT: This study provides potential means to identify women with ovarian cancer who do not have BRCA1 or BRCA2 mutations but who also have a good chance of responding to PARP inhibitors, offering more effective personalized treatment strategies.
**Mobile Application for Genetic Information on Cancer (mAGIC)**

**DESCRIPTION**
Based on data from a focus group of women diagnosed with ovarian cancer who received varying levels of genetic counseling, the mAGIC intervention was developed to motivate ovarian cancer survivors and their families to undergo genetic counseling. The effectiveness of the intervention was tested with a randomized controlled trial of 104 women with a diagnosis of ovarian cancer who had not previously received genetic counseling. Participants in the intervention group reported high satisfaction with the mAGIC application and would recommend the intervention to others. Guidelines published by the National Comprehensive Cancer Network and the Society of Gynecologic Oncology recommend ovarian cancer survivors receive further genetic risk evaluation by a genetic counselor; however, these women under-use genetic services.

**PARTNERS/COLLABORATORS**
University of Minnesota, Twin Cities

**AWARD NUMBER:** W81XWH-14-1-0102

**IMPACT:** This mobile application provides a means to encourage genetic counseling and preventive health care to ovarian cancer survivors.
Olaparib and AT13387 for Recurrent Ovarian Cancer

DESCRIPTION
Heat shock protein 90 (HSP90) was validated as a novel therapeutic target for cyclinE1 (CCNE1)-amplified ovarian cancer, which is the most deadly ovarian cancer due to a lack of responsiveness to standard chemotherapy. In a mouse model of patient-derived CCNE1-amplified ovarian cancer tumors, the HSP90-inhibitor AT13387, synergized with PARP inhibitors and inhibited tumor growth better than either treatment alone. Results from this Ovarian Cancer Academy (OCA) Collaborative Award, which required OCA Early Career Investigators to collaborate with a non-OCA co-PI, developed into a phase 1 clinical trial of the PARP inhibitor, olaparib, in combination with AT13387 for the treatment of recurrent ovarian cancer.

PARTNERS/COLLABORATORS
Dana-Farber Cancer Institute; Wistar Institute; National Cancer Institute (NCI)


IMPACT: This research presents a potential novel therapeutic strategy to treat patients with CCNE1-amplified ovarian cancer tumors who have poor outcomes due to the ineffectiveness of standard treatment.

In a patient-derived CCNE1-amplified ovarian cancer mouse model, the combination of AT13387 and olaparib induced inhibition of tumor growth, as opposed to vehicle control, olaparib alone, and AT13387 alone.
Biomarkers from Pap Tests for Detection of Ovarian Cancer

DESCRIPTION
Early detection of ovarian cancer increases survival, but screening tools for use in the general population are lacking. Pap tests were examined for the presence of proteins (or biomarkers) shed by ovarian cancer cells. When comparing Pap test samples and cervical swabs of ovarian cancer patients with their tumor tissue, more than 2,000 proteins were expressed in the Pap test and cervical swab samples that were also present in the tumor tissue, including several known ovarian cancer biomarkers, such as CA125. These results suggest that Pap test fixatives and cervical swabs may be a rich source of tumor-specific biomarkers for ovarian cancer detection.

PARTNERS/COLLABORATORS
University of Minnesota

AWARD NUMBER: W81XWH-16-1-0070

IMPACT: Identified biomarkers for ovarian cancer detection may be developed into an easy, non-invasive screening test for ovarian cancer that can be incorporated as part of a routine Pap test, so that women can be tested simultaneously for cervical and ovarian cancer.

2,293 tumor tissue proteins were expressed in both Pap tests and cervical swab samples, including known ovarian cancer biomarkers.
A Novel Radiolabeled Tracer to Predict Chemotherapy Response

**DESCRIPTION**

The challenge with PARP inhibitor therapy is that not all ovarian cancers will respond, and there is currently no good indicator as to which will. A novel radiolabeled tracer, \[^{18}\text{F}]\text{FluorThanatrace (}\[^{18}\text{F}]\text{FTT)}\), which identifies PARP-1 protein expression in patient tumors, was evaluated in a predictive assay for tumor response to DNA-damaging agent chemotherapy with the added benefit of PARP inhibitor agents. The \[^{18}\text{F}]\text{FTT tracer is currently being assessed in a phase 1 clinical trial to validate it as a predictor of response to PARP inhibitor therapy in ovarian cancer by imaging patients with \[^{18}\text{F}]\text{FTT before and after initiating PARP inhibitor therapy. Results from this trial will help provide the data needed for larger multicenter clinical trials, with the goal of fully evaluating the importance of PARP-1 expression as a biomarker for cancer therapy and the use of the \[^{18}\text{F}]\text{FTT tracer for measuring PARP-1 expression and PARP inhibitor sensitivity.**

**PARTNERS/COLLABORATORS**

University of Pennsylvania

**AWARD NUMBER:** W81XWH-17-1-0092

**IMPACT:** Clinical trial results may validate a non-invasive screening tool to evaluate PARP-1 expression and identify patients who will benefit from PARP inhibitor and DNA damaging agent therapy, which has the potential to greatly improve treatment for women with ovarian cancer.
Vision: To address the long-term implications of military service as they pertain to Alzheimer’s disease and Alzheimer’s disease-related dementias

Mission: Devoted to (1) understanding the association between military service-related risk factors and Alzheimer’s disease/Alzheimer’s disease-related dementias, and (2) reducing the burden on affected individuals and caregivers, especially in the military and Veteran communities

Years Program Appropriated: FY11-FY21
Total Appropriations: $153M

Military personnel may face an increased risk for developing Alzheimer’s disease (AD) or a related dementia as they age. Risk factors such as traumatic brain injury, vascular disease, lifestyle, and alterations in cognition or behavior may affect military personnel at higher rates or with greater severity than the general public. These risk factors may be linked to early dementia symptoms, such as aggression, memory loss, depression, and symptoms similar to those of other neurological diseases, long before a dementia diagnosis can be established by a medical professional.

The Peer Reviewed Alzheimer’s Research Program (PRARP) emphasizes not only basic research related to understanding and diagnosing the molecular basis of dementia after military Service, but also tools and strategies that can improve the quality of life of individuals living with AD or ADRD by their implementation in care settings.
Roles of Non-Neuronal Cells in Alzheimer’s Disease

**DESCRIPTION**
Mechanisms that link TBI with AD remain a mystery. Researchers hypothesized there is a bridge between TBI and AD through inflammation, and they tracked two different sources of inflammation in mice. These are the peripheral monocytes of the bloodstream and the microglia of the brain. It was discovered that the initial injury continued to grow in the mice that overproduced beta-amyloid. This was also accompanied by a reduction in the immune response when compared to injured controls. The injured mice that overproduced beta-amyloid showed worsening behavioral outcomes. The study has identified a potential driver for this inflammatory response, TREM2.

**PARTNERS/COLLABORATORS**
Indiana University School of Medicine

**AWARD NUMBER:** W81XWH-14-1-0265
Nanobodies to Identify TBI and Alzheimer’s

**DESCRIPTION**
Misfolding and aggregation of the proteins amyloid beta (Aβ) and tau result in the plaques and tangles associated with AD. The PI has developed recombinant antibody fragments, or nanobodies, that selectively recognize different oligomeric Aβ, α-synuclein species, and tau species. The work has developed into a panel of nanobodies that can identify blood-based biomarkers indicative of TBI even 20 years or more after the initial TBI based on neurodegenerative disease markers associated with AD. The work is patented and validated in humans.

**PARTNERS/COLLABORATORS**
Arizona State University

**AWARD NUMBERS:** W81XWH-12-1-0583, W81XWH-14-1-0467

**IMPACT:** This novel diagnostic may potentially identify biomarkers indicative of AD and TBI many years after initial injury.

An Integrative Exercise Program for Individuals with Dementia

**DESCRIPTION**
This work examines whether the Preventing Loss of Independence through Exercise (PLIE) program for an extended period of time will result in neurobiological changes that improve cognitive function, leading to improvements in physical function and quality of life (QOL). This is a combined mindfulness and movement-based intervention. Most importantly, the results will be objectively quantified using fMRI and measurements of cerebral perfusion. Preliminary results in a human-based study are showing efficacy.

**PARTNERS/COLLABORATORS**
Northern California Institute for Research and Education; San Francisco VAMC

**AWARD NUMBER:** W81XWH-17-1-0490

**IMPACT:** PLIE is potentially an inexpensive, easy to administer non-drug treatment for the symptoms of AD subsequent to TBI or either condition separately.
Smart Home Technologies for Individuals with Cognitive Impairments

**DESCRIPTION**
The Electronic Memory and Management Aid (EMMA) is a mobile digital memory notebook (DMN) to enable older adults with cognitive impairment to maintain functional independence in their own homes. The device is integrated with smart home-based technologies in order to monitor and anticipate the completion of essential daily activities.

**PARTNERS/COLLABORATORS**
Washington State University; Managed Health Connections

**AWARD NUMBERS:** W81XWH-16-1-0709, W81XWH-20-1-0654

**IMPACT:** For individuals with memory issues or depressive behaviors, this tool could be used to ensure they complete daily activities such as bathing, medication use, and eating. Caregivers could potentially monitor their activities via the DMN as well.

Transcranial Ultrasound for Alzheimer’s Dementia After TBI In Vivo

**DESCRIPTION**
This project examines if a tool called transcranial near-diagnostic ultrasound (tnDU) can improve AD symptoms after TBI. The grant will explore physiological mechanisms by which tnDU achieves its effects. Researchers will also examine the biology of the brain after treatment and the role of a drug called Idazoxan. Idazoxan may work in conjunction with tnDU to achieve better outcomes. Work is to be completed in animals.

**PARTNERS/COLLABORATORS**
University of Washington

**AWARD NUMBER:** W81XWH-20-1-0479

**IMPACT:** Results of this study may help lead to novel treatment options for AD subsequent to TBI or either condition separately.
Vision: To advance mission readiness of U.S. military members affected by cancer and to improve quality of life by decreasing the burden of cancer on Service Members, their families, Veterans, and the American public

Mission: To successfully promote high-impact research for cancer prevention, detection, treatment, quality of life, and survivorship

Years Program Appropriated: FY09-FY21

Total Appropriations: $654.8M

The Peer Reviewed Cancer Research Program (PRCRP) supports innovative and impactful research in cancers and other specialty areas specifically authorized by Congress. A total of 34 Topic Areas have been eligible for PRCRP funding over the years. Congressional language has directed that research funded by the PRCRP should be relevant to Service Members and their families. It is a central initiative of the PRCRP that applications address how the proposed research is related to military health, mission readiness, and the cancer health needs of both deployed and non-deployed military personnel, their dependents, Veterans, and other military beneficiaries (i.e., family members and retirees). Some cancers, such as mesothelioma, stomach, and blood cancers, are risk factors for active-duty Service Members due to exposures related to military service and deployment. Other cancers may affect the military because a diagnosis may impact mission readiness. In this way, the PRCRP focuses on strategic capabilities of the military and fills knowledge gaps in cancer prevention, detection/diagnosis, treatment, and survivorship.
**XPOVIO® (Selinexor)**

**DESCRIPTION**

This study discovered that overexpression of a protein called exportin (XPO1) leads to blocking tumor suppressors out of the nucleus to ensure their active role in DNA repair. XPO1 was identified as a therapeutic target, with the work culminating in drug combination studies of XPO1 inhibitors (i.e., selinexor). The FDA granted selinexor accelerated approval for relapsed/refractory multiple myeloma in 2019, with full FDA approval anticipated in 2021. In June 2020, the FDA approved selinexor for the treatment of diffuse large B-cell lymphoma. The VA acknowledged that exposures to herbicides (such as Agent Orange) may lead to the development of multiple myeloma and other blood cancers in Veterans. PRCRP funded the groundwork for this breakthrough advancement in blood cancer treatment.

**PARTNERS/COLLABORATORS**
The Ohio State University

**AWARD NUMBER:** W81XWH-14-1-0190

**IMPACT:** XPOVIO is an easy-to-use oral treatment and a major milestone in blood cancer treatment.

**IMPACT:** Therapeutic technologies that enhance the body’s immune system to fight cancer are a new horizon of treatments and may have relevance on multiple cancers related to military health.

**Using Both Immunotherapy and Nanotherapy to Beat Bladder Cancer**

**DESCRIPTION**

Using a two-pronged approach, researchers were able to demonstrate a combination of immunotherapy and photothermal nanotherapy to eradicate focal and distant bladder cancer. With a combination of immune checkpoint inhibitors and plasmonic gold nanostar-mediated photothermal therapy, primary bladder tumors were treated while the immune system was activated to attack distant metastasis in mice. This proof of principle experiment led to the development of SYMPHONY, a potential new therapeutic technology for bladder cancer.

**PARTNERS/COLLABORATORS**
Duke University

**AWARD NUMBER:** W81XWH-17-1-0567
Carcinogenic Risk Factors in Testicular Cancer

DESCRIPTION
Chemical carcinogens pose a great risk to Service Members. To investigate the relationship between per- and poly-fluoroalkyl substances (PFAS) exposure and testicular cancer in U.S. Air Force Servicemen, this research will utilize the DOD Serum Repository to obtain blood serum samples from 500 U.S. Air Force Servicemen diagnosed with testicular cancer several years after serum collection and 500 men without testicular cancer. These serum samples will be analyzed to measure levels of 12 PFAS to determine if there are higher serum PFAS in Servicemen who went on to develop testicular cancer compared to men who did not, in order to discover if there is a link between these chemicals and risk of testicular cancer.

PARTNERS/COLLABORATORS
National Cancer Institute; Uniformed Services University of the Health Sciences

AWARD NUMBER: W81XWH-19-1-0444

Big Data Analysis Shows New Targets for Gastric Cancer

DESCRIPTION
H. pylori, known to be a direct cause of gastric cancer (GC), is endemic across the world. It has been shown that U.S. Veterans have a high prevalence of active H. pylori (28.9%) and are at risk of developing GC. The big data project using the Cancer Genome Atlas sought to assess different tumors’ immune landscapes to discover specific therapeutic targets for GC. The immune landscape elucidated tumor growth and also demonstrated the benefit from RAS-targeting treatment and the feasibility of immunotherapy treatments and DNA repair targets.

PARTNERS/COLLABORATORS
M.D. Anderson Cancer Center, University of Texas

AWARD NUMBER: W81XWH-16-1-0237

IMPACT: This project will shed light on the extent of PFAS exposure among Air Force Servicemen and help researchers better understand the health impacts of PFAS exposure.

IMPACT: The wealth of information gathered from this big data project will inform the clinic on new avenues to this deadliest of cancers and protect both active-duty Service Members and Veterans.
Denosumab to Augment Immunotherapy in Melanoma

**DESCRIPTION**
Researchers investigated whether blocking central tolerance enhances immune checkpoint blockade effects in treating melanoma. A key mediator of central tolerance is the autoimmune regulator, Aire. Antibodies against receptor activator of nuclear factor kappa-B ligand (RANKL) block Aire expression and increase activation of T cells that could potentially target melanoma. Denosumab is an FDA-approved antibody therapeutic that targets RANKL. Denosumab has a synergistic effect with checkpoint inhibitors anti-CTLA4 and anti-PD1 and significantly decreased tumor growth and prolonged survival. The results of this project informed the development of a phase 2 clinical trial for stage III/IV melanoma patients (cutaneous and mucosal), in which denosumab will be used in combination with anti-PD1 immunotherapy.

**PARTNERS/COLLABORATORS**
University of North Carolina at Chapel Hill

**AWARD NUMBER:** W81XWH-15-1-0411
Development of Highly Sensitive Detector for Colorectal Cancer

DESCRIPTION
This research developed a highly sensitive color-fluorescence endoscope, inspired by the mantis shrimp’s eye anatomy, to detect cancerous and pre-cancerous tissue with high specificity and sensitivity in colorectal cancer patients. In this study, nature informed technology, as the detector is based on the mantis shrimp eyes’ very efficient photodetectors and nanoscale optical filters. The endoscope has a multi-spectral imager capable of spatially co-registered hexachromatic vision, with three spectral channels in the visible spectrum (red, green, and blue) and three spectral channels in the near-infrared spectrum. These can be used simultaneously to image multiple tumor-target markers, especially for flat lesions that are often difficult to find with routine detection.

PARTNERS/COLLABORATORS
University of Illinois Champaign/Urbana

AWARD NUMBER: W81XWH-19-1-0299

IMPACT: Increased sensitivity will decrease the false negatives during colorectal screening, leading to earlier diagnoses and better outcomes.
Protection Against the Damaging Effects of Radiation

**DESCRIPTION**
Ionizing radiation induces injuries that may be long-term, including damage to the blood cell proliferation cascade (hematopoiesis) within the bone marrow. Studies show that the deletion of Ca$^{2+}$/calmodulin (CaM)-dependent protein kinase 2 (CaMKK2) promotes hematopoietic recovery following radiation injury. Administration of a small molecule CAMKK2 inhibitor, STO-609, enhances the recovery of hematopoiesis and improves survival in mice. Not only do the studies show the utility of STO-609 in radiation survival, they also demonstrate the importance of CAMKK2 in cellular processes.

**PARTNERS/COLLABORATORS**
Duke University

**AWARD NUMBER:** W18XWH-15-1-0443

**IMPACT:** Exposure to ionizing radiation, which includes high-energy types of radiation like X-rays and gamma radiation, increases the risk of developing blood cancers like leukemia and multiple myeloma. Active-duty Service Members may be exposed to radiation sources during military activities, and thus be at risk for developing different types of cancers, especially blood cancers.
Vision: Improve the health, care, and well-being of all military Service Members, Veterans, and beneficiaries

Mission: Encourage, identify, select, and manage medical research projects of clear scientific merit and direct relevance to military health

Years Program Appropriated: FY99-FY06, FY08-FY21

Total Appropriations: $3.08B

The Peer Reviewed Medical Research Program (PRMRP) supports innovative and impactful research across congressionally directed Topic Areas that address a wide range of disciplines, including cardiovascular health, autoimmune diseases and immunology, infectious diseases, internal medicine, neurological and psychological health, orthopaedic and regenerative medicine, and respiratory and environmental health. Over 210 Topic Areas have been authorized for PRMRP funding over the years. Congressional language has directed that the PRMRP support scientifically meritorious research that is relevant to military health. To accomplish its vision, the PRMRP focuses on advancing knowledge in disease etiology, improving prevention, detection/diagnosis, treatment, and quality of life for those affected by the relevant disease or condition. The PRMRP also emphasizes development and validation of clinical practice or public health guidelines.
Banyan Brain Trauma Indicator (BTI)

DESCRIPTION
Potential blood-based biomarkers were first identified in mouse models and later validated in human studies as indicators of TBI. These biomarkers appear in the blood within 12 hours after brain injury. Alongside the initial discovery and validation studies, the investigators developed semi-quantitative assays as a kit, known as the Banyan BTI, which ultimately became the first blood test approved by the FDA to evaluate mild TBI, as part of its Breakthrough Devices Program in 2018 (DEN170045). The Banyan BTI provides rapid testing (within 3-4 hours) of serum collected within 12 hours of suspected head injury and is used along with other available clinical information to aid in the evaluation of adult patients with suspected TBI (Glasgow Coma Scale score 13-15). A negative assay result is associated with the absence of acute intracranial lesions visualized on a head CT scan and is expected to decrease the number of CT scans performed on patients who seek emergency room care for a possible concussion, reducing both costs and patients’ exposure to radiation.

PARTNERS/COLLABORATORS
Banyan Biomarkers, Inc.; University of Florida; Walter Reed Army Institute of Research

AWARD NUMBERS: DAMD17-03-1-0066, W81XWH-07-2-0075, W81XWH-10-C-0251

IMPACT: The Banyan BTI provides a rapid and cost-effective test that can be used to evaluate Service Members or others who may have experienced a mild TBI.
**BIO 300 (Genistein)**

**DESCRIPTION**
There is a need for improved prevention and/or treatment of damage and scarring in the lungs, especially due to emerging respiratory illnesses and acute radiation exposure. PRMRP- and JWMRP-supported studies are developing and testing novel oral suspension and solid powder formulations of genistein, which have improved bioavailability and anti-inflammatory properties, as therapeutics in preventing negative health effects of radiation exposure (such as pulmonary fibrosis). Initial results and a demonstrated human safety profile supported PRMRP funding of a new preclinical study to evaluate BIO 300 Oral Powder as a post-COVID-19 treatment intended to reduce inflammation and prevent the development of pulmonary fibrosis in survivors of COVID-19-associated acute respiratory distress syndrome.

**PARTNERS/COLLABORATORS**
Humanetics Corporation

**AWARD NUMBERS:** W81XWH-17-1-0584 (PRMRP), W81XWH-19-2-0060 (JWMRP), W81XWH-21-1-0010 (PRMRP)

**IMPACT:** BIO 300 could potentially be used in a variety of shelf-stable forms that are suitable for field operations (tablet, capsule, etc.) to protect against radiological hazards faced by deployed personnel. It may also be effective as a therapeutic to combat emerging respiratory viral threats.
**Everolimus in Pediatric Heart Transplantation**

**DESCRIPTION**
Median survival after pediatric heart transplantation is only 15 years due to the occurrence of late complications after heart transplant, most of which stem from the medications used to suppress the immune system to prevent organ rejection. PRMRP funded a phase 3 clinical trial (TEAMMATE; [http://med.stanford.edu/teammate.html](http://med.stanford.edu/teammate.html)) to determine whether a novel treatment (Everolimus and low-dose tacrolimus) for children who have undergone recent heart transplant can reduce or prevent several key complications of transplant, including rejection, coronary artery disease, and kidney disease, when compared to usual care. TEAMMATE investigators successfully established the first-ever collaborative clinical research network specific to pediatric heart transplantation. Enrollment is now complete, with a total of 211 pediatric heart transplant recipients, and follow-up is underway. Pending results of the trial, this may lead to FDA approval of the first immunosuppression regimen specific to pediatric heart transplantation.

**PARTNERS/COLLABORATORS**
Boston Children’s Hospital; Stanford University; and 23 additional clinical sites across the U.S.

**AWARD NUMBER:** W81XWH-17-1-0532

**IMPACT:** Everolimus may potentially improve the long-term safety and survival of children after heart transplant. It may also have medical applications for treating military injuries that require a vascular composite allograft, such as hand or face transplantation, and for understanding wound healing problems.
Improved Technique for Transplantation of Pancreatic Islets

DESCRIPTION
In patients with chronic pancreatitis, more than 90% have been hospitalized, half use narcotic analgesics, one-fourth are on disability, and there is a 70% increased risk of diabetes mellitus. Veterans are at a higher risk of pancreatitis than the general population. One treatment option that provides sustained pain relief is total removal of the pancreas (pancreatectomy). Current procedure also involves transplanting pancreatic islet cells, which produce insulin and other important hormones, into the liver to maintain some functionality. A PRMFRP-supported pilot clinical trial is investigating transplanting pancreatic islet cells both into the liver and into an alternative site in fatty abdominal tissue following pancreatectomy for chronic pancreatitis. This trial is determining safety and comparing islet cell function between the two transplant techniques.

PARTNERS/COLLABORATORS
University of Minnesota, Twin Cities

AWARD NUMBER: W81XWH-18-1-0687

IMPACT: This technique has the potential to improve the lives of patients with chronic pancreatitis. Better function and preservation of transplanted islets will decrease the number of patients with insulin dependence (diabetes) and reduce complications from islet cell dysfunction following total pancreatectomy, making it a more viable option.

Samples from preliminary studies stained with antibody to insulin or von Willibrand factor (vWF) to demonstrate the functionality of the pancreatic islet cells after implantation.
Long-Acting Lidocaine Formulation

DESCRIPTION
In the military, the incidence of interstitial cystitis/bladder pain over a 10-year period (2000-2009) was 80.4 per 100,000 person-years, which is 4-5 times higher than the female incidence rate estimated in the civilian community. The Alivio microparticle-based hydrogel technology is designed to selectively target inflamed tissue and release an encapsulated therapeutic agent directly to the bladder in response to inflammation levels. The goal is to utilize this technology to deliver lidocaine (Lido) via urinary catheter for prolonged pain relief in interstitial cystitis. This technology is currently being optimized in animal models, where it has shown to be safe and efficacious. The investigators are currently completing the necessary work to submit an IND application to the FDA.

PARTNERS/COLLABORATORS
Alivio Therapeutics, Inc.

AWARD NUMBER: W81XWH-18-1-0566
Modified mRNA-Based Vaccine for Lassa Virus

DESCRIPTION
Lassa virus, which can cause Lassa fever, a hemorrhagic fever with a high mortality rate, is endemic to West Africa and poses a significant public health threat. Although there are multiple strains of Lassa virus with the potential for causing disease, there are currently no vaccines available to protect against any of them. This PRMRP-supported vaccine development uses an innovative, modified mRNA technology for protection against Lassa virus. The mRNA-based vaccine is encapsulated in lipid nanoparticles to enhance shelf life and stability, potentially even at room temperature. Preclinical testing of vaccine constructs for all four lineages (i.e., clades) of Lassa virus is underway in a guinea pig model. If successful, the vaccine would be protective against all clades of the virus and could be rapidly and inexpensively manufactured.

PARTNERS/COLLABORATORS
University of Texas Medical Branch, Galveston; Moderna Therapeutics

AWARD NUMBER: W81XWH-19-1-0019

IMPACT: A vaccine will provide protection against Lassa virus infection to deployed Service Members as well as the general population who live in or visit endemic regions in West Africa.
Neuroimaging-Based Diagnostic Tool for Chronic Tinnitus

DESCRIPTION

Military personnel and civilians in certain professions, such as firefighters and construction workers, are at increased risk for noise trauma. Despite its high prevalence (10%-15% of the population), tinnitus remains a non-observable, self-reported medical condition, and there is no objective mechanism to diagnose and monitor treatment for chronic tinnitus or to explain the biological basis of the condition. A novel approach funded by the PRMRP is developing a tool to analyze imaging data that will diagnose chronic tinnitus with greater than 85% sensitivity and specificity in civilians and military personnel. Following initial algorithm development, the tool is being calibrated with publicly available imaging datasets as well as newly collected data from civilians and Veterans with and without chronic tinnitus. Findings from the current study are expected to demonstrate proof of concept and fulfill 510(k) device requirements set by the FDA for testing in clinical trials.

PARTNERS/COLLABORATORS

University of California, San Francisco; San Francisco VAMC; University of Minnesota

AWARD NUMBER: W81XWH-18-1-0741
(R)-ND-336 for the Treatment of Diabetic Foot Ulcers

DESCRIPTION
Diabetes affects more than 30 million individuals in the United States. Approximately 25% of Veterans receiving care from the VA have diabetes. The inability of wounds to heal, typically occurring in the feet and referred to as diabetic foot ulcers (DFUs), is a common complication of diabetes. Current therapies for DFUs are limited, and the single FDA-approved drug for this condition, becaplermin, is seldom used due to increased risks of cancer and death. The lack of effective therapies for DFUs results in over 100,000 lower-limb amputations annually in the United States. The PRMRP supported preclinical development and testing of a novel topical drug, (R)-ND-336, which selectively inhibits a specific enzyme in diabetic wounds that prevents healing and thereby promotes natural wound healing. Final preclinical development of (R)-ND-336 using a diabetic mouse wound model is providing data to file an IND with the FDA and begin human clinical trials.

PARTNERS/COLLABORATORS
University of Notre Dame

AWARD NUMBER: W81XWH-19-1-0493

IMPACT: If approved, this drug would become a more effective and safer option for treating DFUs and could ultimately reduce the number of lower-limb amputations conducted as a result of diabetes.
Selective Cytopheresis Device Therapy (SCD Rx)

DESCRIPTION
Acute respiratory distress syndrome (ARDS) is a life-threatening inflammation of the lungs brought on by factors released after injury or during infection. The Selective Cytopheretic Device (SCD) is an immune modulating device shown to be effective in reducing inflammation and multi-organ dysfunction, conditions associated with acute lung injury (ALI) and ARDS. A combat-relevant pig model for ALI was developed, and efficacy of SCD therapy to treat ALI/ARDS was assessed. The SCD demonstrated significant therapeutic benefits in the ALI/ARDS porcine model, which provided evidence to advance this technology into clinical trials. The FDA granted Emergency Use Authorization of SCD therapy for COVID-19 patients with acute kidney injury and ARDS, and a multicenter clinical trial is underway.

PARTNERS/COLLABORATORS
Innovative BioTherapies, Inc.

AWARD NUMBER: W81XWH-16-1-0463

IMPACT: If proven effective, SCD therapy could reduce mortality and improve clinical outcomes of critically-ill COVID-19 patients and Service Members who have experienced ALI/ARDS.
Use of Beta Blockers for Chronic Obstructive Pulmonary Disease (COPD)

DESCRIPTION
COPD, a group of inflammatory lung diseases that cause airway blockage, continues to be a leading cause of death in the United States. Due to the cardioprotective effects of beta-adrenergic blocking agents (beta blockers), this therapeutic is desirable for use among COPD patients, but there is conflicting evidence of safety. Prior to this study, the practice of prescribing beta blockers for COPD was controversial. This clinical trial examined whether once-daily metoprolol succinate, a beta blocker, reduced the risk of acute exacerbations (worsening) of COPD. While there was no increased risk of COPD exacerbation among patients receiving metoprolol compared to the placebo group, they demonstrated higher risk of more severe exacerbations leading to hospitalization. These findings resulted in the termination of the trial and led to a Clinical Practice Guideline discouraging the use of beta blockers in COPD patients.

PARTNERS/COLLABORATORS
University of Alabama at Birmingham; more than 25 sites across the U.S., including civilian hospitals and VAMCs

AWARD NUMBER: W81XWH-15-1-0705

IMPACT: Earlier evidence suggested that beta blockers may reduce cardiovascular risk in COPD patients; however, the results of this trial confirmed that beta blocker use among COPD patients increases the risk of exacerbation, requiring hospitalization.
Karen B. Schmaling, PhD, PRMRP Peer Reviewer

“Relevant is a hallmark of the research supported by the PRMRP. The PRMRP integrates scientific, consumer, and military expertise to identify timely and innovative research. Clinical, translational, and basic research is reviewed that has promise to advance diagnosis and treatment of a range of conditions and to enhance the lives of Service Members, their families, and civilians.”

CAPT Eric Hofmeister, MD (U.S. Navy, Ret.)
PRORP Programmatic Panel

“The PRORP really tries to focus on research that’s going to benefit those directly involved and who have been injured in combat situations, and unique combat situations that maybe we don’t see in everyday medical practices—things such as horrific multi-limb injuries, penetrating pelvic injuries, a huge amount of loss of muscle or function to a limb. So the program is really trying to focus on research to bridge those gaps that we have no answers to right now.”
Vision: Provide all military Service Members with orthopaedic injuries the opportunity for optimal recovery and restoration of function

Mission: Address the most significant gaps in care for the leading burden of injury and for facilitating return-to-duty by funding innovative, high-impact, clinically relevant research to advance optimal treatment and rehabilitation from musculoskeletal injuries sustained during combat and combat-related activities

Years Program Appropriated: FY09–FY21

Total Appropriations: $458.5M

A large majority of the injuries sustained by military personnel in U.S. combat efforts involve soft tissue wounds and skeletal fractures, pointing to an urgent need for orthopaedic research that will provide superior medical care and treatment options for injured Service Members. Orthopaedic injuries sustained during combat-related activities tend to occur in harsh environments where access to optimal acute care can be limited. They are also distinct from those seen in the civilian setting, frequently involving multiple limb trauma, open fractures, major tissue loss, and a high degree of wound contamination. The Peer Reviewed Orthopaedic Research Program (PRORP) provides funding for high-impact, clinically relevant research projects that address the most significant gaps in orthopaedic injury care to facilitate return to duty and return to work.
Repairing Large Gaps in Injured Peripheral Nerves

DESCRIPTION
Repair of large gaps in the peripheral nerve after blast injury is a significant challenge in restoring function to injured limbs. Researchers created a light-activated material that can be used to wrap the injured peripheral nerve. When light is applied to the wrap, it creates a seal and also releases compounds that help the injured nerve regenerate and prevent inflammation.

PARTNERS/COLLABORATORS
Massachusetts General Hospital; Walter Reed National Military Medical Center

AWARD NUMBERS: W81XWH-12-1-0511, W81XWH-12-1-0512, W81XWH-12-1-0513; follow-on funding from JWMRP W81XWH-17-1-0059

IMPACT: Restoring function to a limb that has sustained a large-gap peripheral nerve injury could significantly improve an injured Service Member’s quality of life by preventing paralysis, increasing independence, and decreasing neuropathic pain.

Schematic of photosealing approach. The nerve is wrapped with the graft device. When the pink dye is illuminated with green light, the graft is sealed and releases compounds to help the nerve regenerate. (Modified from image in Final Report, W81XWH-17-1-0059)
SPRINT Peripheral Nerve Stimulation System

DESCRIPTION
The SPRINT Peripheral Nerve Stimulation (SPRINT PNS) System consists of a microlead that is placed under the skin by a physician during an outpatient procedure without surgery, incisions, tissue destruction, or anesthesia. The microlead, connected to a wearable stimulator, can be left in place up to 60 days and delivers small pulses of electrical stimulation. The stimulation therapy is intended to produce a comfortable sensation where the pain is felt and decrease or eliminate the perception of pain. Additional study of the therapeutic effects of the SPRINT PNS are being explored for relief of low back pain and after knee replacement surgery. Researchers believe the knee replacement model may be an appropriate pain model for military trauma surgery.

PARTNERS/COLLABORATORS
SPR Therapeutics; Naval Medical Center San Diego; VA Palo Alto Health Care System; and several other clinical sites

AWARD NUMBERS: W81XWH-12-2-0132; follow-on funding from JWMRP W81XWH-17-C-0019, PRORP W81XWH-18-1-0799, and PRMRP W81XWH-18-1-0800

IMPACT: The SPRINT PNS has been shown to provide relief from residual limb pain and phantom limb pain in patients with amputations and a decrease in opioid usage due to sustained pain relief even after the device was removed.
Four-Drug Cocktail to Relieve Post-Traumatic Acute Pain

DESCRIPTION
Study data provides evidence that single-injection combinations of four drugs (bupivacaine-bupivacaineclonidine-buprenorphine-dexamethasone and midazolam-bupivacaineclonidine-buprenorphine-dexamethasone) are safe, chemically compatible with each other, and have the apparent potential to provide long-term analgesia. Additional benefits will include the development of a continuous nerve block drug combination that (1) preserves active range-of-motion while acute pain is controlled without using conventional narcotic drugs and (2) allows for pain-free evacuation and transport of injured Warfighters.

PARTNERS/COLLABORATORS
University of Pittsburgh; Walter Reed Army Medical Center

AWARD NUMBERS: W81XWH-10-2-0097; follow-on funding from DMRDP W81XWH-15-1-0294

IMPACT: This combination nerve block will reduce or eliminate the complexity involved with inserting nerve block catheters in injured soldiers while preserving active range-of-motion and minimizing pain during evacuation.
New Approaches to Prevent Cartilage Degeneration and Treat Post-Traumatic Osteoarthritis (PTOA)

DESCRIPTION
Understanding the mechanism of development of OA is critical in advancing OA treatments for both Service Members and the general public who are suffering from chronic joint disease. This study is identifying new agents that can rescue osteocyte (bone cell) remodeling and testing their ability to protect cartilage from conditions that drive PTOA or osteonecrosis. This work identified the pathway by which heavy loads, such as those experienced by fully-outfitted Warfighters, compromise bone quality, which in turn promotes cartilage degeneration. It also found that this pathway is impaired in, contributes to, and can be targeted for prevention of the progression of PTOA. The knowledge gained from this research will be applied to develop novel therapies that prevent or mitigate PTOA and osteonecrosis.

PARTNERS/COLLABORATORS
University of California, San Francisco; San Francisco VAMC

AWARD NUMBERS: W81XWH-14-1-0497; follow-on funding from DMRDP W81XWH-18-1-0155

IMPACT: Results from this research could accelerate the development of novel therapies to improve the skeletal health of the military population.
Local Vancomycin Powder Administration at a Surgical Fracture Site

DESCRIPTION
During military combat operations, Service Members have a high risk of fractures with open wounds, which can easily become contaminated. Surgical repair of traumatic bone fracture sites using plates, screws, and other metal hardware is associated with a high rate of infection and subsequently poor outcomes. Use of vancomycin powder at the surgical site prior to closing the wound significantly decreases deep surgical site infections. Building on this, researchers are investigating whether use of vancomycin powder in the emergency department before surgical repair will reduce wound infections. Vancomycin powder is an FDA-approved topical antibiotic that is available as a low-cost generic drug, requires no refrigeration, and could easily be carried in a medic’s bag and potentially be used for battlefield treatment.

PARTNERS/COLLABORATORS
University of Maryland, Baltimore; Johns Hopkins University; METRC consortium clinical sites; University of Texas, Health Science Center at San Antonio; U.S. Army Institute of Surgical Research

AWARD NUMBERS: W81XWH-10-2-0134, W81XWH-18-2-0074

IMPACT: Preventing infections in open fractures will reduce the risk of long-term infection-related complications and the need for additional treatments and prolonged recovery time, which impact mission readiness and delay return to duty.
Keratin HaloGel Drug Delivery System

DESCRIPTION
Keratin hydrogels are effective biocompatible carriers of a variety of drugs and have anti-inflammatory effects. This work demonstrated that an application of a Halo-infused keratin hydrogel in immobilized knees prevents post-traumatic contracture resulting from inflammation and TGF-β-induced excessive synthesis and deposition of type 1 and 3 collagens. This mechanism of drug delivery is now applied for treating infections, wound healing, and functional tissue regeneration.

PARTNERS/COLLABORATORS
KeraNetics LLC; Wake Forest University Health Sciences; Synecor Labs

AWARD NUMBER: W81XWH-13-1-0466; follow-on funding via multiple SBIR awards

IMPACT: Success of the Keratin hydrogel drug delivery system resulted in its application in various fields, such as prevention of scar contracture after burn injuries, prevention of post-traumatic joint contracture, functional tissue regeneration, and bone graft.
Prevention of Neuropathic Pain in Limb Amputations Using Targeted Muscle Reinnervation (TMR)

DESCRIPTION
TMR is a surgical nerve-transfer procedure, originally developed to provide more intuitive control for upper limb prosthetics users. In TMR the residual nerve stumps are coapted to cut motor nerves that innervate new target muscles. Investigators hypothesize that the TMR works because it provides a physiologically appropriate environment for regenerating axons, encouraging organized nerve regeneration into target muscles and preventing the chaotic and misdirected nerve growth that leads to neuroma formation. By preventing development of phantom limb pain and residual limb pain, TMR has the potential to improve patient-reported outcomes and decrease opioid medication use. In addition to publishing their results, the research team shared their skills and knowledge with over 100 surgeons during several in-person, interactive surgical learning sessions. The website www.tmrnerve.com is an excellent resource for patients who are looking for more information or a provider who can perform TMR surgery.

PARTNERS/COLLABORATORS
Northwestern University; Rehabilitation Institute of Chicago; The Ohio State University; Walter Reed National Military Center; Henry M. Jackson Foundation

AWARD NUMBER: W81XWH-13-2-0100

IMPACT: This study was instrumental in changing the standard of care for both upper and lower limb amputations and has also impacted the treatment of neuroma pain.
Optimizing Repair of Musculoskeletal Injuries to Improve Bone Healing and Muscle Function

DESCRIPTION
Musculoskeletal injuries with complicated bone fractures and significant muscle loss are a hallmark of military trauma and often result in disability and medical discharge of wounded Service Members. Current treatment of these injuries involves multiple surgeries, and fully restored function is rarely achieved. Through this work, a large animal model was developed that uses pieces of an individual’s own muscle and optimized biomaterials to study the healing process of these types of injuries and advance treatment options. This novel strategy has the potential to reduce complicated musculoskeletal healing by improving impaired fracture healing and muscle strength.

PARTNERS/COLLABORATORS
Indiana University; Uniformed Services University of the Health Sciences; Walter Reed National Military Medical Center; KeraNetics, LLC; Henry M. Jackson Foundation

AWARD NUMBER: W81XWH-13-1-0500; follow-on funding from PRORP and PRMRP

IMPACT: Accelerated healing timelines of complex fractures and therapeutic enhancement of muscle repair will reduce complication, allow earlier entry into and greater efficacy of physical rehabilitation programs, improve the overall functionality of the injured limb, and ultimately elevate the wounded Service Member’s quality of life.
State of the Art Prosthetic Socket

DESCRIPTION
This high-performance prosthetic socket consists of pressure and shear sensors, variable volume, and hepatic feedback systems for proprioception. For example, the residual limb sometimes undergoes shape and volume fluctuations, is unable to bear weight or load, or includes sensitive tissue resulting from vascular disease. The multi-axis tactile sensors provide normal and shear sensing at the residual limb interface and automatically adjust socket surfaces and tactile feedback. The device allows chronic monitoring of socket interface leads and adjustment of socket shape. It has been tested on limited amputees and received positive feedback.

PARTNERS/COLLABORATORS
Sandia National Laboratories; Walter Reed National Military Medical Center; Texas Scottish Rite Hospital; Simbex LLC

AWARD NUMBER: MIPROLDATM0147; follow-on funding from JWMRP Interagency Service Agreement

IMPACT: The newly designed shear sensors maintain a comfortable socket-residual limb interface and provide additional comfort and functionality to lower limb amputees, particularly those who desire to live an active lifestyle.
The Dynamic Air Exchange Prosthesis

DESCRIPTION
Advances in prosthetics technology have allowed more Service Members, Veterans, and civilians living with lower limb amputations the opportunity to return to work and maintain active lifestyles. However, those who engage in vigorous activities or work in hot, humid environments may still experience uncomfortable skin temperatures and the accumulation of perspiration inside their prostheses, which negatively impacts residual skin health and increases fall risk. The novel Dynamic Air Exchange prosthetic system creates an air flow inside the prosthesis, providing a means for decreasing perspiration while maintaining a secure suspension for lower limb amputees who work in demanding environments.

PARTNERS/COLLABORATORS
Veterans Affairs Puget Sound Health Care System; Arusha Control, Inc.

AWARD NUMBERS: W81XWH-14-1-0188, W81XWH-18-1-0559

IMPACT: This significant advance may provide Service Members with lower limb amputations an option to return to duty in demanding environments (deployability) and may impact prosthetic prescription for all lower limb amputees.
Matt Anderson
PRORP Programmatic Panel Member and Consumer

“I’ve had a long, rocky road with my injury, starting after a landmine blast in Kandahar Province, Afghanistan, on October 16, 2010. I was the first landmine injury that did not result in some version of traumatic amputation on site.... The DOD PRORP addresses novel and cutting-edge approaches to blast and battlefield trauma injuries to give our nation’s Warriors the best recovery possible, allowing them to return to duty or, with more extensive injuries, to have a productive and active lifestyle.”

Virgil Simons, MPA
PCRP Programmatic Panel Member and Consumer

“Clinical cancer research and therapeutic healthcare are in the midst of an evolutionary process driven by expansion of the concepts of big data, artificial intelligence, and technological integration. Many research organizations are unclear as to direction or constrained by traditional research foci. The PCRP has no such boundaries because, each year, it will reinvent itself to meet the needs of the patient and professional communities in funding research. While broad in scope, the PCRP is precise in patient-centered delivery. Vision is the driving force for the PCRP.”
**Vision:** Conquer prostate cancer

**Mission:** Fund research that will lead to the elimination of death from prostate cancer and enhance the well-being of Service Members, Veterans, and all the men and their families who are experiencing the impact of the disease

**Years Program Appropriated:** FY97-FY21

**Total Appropriations:** $2.04B

Prostate cancer is the most commonly diagnosed non-skin cancer in men and is the second most common cause of male death from cancer. In 2020, approximately 191,930 men in the U.S. were expected to be diagnosed with prostate cancer, with an estimated 33,330 deaths from the disease. Prostate cancer is a real threat to U.S. Service Members, as 80% of the active-duty population are men. While the PCRP has been successful in supporting advancements that have changed clinical practice, the program remains focused on addressing the knowledge, research, and clinical gaps that continue to make prostate cancer a global health issue. For the PCRP to accomplish its goal, all applicants are required to address overarching challenges that focus on developing treatments that improve outcomes for men with lethal prostate cancer, reducing lethal prostate cancer in African Americans, Veterans, and other high-risk populations, defining the biology of lethal prostate cancer to reduce death, and improving quality of life for prostate cancer survivors.
**XGEVA® (Denosumab)**

**DESCRIPTION**
XGEVA is an antibody that slows the progression of prostate cancer bone metastases. It blocks the bone resorption protein RANKL, thus slowing bone loss during cancer treatment and preventing fractures or skeletal-related events for cancer patients.

The drug indication has been expanded to include multiple myeloma patients.

**PARTNERS/COLLABORATORS**
University of Michigan

**AWARD NUMBER:** DAMD17-03-1-0092

**IMPACT:** Approved by the FDA in 2010, XGEVA is the number one oncologist-prescribed agent in the U.S. for the prevention of skeletal-related events in patients with bone metastases, including those for prostate cancer.

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**NuSAP1 Biomarker**

**DESCRIPTION**
NuSAP1 is a gene that promotes invasion and metastasis of prostate cancer and is overexpressed in recurrent prostate cancer tumors. The PCRP funded the early work characterizing NuSAP1 overexpression and validating its potential as a prognostic marker. NuSAP1 has been incorporated into the Prolaris® and Decipher® commercial gene expression assays that have been validated in several clinical contexts and are used in the clinic to determine prognosis in men with early-stage prostate cancer.

**PARTNERS/COLLABORATORS**
Leland Stanford Junior University

**AWARD NUMBER:** W81XWH-11-1-0447

**IMPACT:** Assays incorporating NuSAP1 are widely available and their use can help newly diagnosed patients with localized prostate cancer decide their likelihood of disease progression and therefore, make better informed treatment decisions.
ZYTIGA® (Abiraterone Acetate)

DESCRIPTION:
ZYTIGA is an oral anti-androgen used to treat prostate cancer by blocking testosterone activity. Mechanistically, ZYTIGA blocks the enzyme CYP17A1, which is responsible for the production of circulating androgens in the body. When used in combination with the corticosteroid prednisone, ZYTIGA is effective at stopping the growth of prostate cancer cells that have metastasized to other parts of the body. Approved by the FDA in 2011 in combination with prednisone, ZYTIGA was the first approved hormone therapy to demonstrate a survival benefit for men with late-stage metastatic castration-resistant prostate cancer (CRPC) who have received prior docetaxel (chemotherapy).

PARTNERS/COLLABORATORS
Memorial Sloan Kettering Cancer Center; The Prostate Cancer Clinical Trials Consortium: includes University of Michigan; M.D. Anderson Cancer Center; The University of Wisconsin; The University of Chicago; Duke University Medical Center; Dana Farber Cancer Institute; Oregon Health and Science University; Johns Hopkins Kimmel Cancer Center; Rutgers University; Wayne State University; University of California, San Francisco; University of Washington

AWARD NUMBER: W81XWH-09-1-0147 (Clinical Consortium Award)

IMPACT: ZYTIGA provides a new treatment option for men with late-stage prostate cancer who have received prior treatment and were left with very few therapeutic options to stop their prostate cancer from progressing further, changing clinical practice.
**XTANDI® (Enzalutamide)**

**DESCRIPTION**
XTANDI is an oral androgen receptor inhibitor for the treatment of prostate cancer. It is able to block testosterone activity at multiple steps of the androgen receptor signaling pathway, which are required for the growth of prostate cancer cells. Initially FDA-approved in 2012 for men with metastatic CRPC, XTANDI has been associated with better overall survival and significantly lower resource use and health care costs than ZYTIGA.

**PARTNERS/COLLABORATORS**
Memorial Sloan Kettering Cancer Center; The Prostate Cancer Clinical Trials Consortium

**AWARD NUMBER:** W81XWH-09-1-0147 (Clinical Consortium Award)

**IMPACT:** The FDA expanded the indication of XTANDI in 2018 for men with non-metastatic CRPC and in 2019 for men with metastatic Castration Sensitive Prostate Cancer.

**ERLEADA® (Apalutamide)**

**DESCRIPTION**
ERLEADA is an oral anti-androgen used for the treatment of prostate cancer that selectively blocks the function of the androgen receptor. ERLEADA is structurally and functionally similar to XTANDI but has been shown to have higher anti-androgen activity. In 2018, ERLEADA became the first medication to be FDA-approved for non-metastatic CRPC.

**PARTNERS/COLLABORATORS**
Memorial Sloan Kettering Cancer Center; The Prostate Cancer Clinical Trials Consortium

**AWARD NUMBER:** W81XWH-15-2-0018 (Clinical Consortium Award)

**IMPACT:** Approval of new treatment options for this group of patients was critical, as men with non-metastatic CRPC and a rapidly rising PSA are at high risk for developing metastatic disease, which is lethal if unsuccessfully treated.
**Oncotype DX AR-V7 Nucleus Detect Test**

**DESCRIPTION**
This liquid biopsy assay measures levels of a variant of the androgen receptor, AR-V7, in the nucleus of prostate cancer cells in the blood and can help predict whether or not a patient will respond to certain prostate cancer treatments. Detection of AR-V7 predicts which patients with metastatic CRPC may not respond to androgen-receptor signaling inhibitors and should consider taxane therapy instead, helping patients avoid costly treatments that may not provide any benefit.

**PARTNERS/COLLABORATORS**
Sloan Kettering Institute for Cancer Research; University of Michigan; Johns Hopkins University; University of Washington; Dana-Farber Cancer Institute; Fred Hutchinson Cancer Research Center

**AWARD NUMBER:** W81XWH-13-2-0070

**IMPACT:** This assay is commercially available through Genomic Health/Epic Sciences and is used clinically as a non-invasive tool to better guide treatment decision-making.
AdnaTest ProstateCancer

DESCRIPTION
AdnaTest ProstateCancer is a clinically validated, non-invasive assay that enriches tumor cells from whole blood samples and detects the androgen receptor variant AR-V7 (a biomarker for CRPC) in enriched tumor cells. The AdnaTest ProstateCancer assay is commercially available through Qiagen for research use to investigate drug resistance, and it was clinically validated by the Prostate Cancer Clinical Trials Consortium in the PROPHECY trial to be clinically relevant for identifying patients who are likely to not respond well to treatment with androgen signaling inhibitors, such as abiraterone and enzalutamide. Exclusive licensing from Johns Hopkins University allows for the assay to also be used for diagnostic purposes.

PARTNERS/COLLABORATORS
Johns Hopkins University; University of Washington; Institute of Cancer Research Royal Cancer Hospital


Elekta Synergy CT System

DESCRIPTION
The Elekta Synergy CT System is a high-precision cone-beam CT imaging system that is capable of pinpointing the position of the prostate and support structures to deliver high doses of radiation to the tumor while minimizing damage to adjacent normal tissues. This imaging system received FDA clearance in 2003. Prior to its approval, curative doses of radiation therapy were sometimes unsuccessful due to the uncertain position of the prostate during treatment. Instead of increasing the radiation field size, which increased radiation exposure to normal tissues surrounding the prostate, this technology better targeted the curative radiation doses to the prostate.

PARTNERS/COLLABORATORS
William Beaumont Hospital Research Institute

AWARD NUMBER: DAMD17-98-1-8497

IMPACT: The AdnaTest ProstateCancer assay provides a non-invasive way to help determine the most effective treatment options and is also used as a diagnostic.

IMPACT: Today, this approach is used as the standard for precision radiation treatment of prostate and other cancers. Over 80% of radiation machines sold in 2014 were equipped with it.
Quantitative Total Extensible Imaging Software (QTxl)

DESCRIPTION
QTxl is imaging software that automatically identifies and contours lesions of interest from PET/CT scans using patented statistical optimized regional thresholding and deep learning. QTxl then automatically corrects for patient positioning and aligns lesions of interest to allow quantification of change in individual lesions to assess patient- and individual lesion-level treatment response. QTxl is an imaging tool that provides spatial-temporal information to improve clinical management of patients with metastatic cancer. Originally developed to track treatment response and lesion progression in prostate cancer patients, the tool received FDA 510(k) clearance in 2018 and is now licensed to AIQ Solutions (Madison, WI) to provide detailed information about individual lesion response for all cancers.

PARTNERS/COLLABORATORS
University of Wisconsin

AWARD NUMBER: W81XWH-14-2-0155

IMPACT: Oncologists use QTxl to make precise and informed changes in real time to the patient’s care plan, and its use has also been expanded for metastatic bone disease in breast cancer.
David Quinn, MBBS, PhD, FRACP, FACP
PCRP Programmatic Panel Member

“For more than 20 years, the program has leveraged cutting edge prostate cancer biology and innovative clinical trials to reduce the lethality of prostate cancer. Success measured through innovative new drug therapies and better understanding of the underlying mechanisms of prostate cancer risk and response is uniquely focused and delivered to prostate patients and their families through the PCRP.”

Wendy Dean, MD, RTRP Programmatic Panel Member

“The CDMRP RTRP has been instrumental in moving the field of VCA [vascularized composite allotransplantation] forward, ensuring sound research. The long term, strategic program goals of increased access to VCA and reduced morbidity from immunosuppression will ensure the procedure is available to those catastrophically wounded Service Members for whom there are no other options to restore form, function and appearance.”
Vision: Reconstructive transplant: an accessible reality and viable choice

Mission: Advance science, education, and clinical practice of vascularized composite allotransplantation to improve access and safety; implement a comprehensive approach for consideration of all variables influencing outcomes of VCA for catastrophically injured Service Members, Veterans, and American civilians

Years Program Appropriated: FY12; FY14-FY21
Total Appropriations: $117M

The Reconstructive Transplant Research Program (RTRP) supports research to advance vascularized composite allotransplantation procedures (i.e., face and hand transplants) in the effort to optimize form, function, appearance, and psychosocial health for catastrophically injured Service Members, Veterans, and American civilians. VCA refers to the transplantation of multiple tissues such as muscle, bone, nerve, vasculature, and skin, as a functional unit (e.g., a hand or face) from a deceased donor to a recipient with a severe injury. The ultimate goal is to return injured Service Members to duty and restore their quality of life.
**Actigraphy to Quantify Functional Hand Use in Hand Transplant and Replant Recipients and Amputees**

**DESCRIPTION**

Actigraphy allows objective quantification of limb activity in daily life via Fitbit-like sensors that can be worn on a participant’s arm and wrist. This allows for the evaluation of how people with hand transplants, replants, and peripheral nerve repair use their affected limbs in daily life compared to prosthesis users and healthy individuals. For the first time, the hand and arm use patterns of hand transplant recipients, prosthesis users, and healthy individuals was quantified and compared. These findings revealed that hand transplant recipients demonstrated a pattern of bilateral symmetry more similar to healthy controls than to prosthetic users.

**PARTNERS/COLLABORATORS**

University of Missouri; Washington University in St. Louis; University of Louisville

**AWARD NUMBER:** W81XWH-15-2-0037

*Upper limb activity in unilateral prosthesis users, healthy controls, and hand replants/transplants. During everyday life, hand transplant recipients use their affected hands more than amputees use their prostheses, but less than controls use their intact limbs. Open circles represent individuals’ average data across three days.*
Engineered Microparticles to Promote Transplant Tolerance

DESCRIPTION
Two sets of engineered microparticles (MPs) were designed to work together to promote transplant tolerance. Recruitment-MPs were designed to recruit a subset of lymphocytes called regulatory T cells (Tregs), which suppress the effects of other T cells that would ordinarily attack cells recognized as foreign, (e.g., a donor graft). Tregs are a rare population of lymphocytes (~2%-3%), however, and they may not be present in sufficient quantities to prevent graft rejection. To address this problem, Treg-inducing (TRI)-MPs were designed to induce production of more Tregs by converting the more populous naïve CD4+ T cells into Tregs. This combination approach resulted in significantly longer graft survival in an animal model.

PARTNERS/COLLABORATORS
University of Pittsburgh; Wake Forest University

AWARD NUMBER: W81XWH-15-1-0244

IMPACT: Face and hand transplantation currently requires recipients to take immunosuppression medication with known negative side effects to minimize the risk of graft rejection. Promoting tolerance of the transplanted face or hand will minimize or eliminate the need for such harsh drug regimens.
Biomarkers to Predict Rejection in VCA Grafts

DESCRIPTION
More than 80% of VCA recipients experience an episode of acute rejection within the first year of their transplant. Rejection can often be observed visually on the skin, but it would be ideal to identify rejection before changes are visible to the eye. Skin biopsies and the Banff classification system are currently the standard for detection of graft rejection, but the biopsy itself can cause additional morbidity for the patient (e.g., scarring, bleeding, infection). Matrix metalloproteinase 3 (MMP3) has been identified as a biomarker in blood samples that can discriminate severe and non-severe episodes of VCA graft rejection from samples with no rejection in face transplant recipients.

PARTNERS/COLLABORATORS
Brigham and Women’s Hospital

AWARD NUMBER: W81XWH-16-1-0647
Cyclosporine A (CsA) and Cofilin for Accelerated Nerve Regeneration in VCA

DESCRIPTION
Two of the most critical factors for successful face and hand transplantation are the immunological acceptance of the graft and the ability to regain full function after transplant. Little is known, however, about how the required immunosuppression regimens affect nerve regeneration and reinnervation of the graft. CsA is a common immunosuppression medication for prevention of graft rejection after face and hand transplantation. CsA was found to also significantly increase nerve regeneration in a small animal model of nerve transection. Results suggest that cofilin, a protein that leads to an increased rate of axon growth when active, is more active after CsA treatment.

PARTNERS/COLLABORATORS
University of California, Los Angeles

AWARD NUMBER: W81XWH-16-1-0449

IMPACT: This research demonstrates that CsA serves not only to suppress the immune system, but also to work in conjunction with cofilin to accelerate nerve regeneration—potentially aiding in successful acceptance of the graft and regain of function.
Histone Deacetylase (HDAC) Inhibition to Improve VCA Graft Preservation and Increase Immunological Tolerance

**DESCRIPTION**
Use of VCA as a treatment option for patients suffering significant traumatic injury has been limited, in part due to the extreme difficulty in finding matching donors (e.g., blood type, immunological compatibility, gender, skin tone). Current standards for preservation of VCA grafts result in degradation of the tissue over time, limiting the time from procurement to transplant to about 6 hours and shrinking the potential donor pool. HDACs are responsible for regulating gene expression by modulating access to the DNA strands (i.e., winding and unwinding of tightly packed DNA in chromosomes). Inhibiting HDAC activity was shown to significantly reduce tissue injury in a small animal model.

**PARTNERS/COLLABORATORS**
University of Pennsylvania

**AWARD NUMBER:** W81XWH-16-1-0780

**IMPACT:** This research provides novel strategies to extend the amount of time that a graft can remain viable and will allow improved access to VCA for military Veterans and civilians alike.

*Reduced muscle damage after treatment with three different HDAC inhibitors.*
Vision: Advance the treatment and management of spinal cord injury and ameliorate its consequences relevant to injured Service Members

Mission: To fund research and encourage multidisciplinary collaborations for the development and translation of more effective strategies to improve the health and well-being of Service Members, Veterans, and other individuals with spinal cord injury

Years Program Appropriated: FY09-FY21
Total Appropriations: $357.85M

The Spinal Cord Injury Research Program (SCIRP) was established to support medical research into traumatic spinal cord injury and treatments, with the goal of enhancing the long-term care of wounded Soldiers. The language provided by Congress specifically highlighted the complexity of neurotraumatic wounds as well as promising treatment regimens including regenerating/reparing damaged spinal cords and improving rehabilitation therapies. To meet this directive, the SCIRP focuses on funding within strategic priority areas that meet the needs of the SCI consumer community and address critical gaps in SCI research, patient care, and quality of life.
Exoskeletal-Assisted Walking to Improve Mobility

DESCRIPTION
This project is a multi-site clinical trial exploring the benefits of exoskeletal-assisted walking in 50 non-ambulatory participants. The results from this study provide guidelines for estimating the potential of individuals with SCI to achieve proficient and safe walking skills and include the proposed time commitment necessary to obtain meaningful functional gains. These guidelines are targeted to medical professionals, caregivers, and people living with a spinal cord injury regarding utilization of two commercially available exoskeleton devices in both institutional and personal use settings. The research team also investigated secondary health benefits to exoskeletal-assisted walking and observed significant improvements in bowel measures, cardiovascular function, and body composition in chronically injured participants.

PARTNERS/COLLABORATORS
Bronx Veterans Medical Research Foundation; University of Maryland; Kessler Foundation

AWARD NUMBER: W81XWH-14-2-0170

IMPACT: The major takeaway from this study was that exoskeleton technology made walking possible in over 80% of individuals with chronic non-ambulatory spinal cord injury.
Improved Bladder and Bowel Function via an Implantable Stimulator

DESCRIPTION
Electrical stimulation via an implantable, pacemaker-like, stimulator is being tested to aid in bladder and bowel continence and voiding in SCI patients. This technology has been available for over 10 years but was not widely adopted by the community due in part to the practice of severing sensory nerves at the time of implantation to permanently abolish the bladder reflexes. This study, however, is modulating the nervous system and observing functional improvements without purposefully damaging sensory nerves. Promisingly, the device allowed urination without catheterization and continence without medication for the first time in 41 years for a recent participant, illustrating for the first time that this technology can be utilized in SCI patients without permanent and purposeful nerve damage.

PARTNERS/COLLABORATORS
Leland Stanford Junior University and VA Palo Alto HC System; MetroHealth Medical Center; Santa Clara Valley Medical Center; University of New Mexico School of Medicine

AWARD NUMBER: W81XWH-14-2-0132

IMPACT: The use of electrical stimulation to restore both bladder continence and emptying without destructive surgery is a game changer for the field and has the potential to significantly change clinical practice, allowing for a less invasive, non-destructive method to restore bladder function in individuals with an SCI.
Novel Neuroprotective Intervention, 4-Aminopyridine (4AP)

DESCRIPTION
4AP promotes extensive and durable behavioral recovery and decreased tissue damage when administered early after injury in models of SCI. 4AP can improve brain physiology and outcomes after TBI, and the therapeutic windows for SCI administration of this drug means it can easily be administered in far-forward environments. The team is working toward FDA IND application approval to begin clinical trials in SCI patients.

PARTNERS/COLLABORATORS
University of Rochester; Uniformed Services University of the Health Sciences; Methodist Hospital Research Institute

AWARD NUMBER: W81XWH-17-1-0331

IMPACT: These preliminary findings regarding the neuroprotective efficacy of 4AP after SCI have the potential to greatly impact clinical practice, and the ease of application makes it ideal for far-forward environments.
Near-Infrared Spectroscopy Sensor (NIRS)

**DESCRIPTION**
The NIRS system is a near-infrared spectroscopy sensor designed to monitor the oxygenation and hemodynamics of the spinal cord and surrounding tissue in real time immediately after SCI. The NIRS is able to detect local tissue changes within the injured spinal cord that are reflective of systemic hemodynamic changes (i.e., mean arterial pressure, or MAP) over the first 7 days post-injury in large animal models of SCI.

**PARTNERS/COLLABORATORS**
University of British Columbia

**AWARD NUMBER:** W81XWH-16-1-0602 (Work is being continued in an FY19 DARPA contract for further device development and testing)

**IMPACT:** A monitoring tool that can provide clinicians with real-time information on how their adjustments in MAP are actually affecting the tissue within the injured spinal cord will ultimately be necessary to empower them to optimize this aspect of care. Until a monitoring system is in place, we must rely on clinician’s “best guess” regarding MAP management protocols.

Intraparenchymal monitoring of the acutely injured spinal cord of the pig; probes for measuring oxygenation/blood flow, hydrostatic pressure, and microdialysis.
Transforming Research and Clinical Knowledge in SCI (TRACK-SCI)

DESCRIPTION
TRACK-SCI is an ongoing effort collecting patient demographics, treatment, and outcomes data to establish evidence-based standards of care for SCI. TRACK-SCI was developed due to a surprising lack of knowledge about early SCI physiology and evidence-based care practices. This presents a unique challenge for physicians to coordinate effective treatments early after injury. This collaboration involves clinicians making critical care decisions, data scientists employing big-data techniques, and researchers translating findings between humans and rodent SCI models. Based on the data collected, the TRACK-SCI team has (1) established a classification system that may help distinguish which patients will show functional improvement prior to hospital discharge, (2) provided evidence supporting spinal decompression surgery as an early intervention for SCI, as it leads to better functional outcomes for patients, and (3) instituted a new standard of care for the stabilization of spinal cord perfusion pressure, rather than MAP, when managing traumatic SCI at Zuckerberg San Francisco General Hospital. As more data is collected and analyzed, it is expected that more changes to clinical practice will occur.

PARTNERS/COLLABORATORS
University of California, San Francisco; University of California, Fresno; Zuckerberg San Francisco General Hospital; Ohio State Wexner Medical Center

AWARD NUMBERS: W81XWH-13-1-0297, W81XWH-16-1-0497, W81XWH-20-1-0245
Vision: To prevent the occurrence, better diagnose, and resolve or minimize the impact of Lyme disease and other tick-borne illnesses, with emphasis on burden of disease

Mission: To understand the pathogenesis of Lyme disease and other tick-borne illnesses, to deliver innovative solutions to prevent, diagnose, and treat their manifestations for the benefit of U.S. Service Members and the American public, and to disseminate this knowledge

Years Program Appropriated: FY16-FY21
Total Appropriations: $34M

The Tick-Borne Disease Research Program (TBDRP) seeks to reduce the significant burden of Lyme and other tick-borne diseases (TBDs) on the health and welfare of civilian and military populations by funding innovative and impactful research to better understand disease processes and thereby develop improved diagnostic methods, prevention measures, and treatment regimens. The program offers award mechanisms for career development to recruit new investigators mentored by established TBD scientists, and for idea development to support existing TBD researchers and foster collaboration among research fields. The TBDRP’s vision places emphasis on the burden of disease, and the program encourages investigators to focus their efforts on TBDs that are prevalent in the U.S., of concern to military personnel and their beneficiaries in the U.S. and overseas, and/or in understudied patient populations. Applications submitted to the TBDRP must address at least one of the following Focus Areas in Lyme disease and other TBDs: diagnosis, pathogenesis, prevention, and treatment.
Vaccine Candidate for Ehrlichiosis

**DESCRIPTION**
In the U.S., the bacteria *Ehrlichia chaffeensis* (Ech) is responsible for the majority of cases of ehrlichiosis, a tick-borne illness that if left untreated, can be fatal. Researchers developed a vaccine candidate for Ech and demonstrated that antibodies generated from this candidate limit bacterial spread from tick to human cells in cell culture models of infection. In preclinical tick-bite animal infection studies, the vaccine candidate limits *ehrlichia* replication, elicits an immune response, and facilitates pathogen clearance.

**PARTNERS/COLLABORATORS**
The Ohio State University

**AWARD NUMBER:** W81XWH-17-1-0519

**IMPACT:** Because there is currently no vaccine or prophylaxis for the prevention of ehrlichiosis, a candidate human vaccine would significantly improve care in both military and civilian populations.

Multitarget-Display Virus-Like Particle-Based Vaccine to Combat Lyme Disease

**DESCRIPTION**
Current Lyme disease prevention strategies include spatial and contact tick repellents that require reapplication and user compliance. This cost-effective Lyme disease vaccine candidate expresses outer membrane surface protein(s) of *Borrelia burgdorferi*, the bacteria that causes Lyme disease. The vaccine uses a plant-based system for the scalable production of virus-like particles that can easily be produced, purified, and formulated. In preclinical studies, lead vaccine candidates demonstrate an appreciable antibody response that correlates with protective efficacy in animal infection models.

**PARTNERS/COLLABORATORS**
Fraunhofer USA Center for Molecular Biotechnology; Tufts University

**AWARD NUMBER:** W81XWH-17-1-0604

**IMPACT:** A cost-effective, safe, efficacious vaccine against Lyme disease would protect the general public and Service Members from acute illness and possible severe complications.
Pathogen-Host Molecular Biosignature Lyme Disease Diagnostic Assay

DESCRIPTION
Diagnostic assays for all tick-borne illnesses, particularly the most common TBD, Lyme disease, are lacking or have significant limitations. Researchers are working to develop a Lyme disease diagnostic assay capable of accurately differentiating acute Lyme disease from other acute illnesses that may present with similar symptoms, such as influenza or sepsis. Toward this assay, genes that are differentially expressed in acute Lyme disease patients, as compared to non-Lyme and healthy controls, were identified, leading to the discovery of a Lyme disease-specific biomarker signature. Using machine learning analysis of this signature, a predictive model was developed for distinguishing the blood samples of acute Lyme disease patients from healthy patients or those suffering from other acute illnesses.

PARTNERS/COLLABORATORS
University of California San Diego; Johns Hopkins University; Bay Area Lyme Foundation’s Lyme Disease Biobank; Harvard/Boston Children’s Hospital; American Red Cross

AWARD NUMBER: W81XWH-17-1-0681

IMPACT: The ability to diagnose Lyme disease at all stages of infection using a non-invasive, specific, sensitive, rapid assay would improve overall patient care and result in prompt treatment that could mitigate disease progression and limit severity.
Pre-Exposure Prophylaxis (PrEP) for the Prevention of Lyme Disease

DESCRIPTION
Currently, no approved vaccine or prophylaxis exists for the prevention of Lyme disease and as a result, prevention relies on avoidance and compliance with the application of tick repellent. Researchers are working to develop a bactericidal, long half-life, human monoclonal antibody as a PrEP for Lyme disease. This human antibody against the outer membrane surface protein of *Borrelia burgdorferi*, a causative agent of Lyme disease, is stable in animal models of infection and capable of protecting 80% of animals from tick-bite transmitted *Borrelia* infection in preclinical studies.

PARTNERS/COLLABORATORS
MassBiologics, University of Massachusetts Medical School; Tufts University; New York State Department of Health, Wadsworth Center

AWARD NUMBER: W81XWH-18-1-0375
Warfighter Adaptive Barrier Controlled-Release Device (AB-CRD) for Active Protection Against Ticks

DESCRIPTION
Currently there are 18 infectious tick-borne pathogens, 20 conditions, and 13 illnesses known to result from tick bites, and as tick populations continue to increase and expand geographically, the threat to Service Members in the field is significant. Current prevention strategies rely on the permethrin treatment of Service Member uniforms, which wanes over time, and/or the frequent application of tick repellent, which may not always be practical. Researchers are developing an AB-CRD that uses micro-electro-mechanical systems technology to provide controlled and sustained release of a low toxicity tick spatial repellent (SR). AB-CRD design includes remote wireless control and programming and allows for receipt of device updates. The AB-CRD is compact, so one or more devices can be worn by the Soldier or affixed to mobile infrastructure.

PARTNERS/COLLABORATORS
GearJump Technologies, LLC; Instituto Tecnológico de Buenos Aires; University of Pennsylvania; University of Massachusetts Amherst; U.S. Department of Agriculture; U.S. Army Combat Capabilities Development Command-Soldier Center

AWARD NUMBER: W81XWH-19-2-0028

IMPACT: The AB-CRD, worn as an ankle bracelet or incorporated into the uniform or unit infrastructure, would provide the Warfighter with an additional line of defense against tick bites, thus reducing TBD incidence.
Col Nicole Malachowski (U.S. Air Force, Ret.)
TBDRP Consumer Peer Reviewer

“What cohort of the American public is exposed to more global tick-borne illnesses than our Service Members and military families? After being medically retired from a career as a fighter pilot due to ‘chronic systemic tick-borne illness,’ I needed a new mission. The TBDRP allows me to be a part of the solution by sharing my own experience and helping to advance the science as a consumer peer reviewer. The patient-centered approach of the CDMRP is unique among federal funding agencies and the TBDRP ensures that the voices of tick-borne illness patients are heard. This program gives me hope for bridging the gap between basic research and urgent patient needs.”

Helen Bramlett, PhD, TBIPH Scientific Peer Reviewer

“[The TBIPH] program has been instrumental in funding much needed research in the area of psychological health and TBI that impacts our Warfighters. The hope is that the results from this program will be able to provide treatments in several different areas of trauma that our wounded warriors experience.”
Vision: Optimize psychological health and reduce or eliminate the effects of traumatic brain injury and traumatic stress

Mission: Fund research to understand, prevent and treat traumatic brain injury and psychological health conditions that accelerates solutions to improve health and healthcare of Service Members, DOD beneficiaries, Veterans, and the American public

Years Program Appropriated: FY07; FY09-FY21

Total Appropriations: $2.0465B

The Peer Reviewed Traumatic Brain Injury and Psychological Health Research Program (TBIPHRP) complements ongoing DOD efforts toward promoting a better standard of care for psychological health (PH) and TBI in the areas of prevention, detection, diagnosis, treatment, and rehabilitation.

The CDMRP managed the initial appropriations in FY07, and from FY09-FY20 the Joint Program Committees (JPCs) for Military Operational Medicine (JPC-5), Combat Casualty Care (JPC-6), and Clinical and Rehabilitative Medicine (JPC-8) provided strategic oversight and management of research gaps, Focus Areas, and funding options for the TBIPHRP. The CDMRP worked closely with the JPCs to provide execution management support as requested, including development of funding opportunities, review of applications, and full lifecycle management of awards. The CDMRP is managing the FY21 TBIPHRP and is including input from the JPCs as well as consumers, government partners, and academia to fund research that is a benefit to Service Members, DOD beneficiaries, Veterans, and the public.
Consortium to Alleviate PTSD (CAP)

DESCRIPTION
PTSD remains the single most significant psychological health condition that is directly related to combat and operational deployments in active-duty military personnel and Veterans. CAP was jointly funded by the DOD and the VA, with the goal of advancing treatments and discovery of diagnostic and prognostic biomarkers for PTSD. The CAP completed 11 independent studies performed by DOD, VA, and academic investigators – two biomarker studies, three pilot interventions, and six randomized clinical trials. CAP studies focused on diagnosing PTSD and predicting response to treatment as well as examining novel PTSD treatments, treating co-morbid PTSD conditions (e.g., sleep disruption, post-traumatic headache, depression, alcohol use disorder), and comparison of treatment efficacy. CAP Data Repository houses an extensive amount of clinical/medical data available for sharing and informing future research and clinical decision-making models. A treatment manual for emotion regulation and web-based training for insomnia and nightmares are available for clinician use.

PARTNERS/COLLABORATORS
University of Texas Health Science Center at San Antonio; Emory University; VAMC Charleston; Duke University; University of North Texas Denton; Pennsylvania State University; University of Memphis; James A. Haley VAMC Tampa; Boston VA Research Institute; Brooke Army Medical Center; Carl R. Darnall Army Medical Center; Central Texas Veterans Health Care System; Medical University of South Carolina; San Antonio Military Medical Center; South Texas Veterans Health Care System; Texas Biomedical Research Institute; VA Connecticut Healthcare System; Laurel Ridge Treatment Center; Durham VAMC; Yale University

AWARD NUMBER: W81XWH-13-2-0065

IMPACT: CAP clinical teams delivered high-quality care to over 1,000 active-duty Service Members and Veterans. Results from CAP studies testing novel PTSD treatments offer scalable treatment options for use in the Military Health System and new directions for future research.
Military Suicide Research Consortium

DESCRIPTION
The Military Suicide Research Consortium (MSRC) aims to develop more effective suicide prevention interventions, risk assessment methods, treatments, and postvention strategies. The MSRC funded over 50 studies conducted at numerous DOD, VA, and civilian sites, and many of these studies have yielded important results. The MSRC developed a database to capture common data elements and common demographics that are consistent across all projects, which allows for secondary analysis of aggregate data across funded studies. At this time, data from more than 6,500 participants are publicly available to qualified researchers who request access.

PARTNERS/COLLABORATORS
Florida State University; Denver Research Institute/ Denver VAMC

AWARD NUMBERS: W81XWH-16-2-0003, W81XWH-16-2-0004

IMPACT: MSRC-funded study results informed the VA/DOD Clinical Practice Guideline for the Assessment and Management of Patients at Risk for Suicide. Two interventions, Crisis Response Planning and Caring Contacts, have been included in the Penn State University Clearinghouse for Military Family Readiness database.
Telehealth Delivery of Evidence-Based Therapies

DESCRIPTION
Access to trauma-specific mental health services can be limited in rural and remote areas. TBIPHRP-funded studies developed approaches and evaluated the effectiveness of delivering PTSD-specific evidence-based treatment interventions through a video teleconferencing (VTC) format. This included the addition of a female treatment arm to a study with male Veterans comparing in-person treatment modalities of Cognitive Processing Therapy (CPT) for treatment of PTSD. Results from these studies demonstrated that VTC produces outcomes comparable to in-person treatment for CPT. These findings, combined with those of other DOD-funded studies conducted by Charleston Research Institute/Charleston VAMC, the University of Texas Health Science Center at San Antonio, and the Veterans Medical Research Foundation of San Diego/San Diego VAMC, contributed to the critical body of evidence supporting the validity of evidence-based therapies delivered via telehealth.

PARTNERS/COLLABORATORS
VA Research & Education Corporation of the Pacific/VA Pacific Islands Health Care System

AWARD NUMBERS: W81XWH-08-2-0063, W81XWH-10-1-1037
Written Exposure Therapy (WET) for Treatment of PTSD

DESCRIPTION
WET provides evidence-based PTSD treatment that is appealing and accessible to many Service Members who have avoided or discontinued other treatments, because it uses a brief five-session narrative therapy approach. This type of treatment tends to be shorter, with no out-of-office homework assignments, making it easier for patients to complete. Preliminary results suggest that WET is as effective as CPT, a gold-standard therapy for PTSD, in alleviating symptoms and helping patients recover from PTSD. WET was selected by the Behavioral Health Clinical Community for a FY20 Practice-Based Implementation Network pilot implementation project in the Military Health System.

PARTNERS/COLLABORATORS
Boston VA Research Institute, Inc.

AWARD NUMBER: W81XWH-15-1-0391

IMPACT: WET offers a more efficient, yet effective, PTSD treatment approach for active-duty Service Members as well as others.
Veteran-Centric Mindfulness-Based Interventions for Chronic Musculoskeletal Pain

DESCRIPTION
Mindfulness-based interventions are methods to train individuals to focus and attend to their present experience and have been utilized to support improved physical and mental health. Building on the feedback received from Veterans, individuals with chronic pain, and experts, existing mindfulness-based interventions were adapted to the specific needs of the Veteran community. Researchers developed a series of iterative refinements in delivering mindfulness-based interventions to Veterans via mobile platforms. The final mindfulness-based interventions, consisting of online training modules and mobile applications, are currently under evaluation for effectiveness in treating chronic musculoskeletal pain in a large multi-site three-arm pragmatic clinical trial.

PARTNERS/COLLABORATORS
Center for Veterans Research and Education Foundation; Durham VAMC; Indianapolis VAMC; West Los Angeles VAMC; University of Minnesota

AWARD NUMBER: W81XWH-18-2-0003 via the NIH, DOD, and VA Pain Management Collaboratory

IMPACT: The developed mindfulness-based interventions are non-pharmacological approaches for the treatment of chronic pain and comorbid conditions, providing safer care via opioid alternatives.
**BrainPort Vision Pro**

**DESCRIPTION**
The BrainPort Vision Pro device is a wearable, non-invasive, visual prosthetic device that translates images captured by a digital camera into electrotactile stimulation presented on the user’s tongue. Through a process known as “sensory substitution,” it significantly improves real-world functional task performance in persons who are profoundly blind, allowing individuals with no better than light perception to “see,” perceiving shape, size, location, and motion of objects within their environment. TBIPHRP funded development and early testing in individuals blinded by traumatic injuries, which provided data to support FDA approval of the first BrainPort device in 2015. Currently, the BrainPort Vision Pro (https://www.wicab.com/brainport-vision-pro) is commercially available in the USA, European Union, Chile, Peru, and Hong Kong.

**PARTNERS/COLLABORATORS**
Wicab, Inc.; Carnegie Mellon University; University of Pittsburgh Medical Center; The Chicago Lighthouse for People Who are Blind or Visually Impaired; Lighthouse International; Google provided additional funding for FDA clinical trials

**AWARD NUMBERS:** W81XWH-10-1-0998, W81XWH-14-2-0128

**IMPACT:** Offers significantly improved quality of life and independence for profoundly blind individuals, including those blinded by traumatic injuries.
NCAA-DOD Grand Alliance: Concussion Assessment Research Education (CARE) Consortium

DESCRIPTION
The CARE Consortium is a joint DOD and National Collegiate Athletic Association (NCAA) research effort dedicated to studying concussion to better understand the development of injury and trajectory of recovery utilizing a multi-site, longitudinal investigation of concussive and repetitive head impacts. The study also allows for more advanced research projects, such as testing impact sensors, studying potential biomarkers, and evaluating concussions with advanced neuroimaging. Since initially receiving funding in 2014, the CARE Consortium has enrolled over 50,000 student athletes and Service academy cadets at 30 sites. The CARE Consortium will allow development of evidence-based approaches to understanding the risks, management, and possible treatment strategies for concussion.

PARTNERS/COLLABORATORS
Indiana University; NCAA; University of Michigan; Medical College of Wisconsin; Uniformed Services University of the Health Sciences; U.S. Military Academy; U.S. Air Force Academy; U.S. Coast Guard Academy; U.S. Naval Academy; University of North Georgia; University of California, San Francisco; Datalys Center for Sports Injury and Prevention; The Mind Research Network; NIH; University of Oklahoma; University of Delaware; Humboldt State University; University of Wisconsin; University of North Georgia; University of California, Los Angeles; University of Washington; Wilmington College; Princeton University; University of Pennsylvania; Virginia Tech; University of North Carolina; Wake Forest University; University of Miami; University of Pittsburgh; University of Georgia; University of Florida; University of Rochester; Temple University; Bloomsburg University; California Lutheran University; University of Chicago; Azusa Pacific University; Winston-Salem State University

AWARD NUMBERS: W81XWH-14-2-0151, W81XWH-18-2-0047; Combat Casualty Care, NCAA, and NIH provided additional funding and support for the CARE Consortium

IMPACT: The work of the CARE Consortium is answering critical questions about head impact exposures and concussions, filling important knowledge gaps, and leading to changes in clinical practice guidelines that are improving care for those suffering from concussions. The vast amount of information gathered by this research team will continue to provide scientific and clinical advancements for years to come.
Swoop™ Imaging Device

DESCRIPTION
The Swoop is a portable MRI device developed by Hyperfine, Inc., and cleared by the FDA for brain scanning in neonatal through adult patients. The device is intended to complement conventional high-field brain imaging that is typically limited to specific hospital settings. This study funded the development of low-magnetic field imaging technologies and techniques that would enable the use of brain imaging in non-hospital settings. The Hyperfine MRI can be used on patients with imbedded metal fragments or devices and patients on ventilator support in complex clinical environments.

PARTNERS/COLLABORATORS
Harvard University; Massachusetts General Hospital; Hyperfine Research, Inc.

AWARD NUMBER: W81XWH-11-2-0076

IMPACT: Availability of a less expensive, portable, low-field MRI expands use outside of controlled hospital imaging facilities and into bedside and field-based applications.
OsiriX CDE Software Module

DESCRIPTION
The OsiriX CDE is a software tool that can be used as a biomarker test for TBI. It assists health care providers, such as physicians in neurological specialties, by providing a standardized way to identify and analyze injured brain tissue using common criteria and to label abnormalities on MRI images for the purpose of improving enrollment in clinical trials intended to improve outcomes of patients with mild TBI. The OsiriX CDE Software Module is recognized by the FDA under the Medical Device Development Tool program as a tool that can be used by other medical device companies/sponsors in the development and evaluation of devices as part of the FDA clearance process.

PARTNERS/COLLABORATORS
University of California, San Francisco; TBI Endpoints Development Initiative Investigator Team; TRACK-TBI Network

AWARD NUMBER: W81XWH-14-2-0176

IMPACT: The OsiriX CDE can be used to improve TBI-related clinical trials and facilitate FDA clearance of devices used in the diagnosis and treatment of TBI.
Vision: Improve prevention strategies and treatments to lessen the impact of TSC while striving for a cure

Mission: Support innovative and high-impact research that promotes discoveries in TSC, from mechanistic insights to clinical application across all ages, by fostering new ideas and investigators for the benefit of Service Members, their beneficiaries, and the American public

Years Program Appropriated: FY02-FY06; FY08-FY21

Total Appropriations: $97M

Tuberous sclerosis complex (TSC) is a rare genetic disorder that is caused by a spontaneous genetic mutation in the TSC1 or TSC2 gene. It affects approximately 50,000 individuals in the United States and 1 to 2 million individuals worldwide. TSC causes non-malignant tumors in many different organs, primarily in the brain, eyes, heart, kidneys, skin, and lungs. It presents itself in a variety of clinical manifestations; the most severe impact is associated with the brain, which causes seizures, developmental delay, intellectual disability, and autism. Currently, there is no cure for TSC.

The Tuberous Sclerosis Complex Research Program (TSCR) was established in FY02 with a congressional appropriation of $1M. It is the second largest government funding source supporting TSC research in the United States. Since its inception, the TSCR has played a critical role in supporting high-impact research, fostering new ideas, encouraging innovation, and bringing new investigators into the TSC field.
Topical Rapamycin Therapy for Facial Tumors

DESCRIPTION
Angiofibromas are acne-like benign skin lesions found on the faces of 80% of patients with TSC and appear in early childhood. Although facial angiofibromas are not life-threatening, they cause notable disfigurement and impact a patient’s quality of life. This project formulated and optimized a topical rapamycin treatment for angiofibromas. The treatment was tested in a clinical trial and the product was shown to be safe, well tolerated, with no systemic absorption and no significant adverse events. Moreover, it showed efficacy in improving the appearance of the facial lesions, allowing them to look more “normal.” The investigators are pursuing avenues to obtain FDA indication for this product.

PARTNERS/COLLABORATORS
University of Texas Health Science Center at Houston; additional clinical sites: Clinic Without Walls, Minnesota Epilepsy Group; University of Alabama Birmingham; Texas Scottish Rite Hospital for Children and University of Texas Southwestern Medical Center; Massachusetts General Hospital; Cincinnati Children’s Hospital; Kennedy Krieger Institute and Johns Hopkins University; Children’s Hospital UCLA; Children’s Hospital and Research Center at Oakland; Sydney Children’s Hospital

AWARD NUMBER: W81XWH-11-1-0240
Early Predictors of Neurodevelopmental Disorders in TSC

**DESCRIPTION**
Nearly 60% of children with TSC suffer from developmental delay, cognitive impairment, and autism. Early detection, which can lead to early intervention, is essential to improve developmental outcomes. This study identified early predictors of neurocognitive and behavioral outcomes in infants with TSC before clinical diagnosis. Delays in social and communication skills were evident as early as 6 months of age, with clear signs apparent by 9 months of age. These early predictors led to a pilot clinical trial for an early behavior intervention in children with TSC funded by TSCRP, followed by a full, randomized, and controlled clinical trial funded by NIH.

**PARTNERS/COLLABORATORS**
Boston Children’s Hospital; University of California, Los Angeles

**AWARD NUMBER:** W81XWH-11-1-0365

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Sirolimus and Autophagy Inhibition in LAM (SAIL)

**DESCRIPTION**
A common comorbidity of TSC is the lung disease lymphangioleiomyomatosis (LAM), which leads to breathing problems and lung failure. Sirolimus therapy is effective in reducing lung tumor burden; however, the tumors return when treatment is stopped. Hydroxychloroquine has been shown to block autophagy, a process of controlled cellular self-destruction. A phase 1 clinical trial using a combination of Sirolimus and hydroxychloroquine was well tolerated and led to lung function improvement.

**PARTNERS/COLLABORATORS**
Brigham and Women’s Hospital

**AWARD NUMBER:** W81XWH-12-1-0578
Joint Attention, Symbolic Play, Engagement, and Regulation (JASPER)

DESCRIPTION
Children with TSC are at high risk for neurodevelopmental disorders, including autism. Infants with TSC show signs of delays in social and communication skills as early as 6 months of age, highlighting the need for interventions targeting these skills prior to developing autism. This study investigated whether an early behavioral intervention called JASPER will improve the developmental skills of infants with TSC. Combining behavioral and brain-based measures to study outcomes with this early intervention, the study showed improvements in their developmental skills after JASPER, and they made substantial gains in their development at a rate not seen in infants who did not receive this targeted early intervention. This work led to a large randomized, controlled clinical trial and provided the evidence that treating infants with early interventions will improve long-term developmental outcomes.

PARTNERS/COLLABORATORS
University of California, Los Angeles; Boston Children’s Hospital

AWARD NUMBER: W81XWH-15-1-0183
Gene Therapy for TSC

DESCRIPTION
TSC is caused by loss of function of hamartin or tuberin proteins encoded by the TSC1 and TSC2 genes, respectively. Mutations in these genes lead to development of non-malignant tumors throughout the body. This study first developed a mouse model of TSC in which the TSC1 or TSC2 gene is missing in specific brain cells starting at the time of birth. These mouse models led to early death due to accumulation of fluid in the brain (hydrocephalus) and abnormal electrical activity (epilepsy). Re-introduction of the missing gene normalized brain structures and extended lifespan to almost normal length in mouse models of both TSC1 and TSC2.

PARTNERS/COLLABORATORS
Massachusetts General Hospital

AWARD NUMBERS: W81XWH-13-1-0076, W81XWH-16-1-0134

IMPACT: Since this method of gene therapy has proven safe and beneficial for a number of human diseases, this approach could lead to an effective new treatment of TSC. This study is currently funded by the NIH to refine and optimize this therapeutic strategy.

Immunotherapy for TSC Tumors

DESCRIPTION
Blood vessel-filled tumors called angiomyolipomas occur in the kidneys of most children and adults with TSC. Current therapies only partially decrease the size of the tumor, and the angiomyolipomas regrow when treatment is stopped. Taking a novel approach called immunotherapy, which has been successful in treating a number of cancers, this study is using the body’s own immune system to treat angiomyolipomas. In a mouse model of TSC, individual treatment using antibodies to block one of two key proteins was successful in decreasing tumor growth, and pre-treatment with combined antibodies led to tumor rejection.

PARTNERS/COLLABORATORS
Brigham and Women’s Hospital

AWARD NUMBER: W81XWH-17-1-0150

IMPACT: Immunotherapy has the potential to become a novel therapy for TSC tumors and could have long-lasting and significant effects on tumor burden and therefore, improve the overall prognosis and quality of life for those living with TSC.
“There have been great leaps in the research and treatment options due to the work that we look to advance through the TSCRP. I am confident, when looking at what has been accomplished in this short time that we can, and will, have a significant, positive impact on those who struggle with the effects of TSC every day.”

Tom Zampieri, PhD, Vision Research Program (VRP) Programmatic Panel Member and Consumer

“The Vision Research Program is vital for our wounded warriors to meet the goal of “Save Life, Eyesight, and Limb” on the battlefield. Both penetrating eye injuries and blast TBI vision dysfunction are critical trauma research areas that have been funded through VRP. Gaps in vision injuries are used to determine priorities for funding to improve outcomes in our Service Members and Veterans with ultimate goal to restore vision from these catastrophic injuries.”
Vision: Transform visual system trauma care for our armed forces and the nation

Mission: To address clinical needs through innovative research targeting the mechanism, effects, and treatment of Service-connected eye injuries and vision dysfunction

Years Program Appropriated: FY09-FY21

Total Appropriations: $144.95M

The VRP is the nation’s primary funder of visual system trauma research. The VRP aims to transform visual system trauma care by advancing the understanding of visual system trauma, advancing therapeutic development, and expanding forward care capability. VRP-funded research covers injuries across the visual pathway, from the cornea to the visual cortex, and spans the continuum of care from battlefield to chronic care.
HEyeDrogel Sealant System

DESCRIPTION
The HEyeDrogel Sealant System is designed to allow temporary, sutureless, and reversible sealing of open globe injury so the wound can be stabilized under austere conditions. It can be easily applied and easily removed by changing its temperature. It does not require a specialist and can be applied by forward medical personnel. It has transitioned from the VRP to the JWMRP and then to the U.S. Army Medical Materiel Development Activity for further product development. A request for FDA Breakthrough Device designation is pending.

PARTNERS/COLLABORATORS
University of Southern California

AWARD NUMBERS: W81XWH-12-1-0314, JWMRP
W81XWH-16-C-0086

USB005 Eye Drop

DESCRIPTION
USB005 is a sterile eye drop formulation of a peptide stimulator of epithelial wound repair. USB005 has recently successfully completed phase 1 clinical trial and was determined to be safe. It has the potential to become the first FDA-approved drug to regenerate cornea epithelium and stroma.

PARTNERS/COLLABORATORS
U.S. Biotest, Inc.

AWARD NUMBERS: W81XWH-15-1-0057,
W81XWH-16-1-0757, W81XWH-20-1-0388
Retinal Thermofusion

**DESCRIPTION**
Retinal thermofusion (RTF) is a novel procedure that seals retinal tear margin during retinal detachment repair surgery and prevents intraoperative fluid flow through the retina break into the subretinal space. RTF has been tested in two large animal models and on ex vivo human donor eye tissue with promising results. The traditional method of sealing is via gas tamponade, which may expand during air evacuation. In comparison to gas tamponade, RTF is expected to reduce surgical time, reduce recovery time, reduce potential complications, and enable immediate post-operative aeromedical evacuation.

**PARTNERS/COLLABORATORS**
Centre for Eye Research Australia Limited

**AWARD NUMBER:** W81XWH-16-1-0787

Photovoltaic Subretinal Prosthesis

**DESCRIPTION**
The photovoltaic subretinal prosthesis is a wireless, easy-to-implant device that holds the promise to restore sight up to 20/80 and maybe even 20/40 in patients blinded by the loss of photoreceptors. The modular design of the photovoltaic arrays allows scalability to thousands of pixels. Visual information is projected onto the retina by augmented-reality goggles using pulsed near-infrared light. Light is converted into pulsed electric current in each pixel, stimulating the nearby neurons. The prosthesis is being tested in an externally funded clinical trial. Efforts are also ongoing to increase the resolution by up to ten-fold, from the current 100μm to 10μm.

**PARTNERS/COLLABORATORS**
Stanford University

**AWARD NUMBERS:** W81XWH-15-1-0009, W81XWH-19-1-0738

**IMPACT:** RTF is a new procedure that will improve care by reducing surgical time and post-surgery complications.

**IMPACT:** The photovoltaic subretinal prosthesis is a new technology that will improve care by restoring functional vision in retinal blind patients.
Intracortical Visual Prosthesis (ICVP)

DESCRIPTION
ICVP produces artificial vision via wireless floating microelectrode arrays that are implanted in the cortical vision processing regions of the brain. A cortical prosthesis, it is designed to produce vision for patients blinded by damage to the retinal ganglia cells or optic nerve. The ICVP is currently being tested in a phase 1 feasibility trial funded by the NIH Brain Initiative.

PARTNERS/COLLABORATORS
Illinois Institute of Technology

AWARD NUMBER: W81XWH-12-1-0394

IMPACT: The ICVP is a new technology that is expected to improve care by restoring vision in neural blind patients.
Mesenchymal Stem Cell Therapy for Severe Ocular Surface Chemical Burn

**DESCRIPTION**
This phase 1/2 clinical trial is investigating the use of mesenchymal stem cell (MSC) therapy for promoting corneal repair in non-healing corneal wounds, including those after chemical and thermal injuries. The goal is to prevent the sequelae, including corneal scarring, neovascularization, and risk of corneal perforation due to non-healing ulceration. MSC therapy has been shown to accelerate corneal wound healing and limit destructive inflammation in preclinical models. It is hoped that MSCs can overcome the limitation of current standard of care, which is primarily supportive.

**PARTNERS/COLLABORATORS**
University of Illinois at Chicago

**AWARD NUMBERS:** W81XWH-14-1-0585, W81XWH-18-1-0661

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Portable Eye Imaging System

**DESCRIPTION**
Optical coherence tomography (OCT) is a non-invasive infrared imaging technique widely used in ophthalmology clinics. This portable diagnostic device will bring OCT to the forward environment, greatly enhancing forward care capability. It is compact, telemedicine-compatible, automated, and can be operated by trained non-specialists. Its successful development and deployment will enable early responders to assess ocular trauma and intraocular inflammation in austere/remote conditions.

**PARTNERS/COLLABORATORS**
Duke University

**AWARD NUMBERS:** W81XWH-16-1-0498, W81XWH-20-1-0660

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**IMPACT:** The MSC therapy is expected to shorten the time to epithelial closure and improve outcome of severe ocular surface chemical burns.

**IMPACT:** The portable OCT system is expected to improve forward care for military personnel affected by eye injury or visual dysfunction.
Transcriptome Databases for Normal and Blast-Injured Retina

DESCRIPTION
Three transcriptome databases were generated in the mouse model. Two databases describe gene expression in the normal retina, one of which describes the changes in gene expression that occur following a 50-psi blast injury to the eye. Analysis of the databases and follow-up investigations have generated a wealth of knowledge about retinal pathobiology after blast, including but not limited to the role for the immune system, the identification of individual genes as potential therapeutic targets, and the identification of genetic loci as risk factors for traumatic glaucoma.

PARTNERS/COLLABORATORS
Emory University

AWARD NUMBER: W81XWH-12-1-0255 (co-funded by VRP and PHTBIRP)

IMPACT: These two transcriptome databases significantly advanced the molecular understanding of blast injury to the eye, facilitating therapeutic development and prognosis.
**Molecular Regulators of Optic Nerve Regeneration**

**DESCRIPTION**
In optic nerve injuries, vision loss and blindness are caused by a failure of the severed retinal ganglion cell (RGC) axons to regenerate back to their targets in the brain. The identification of a family of genes as critical regulators of axon regeneration after optic nerve injury has generated a new avenue of research and pointed to new therapeutic targets. Follow-up investigation is ongoing and is funded by the National Eye Institute Audacious Goal Initiative.

**PARTNERS/COLLABORATORS**
Stanford University

**AWARD NUMBER:** W81XWH-12-1-0254

**IMPACT:** Significantly advanced research toward the regeneration of axons after optic nerve injury, opening up new possibilities for therapies to restore vision after such injuries.

*Axons regenerating long distance of a mature 129X1/svj wild type mouse optic nerve 2 weeks after injury.*
Outer Retina Reconstruction for Combat Afflictions (ORRCA)

DESCRIPTION
ORRCA is a precision-based outer retinal cell replacement therapy that reconstructs areas within the central outer retina that are irreversibly damaged by blunt force trauma or laser exposure. ORRCA showcases an international team effort that combines stem cell-based production of retinal cells, bioengineering of outer retina scaffolds, and the development and optimization of surgical techniques into one therapy. ORRCA holds the potential to fill a gap in the treatment of blinding retinal injuries caused by blunt force trauma or laser exposure.

PARTNERS/COLLABORATORS
University of Wisconsin, Madison; National Eye Institute; University of Birmingham, UK

AWARD NUMBER: W81XWH-20-1-0655

IMPACT: ORRCA is a new therapy that will fill a gap in the treatment of blinding retinal injuries.
DOD-NEI Vision Research Collaborative (VRC)

DESCRIPTION
Established in 2018, the VRC is a joint initiative between the National Eye Institute (NEI) and the VRP. Through the VRC, the NEI participates in selected VRP funding opportunities and has the option of selecting meritorious VRP proposals for independent funding consideration. The VRC provides additional funding opportunities for VRP proposals, enhances current NEI program portfolios, expands the scope of research supported by the NEI, and provides support for high-quality projects addressing critical gaps in civilian and military vision research.

PARTNERS/COLLABORATORS
National Eye Institute

AWARD NUMBERS: NIH 1-R01-EY031144 A Stem Cell-Based Treatment Strategy for Laser-Induced Permanent Retinal Damages, NIH 1-R01-EY031167 The Role of Perinuclear cAMP in Retinal Ganglion Cell Neuroprotection and Optic Nerve Regeneration

IMPACT: The VRC promotes synergy and collaboration between federal funding agencies and coordination in the pursuit of the common goals in funding research that (1) prevents and treats the degeneration or injury of critical components of the eye and (2) restores impaired or lost vision.
Dena Battle, KCRP Programmatic Panel Member and Consumer

“When my husband lost his battle to kidney cancer at the age of 45, the landscape for research in kidney cancer looked bleak. There weren’t many therapeutic options available, and kidney cancer just didn’t seem to be a focus at many cancer centers. Today, I have a great sense of optimism for the future. Being part of the Kidney Cancer Research Program has fueled that hope. The KCRP brings doctors, researchers, and patients together to... accelerate research for a cure. While it won’t make a difference for my husband - it might make a difference for our daughters. They carry his genes.”

Patricia Horan
ERP Programmatic Panel Member and Consumer

“The ERP honors my husband’s Service and sacrifice by its mission; to better understand how trauma transforms the brain and disturbs cognitive function. This program is tasked to find and eliminate mechanisms that start the epileptogenic process, which means a better chance for survival, rehabilitation, and quality of life for the next generations of Veterans.”
IMPACTING THE FUTURE

Pancreatic Cancer Research Program

Vision: Reduce the burden of pancreatic cancer among Service Members, Veterans, their families, and the American public

Mission: Promote rigorous, innovative, high-impact research that leads to earlier pancreatic cancer diagnosis and new therapeutic tools through collaboration

Years Program Appropriated: FY20-FY21

Total Appropriations: $21M

The Pancreatic Cancer Research Program’s (PCARP’s) mission is to promote rigorous, innovative, high-impact research that leads to earlier pancreatic cancer diagnosis and new therapeutic tools through collaboration. Based on the program’s mission, the PCARP developed a four-prong strategic direction to fulfill the program’s goal. These include: (1) fill gaps and advance knowledge that will drive new and innovative clinical trials for pancreatic cancer, (2) expand pancreatic cancer expertise by bridging diverse scientific fields, (3) facilitate a multidisciplinary approach to advancing scientific knowledge of pancreatic cancer, and (4) recruit and retain young investigators dedicated to pancreatic cancer research.

Rare Cancers Research Program

Vision: To greatly improve outcomes for people with rare cancers through discovery, community building, and expansion of knowledge across the cancer landscape

Mission: To elevate rare cancers research to enable clinically impactful discoveries for the benefit of active-duty Service Members, Veterans, military beneficiaries, and/or the American public

Years Program Appropriated: FY20-FY21

Total Appropriations: $25M

Based on metrics provided by the American Cancer Society (fewer than 6 per 100,000 incidence), around 380 types of cancers are considered rare forms, and these affect over half a million Americans each year. A quarter of all cancer deaths each year are due to rare cancers. Rare cancer patients are almost seven times less likely to have an approved targeted therapy compared to patients with other cancers. Rare cancer incidences in Service Members and their family members are quite prevalent. To date, 64 cancers have been determined to disproportionately affect Veterans and those in the military. Just over two-thirds of those cancers are rare. The goals of the Rare Cancers Research Program are to develop innovative research, identify therapeutics, develop resources, and share
In order to accomplish the program goals, all applicants are required to address at least one of the Focus Areas. The main focus of the program is to understand the biology and etiology, develop preclinical research models, identify therapy, and build a network among the research and patient communities to enable clinically impactful discoveries for the benefit of Service Members, their families, Veterans, and/or the American public.

**Scleroderma Research Program**

*Vision:* To combat scleroderma through a partnership of scientists, clinicians, and consumers  

*Mission:* To fund and facilitate the most promising, highest quality research aimed at understanding mechanisms, improving therapies, and ultimately curing scleroderma for Service Members, Veterans, and the American public  

*Years Program Appropriated:* FY20-FY21  

*Total Appropriations:* $10M

The Scleroderma Research Program has identified nine research areas of emphasis to address the five overarching challenges of understanding cell biology, understanding disease heterogeneity, identifying therapeutic targets, conducting clinical trials, and addressing quality of life and survivorship:

- Define biomarkers that help inform therapeutic choices or predict course of the disease and/or improve quality of life.
- Utilize systems biology, multi-omics, and preclinical screening approaches with the intent to develop drug testing models in order to understand the heterogeneity of disease as well as to develop prevention and therapeutic interventions.
- Studies of diverse populations, to include the development of cohorts and identification of potential measures of patient outcomes.
- Define the functional role of epigenetic changes, multiple cell types, and molecules that mediate pathogenesis and/or initiate or propagate organ-specific disease activity using preclinical models and clinical samples.
- Conduct population-based or cohort studies to understand the prevalence, heterogeneity, and course of this disease, its manifestations, and its impact on health outcomes and activities for daily living.
- Understand and improve the impact of disease and its treatment on the patient’s experience and quality of life.
- Develop and validate short- and long-term organ-specific and composite clinical outcomes.
- Development of clinical trial platforms that enable rapid comparison of different therapeutic approaches on a pilot basis.
- Conduct secondary analysis of scleroderma and other similar disease datasets to identify novel targets and biomarkers that can be validated in existing or new models.
### Appendix B

**ACRONYMS**

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<td>Alcohol and Substance Abuse Disorders Research Program</td>
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mRCC .......... Metastatic Renal Cell Carcinoma
MRI .............. Magnetic Resonance Imaging
MRP .............. Melanoma Research Program
MS ................ Multiple Sclerosis
MSC .............. Mesenchymal Stem Cell
MSD ............... Musculoskeletal Disorders
MSRC ............. Military Suicide Research Consortium
MSRP ............. Multiple Sclerosis Research Program
NaF ................ Sodium Fluoride
NBWT ............ Narrowing-Beam Walking Test
NCAA ............. National Collegiate Athletic Association
NCI .............. National Cancer Institute
NEI ................ National Eye Institute
NETP ............. Neurotoxin Exposure Treatment Parkinson’s Program
NFCTC ............ Neurofibromatosis Clinical Trials Consortium
NG-tRMS .......... Neuronavigation-Guided Transcranial Magnetic Stimulation
NIAID ............ National Institute of Allergy and Infectious Diseases
NIH .............. National Institutes of Health
NIRS ...... Near-Infrared Spectroscopy Sensor
NSCLC .......... Non-Small Cell Lung Cancer
OA .................. Osteoarthritis
OCA .............. Ovarian Cancer Academy
OCRP .......... Ovarian Cancer Research Program
OCT ............. Optical Coherence Tomography
OPORP ............ Orthotics and Prosthetics Outcomes Research Program
ORRCA .......... Outer Retina Reconstruction for Combat Afflictions
OTTA-SPOT .... Ovarian Tumor Tissue Analysis Consortium – Stratified Prognosis of Ovarian Tumours
OUD ................ Opioid Use Disorder
PARP .......... Poly ADP-Ribose Polymerase
PARS .............. Parkinson’s Associated Risk Syndrome
PCARP .......... Pancreatic Cancer Research Program
PCRP .......... Peer Reviewed Cancer Research Program
PD ................ Parkinson’s Disease
Pfn-1 ............. Profilin-1
PH ................ Psychological Health
PI .................. Principal Investigator
PiPT .......... Psychologically Informed Physical Therapy
PK ................ Pharmacokinetic
PLIE .............. Preventing Loss of Independence Through Exercise
PMC ........ Pain Management Collaboratory
PMS ........ Progressive Multiple Sclerosis
PNS .............. Peripheral Nerve Stimulation
POIP ............ Phases of Illness Paradigm
PRCRP .......... Peer Reviewed Cancer Research Program
PrEP .............. Pre-Exposure Prophylaxis
PRIDE .......... The Parkinson’s Registry Investigation of Diagnosis and Etiology
PRMRP .......... Peer Reviewed Medical Research Program
PRMT5 .......... Protein Methyltransferase 5
PRORP .......... Peer Reviewed Orthopaedic Research Program
PS+ASD .......... Project SEARCH Plus ASD
PSTIM ........ Pudendal Nerve Stimulator
PTE ............. Post-Traumatic Epilepsy
PTEN ...... Phosphatase and Tensin Homolog
PTOA .......... Post-Traumatic Osteoarthritis
PTSD .......... Post-Traumatic Stress Disorder
QOL .............. Quality of Life
QTBI .......... Quantitative Total Bone Imaging
QTxI .......... Quantitative Total Extensible Imaging
RANKLE .......... Receptor Activator of Nuclear Factor Kappa-B Ligand
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<td>ROM</td>
<td>Range of Motion</td>
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<td>RRMS</td>
<td>Relapsing Remitting Multiple Sclerosis</td>
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<td>RTF</td>
<td>Retinal Thermofusion</td>
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<td>SPRINT Peripheral Nerve Stimulation System</td>
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<td>SR</td>
<td>Spatial Repellant</td>
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<td>TBD</td>
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<td>TBDRP</td>
<td>Tick-Borne Disease Research Program</td>
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<td>TBI</td>
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<td>Traumatic Brain Injury and Psychological Health Research Program</td>
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<td>tDCS</td>
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<td>VCA</td>
<td>Vascularized Composite Allotransplantation</td>
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<td>Virus-Like Particles</td>
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