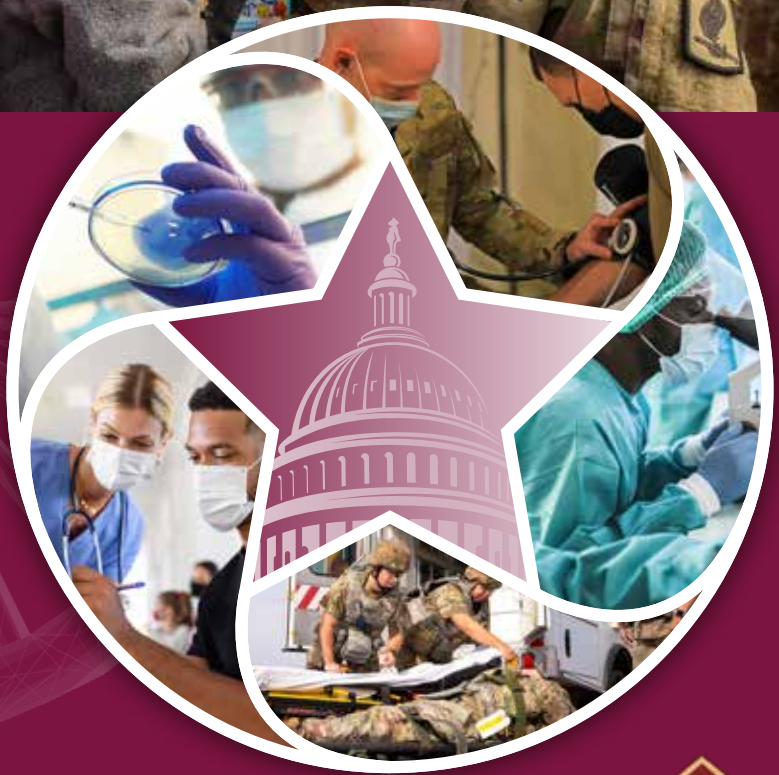
Peer Reviewed Medical Research Program

Congressionally Directed Medical Research Programs

CDMRP

Department of Defense



U.S. Army Medical Research and Development Command

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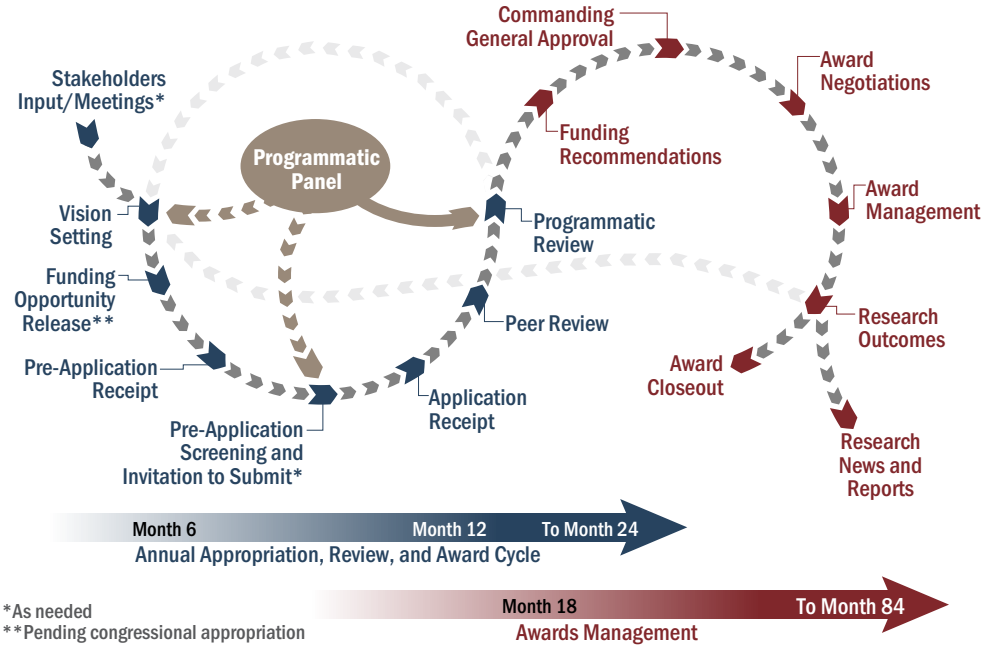
CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

HISTORY

The office of the Congressionally Directed Medical Research Programs (CDMRP) was created in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a congressional appropriation of funds for breast cancer research. This initiated a unique partnership among the public, U.S. Congress, and the military. Since its inception through fiscal year (FY) 2020, the CDMRP has grown to encompass multiple targeted programs and has been responsible for managing over $15.9 billion (B). Funds for the CDMRP are added to the Department of Defense (DOD) budget, in which support for individual programs, such as the Peer Reviewed Medical Research Program (PRMRP), is allocated via specific guidance from congress.

APPLICATION REVIEW PROCESS

The CDMRP uses a two-tier review process for evaluating applications, with both tiers involving dynamic interaction between scientists and disease survivors (consumers). The first tier of evaluation is a scientific peer review of the applications, measured against established criteria for determining scientific merit. The second tier is a programmatic review conducted by the Programmatic Panel, which is composed of leading scientists, clinicians, and consumers, and ad hoc programmatic reviewers as needed. The Programmatic Panel members compare applications to each other and make recommendations for funding based on scientific merit, potential impact, adherence to the intent of the award mechanism, relevance to program goals, and portfolio composition.



CDMRP Two-Tier Review Process

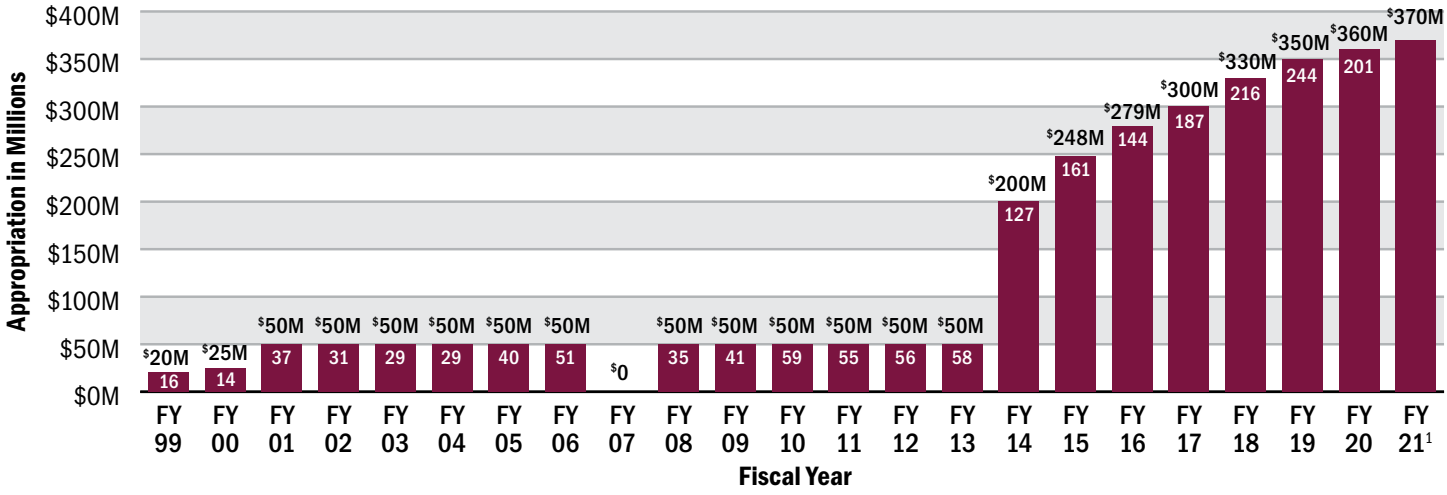
PEER REVIEWED MEDICAL RESEARCH PROGRAM

PRMRP Vision: Improve the health, well-being, and care of all military Service Members, Veterans, and Beneficiaries

PRMRP Mission: Encourage, identify, select, and manage medical research projects of clear scientific merit that lead to impactful advances in military health care

ABOUT THE PROGRAM

The PRMRP was established in FY99 to provide support for military health-related research of exceptional scientific merit toward the goal of improving the health and well-being of military Service Members, Veterans, and their beneficiaries. Through its 22-year history (excepting FY07, when no funds were appropriated), the U.S. Congress has appropriated $3.08B to the PRMRP, which has supported more than 1,800 research awards in 170 unique topic areas representing various diseases and conditions. These research efforts have generated over 3,620 peer-reviewed publications and 332 patent applications or patents granted. The PRMRP emphasizes high-impact, translational research that has near-term benefits for Service Members, Veterans, and their beneficiaries. Supported projects range from exploratory, highly innovative studies to large projects focused on clinical implementation of technologies or interventions.



FY99–FY21 PRMRP Funding History and Awards Made

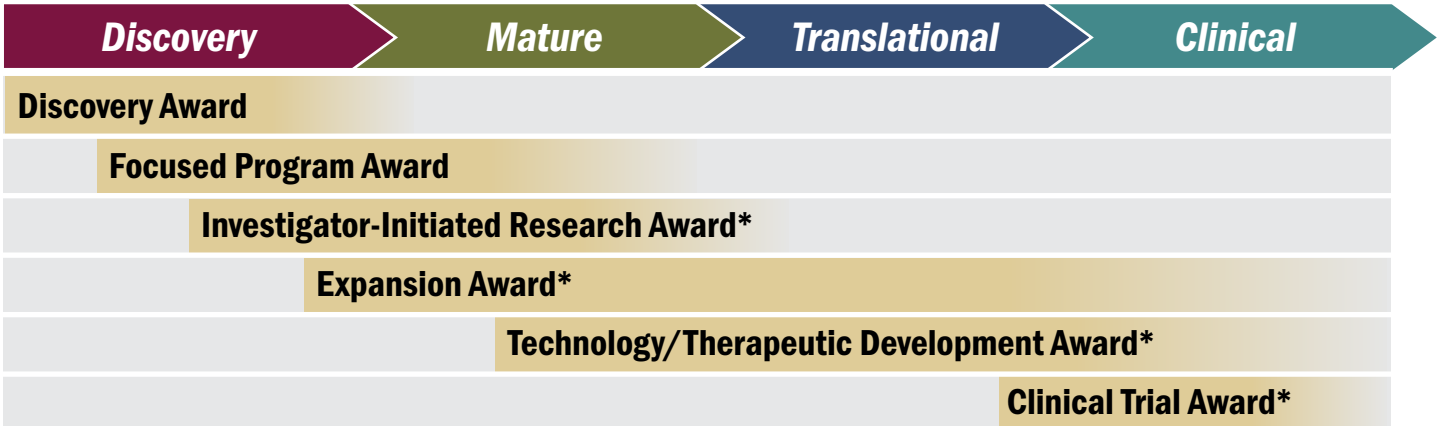
RELEVANCE TO MILITARY HEALTH

Research supported by the PRMRP continues a long tradition of addressing near-term healthcare needs that ultimately benefit Service Members and civilians alike. Service Members, Veterans, and their beneficiaries receive military medical services, creating a critical need to support research on a broad spectrum of medical issues affecting these diverse populations, including children and seniors. Reducing the burden of disease on military families supports mission readiness and fosters solutions for the emotional, psychological, and physical well-being of the Warfighter.

[1] Number of FY21 awards not finalized at this time.

INVESTMENT STRATEGY

Each fiscal year, the PRMRP develops an investment strategy that supports research throughout the continuum of care, from early discovery through the development of ideas and products into clinical applications. The **Discovery Award (DA)** mechanism fosters new ideas by supporting innovative, non-incremental, high-risk/high-reward research. The **Focused Program Award (FPA)** supports multiple distinct but complementary projects that address a central critical problem or question (i.e., overarching challenge). The **Investigator-Initiated Research Award (IIRA)** supports mature ideas (i.e., beyond proof of concept) that have the potential to yield highly impactful data and critical discoveries or major advancements. The **Expansion Award (EA)** supports the continued investigation and further development of highly impactful research projects that were funded through previous PRMRP funding opportunities. Two award mechanisms focus on translational research: the **Technology/Therapeutic Development Award (TTDA)**, a product-driven award mechanism, supports the translation of promising preclinical findings into products for clinical applications, while the **Clinical Trial Award (CTA)** supports rapid implementation of clinical trials with the potential to have a significant impact on a relevant disease or condition.



*COVID-specific program announcements released in FY20.

FY19-FY21 PRMRP Award Mechanisms

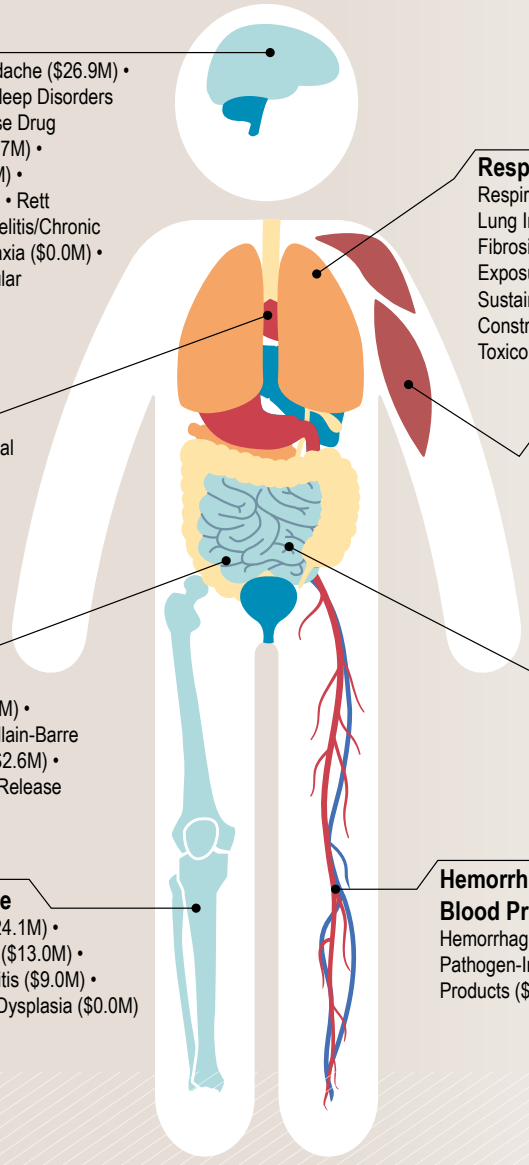
"The PRMRP holds true to its mission, granting multilevel funding through peer review to visionary researchers who answer and provide positive solutions to research questions unique to military health. The program provides a wealth of novel works that span discovery to large-scale clinical trials, all harmonized to benefit the health, care, and treatments available to the Military Serviceperson, Veteran, and their beneficiaries. Finally, the program provides researchers the ability to give back to those that have given much or all for the nation's freedom we so treasure."

Ronald Przygodzki, M.D.
Director of Genomic Medicine, Office of Research and Development
U.S. Department of Veterans Affairs
FY21 PRMRP Programmatic Panel Chair

PRMRP TOPIC AREAS

In pursuit of its vision, the PRMRP supports medical research addressing a variety of challenges affecting the health and well-being of military Service Members, military retirees, Veterans, and their beneficiaries. Each year, the PRMRP solicits research applications under topic areas directed by Congress, which address a wide range of fields of study. The PRMRP is committed to funding research that has the potential to profoundly impact the development and implementation of medical devices, drugs, and clinical guidance that will enhance the precision and efficacy of prevention, diagnosis, and treatment across this wide range of disciplines. These disciplines are grouped into PRMRP portfolios: Autoimmune Diseases and Immunology, Cardiovascular Health, Hemorrhage Control and Blood Products, Infectious Diseases, Internal Medicine, Neuroscience, Nutrition and Metabolism, Orthopaedic Medicine, Regenerative Medicine, and Respiratory Health. Awards under each congressionally directed topic area are managed within one of these PRMRP portfolios.

FY19 and FY20 PRMRP Topic Area Funding by Portfolio



Neuroscience
Chronic Migraine and Post-Traumatic Headache ($26.9M) • Frontotemporal Degeneration ($14.5M) • Sleep Disorders and Restriction ($8.0M) • Sustained Release Drug Delivery ($7.8M) • Myotonic Dystrophy ($4.7M) • Dystonia ($3.6M) • Eating Disorders ($2.9M) • Hydrocephalus ($2.6M) • Fragile X ($1.8M) • Rett Syndrome ($1.5M) • Myalgic Encephalomyelitis/Chronic Fatigue Syndrome ($0.5M) • Cerebellar Ataxia ($0.0M) • Resilience Training ($0.0M) • Spinal Muscular Atrophy ($0.0M) • Tinnitus ($0.0M)

Respiratory Health
Respiratory Health ($92.3M) • Acute Lung Injury ($22.1M) • Pulmonary Fibrosis ($21.5M) • Burn Pit Exposure ($3.4M) • Lung Injury ($0.6M) • Sustained Release Drug Delivery ($0.3M) • Constrictive Bronchiolitis ($0.0M) • Metals Toxicology ($0.0M)

Cardiovascular Health
Cardiomyopathy ($29.9M) • Congenital Heart Disease ($25.6M) • Vascular Malformations ($14.2M) • Familial Hypercholesterolemia ($4.8M) • Women's Heart Disease ($1.2M)

Regenerative Medicine
Tissue Regeneration ($10.9M) • Nanomaterials for Bone Regeneration ($6.0M) • Sustained Release Drug Delivery ($2.4M) • Immunomonitoring of Intestinal Transplants ($0.3M)

Autoimmune Diseases and Immunology
Inflammatory Bowel Disease ($20.1M) • Rheumatoid Arthritis ($12.6M) • Guillain-Barre Syndrome ($4.7M) • Scleroderma ($2.6M) • Food Allergies ($2.0M) • Sustained Release Drug Delivery ($0.3M)

Nutrition and Metabolism
Diabetes ($60.5M) • Mitochondrial Disease ($20.8M) • Nutrition Optimization ($2.0M)

Orthopaedic Medicine
Musculoskeletal Health ($24.1M) • Musculoskeletal Disorders ($13.0M) • Post-Traumatic Osteoarthritis ($9.0M) • Arthritis ($3.8M) • Fibrous Dysplasia ($0.0M)

Hemorrhage Control and Blood Products
Hemorrhage Control ($29.6M) • Pathogen-Inactivated Blood Products ($1.3M)

Infectious Diseases
Emerging Viral Diseases ($49.8M) • Antimicrobial Resistance ($16.9M) • Emerging Infectious Diseases ($15.8M) • Hepatitis B ($6.8M) • Tuberculosis ($5.4M) • Sustained Release Drug Delivery ($0.3M) • Plant-Based Vaccines ($0.0M)

Internal Medicine
Polycystic Kidney Disease ($21.2M) • Pancreatitis ($8.7M) • Pressure Ulcers ($8.4M) • Focal Segmental Glomerulosclerosis ($7.6M) • Interstitial Cystitis ($4.4M) • Endometriosis ($2.2M) • Epidermolysis Bullosa ($0.0M) • Hereditary Angioedema ($0.0M)

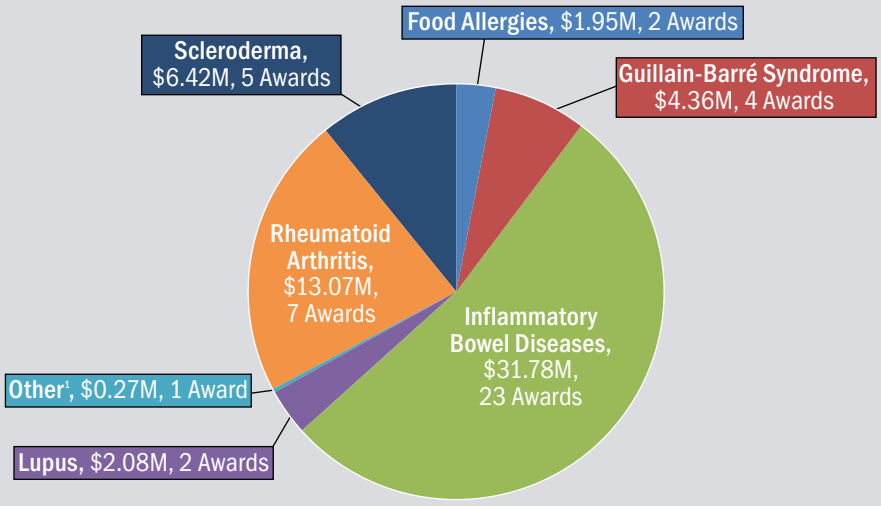
FY16–FY20 Topic Areas Funded

- Food Allergies
- Guillain-Barré Syndrome
- Inflammatory Bowel Diseases
- Lupus
- Rheumatoid Arthritis
- Scleroderma

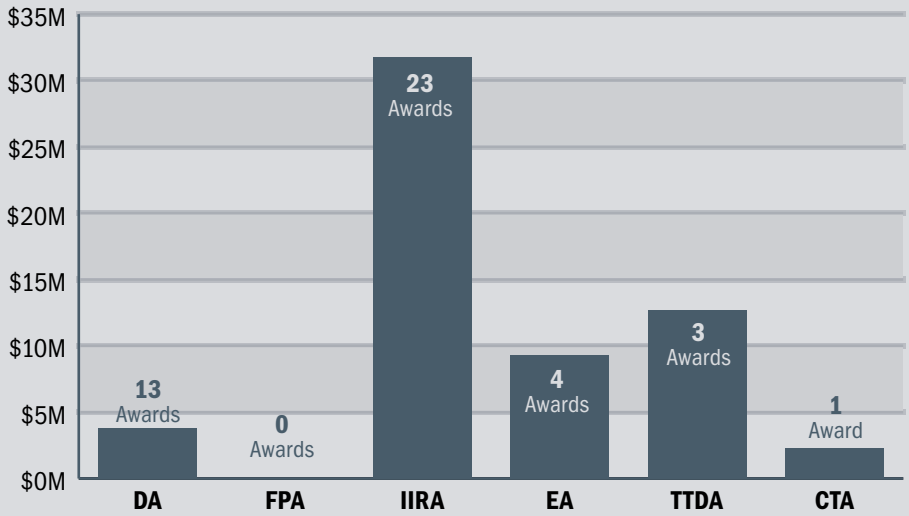
FY21 Topic Areas Offered

- Food Allergies
- Inflammatory Bowel Diseases
- Rheumatoid Arthritis

AUTOIMMUNE DISEASES AND IMMUNOLOGY



FY16–FY20 Autoimmune Diseases and Immunology Funding by Topic Area



FY16–FY20 Autoimmune Diseases and Immunology Funding by Award Mechanism

Estimates suggest that 10 million people in the United States are impacted by autoimmune disorders, which cause serious chronic disease and disability.[2] These disorders impact U.S. Service Members, Veterans, and their beneficiaries and can produce a range of debilitating symptoms that interfere with an individual's daily duties and require long-term care, incurring significant costs for the Military Health System. As a result, autoimmune disorders pose a risk to the effectiveness and readiness of the military force. The PRMRP Autoimmune Diseases and Immunology portfolio supports research into the underlying mechanisms and treatment identification for these disorders with the goal of reducing morbidity. During FY16–FY20, the PRMRP funded 44 awards related to autoimmune disorders totaling $59.9M.

[1] Other includes Topic Areas split between multiple portfolios (e.g., Sustained Release Drug Delivery).

[2] https://pathology.jhu.edu/autoimmune/prevalence

RESEARCH HIGHLIGHTS

Targeting the Intestinal Barrier to Regulate Mucosal Immunity in IBD and Infectious Enterocolitis

Jerrold Turner, M.D., Ph.D.,
Brigham and Women's Hospital and Harvard Medical School

Dr. Jerrold Turner and his colleagues determined that claudin-2, which forms paracellular channels for small molecules (i.e., sodium ions and water), profoundly impacts the evolution of inflammatory bowel disease (IBD). Research has shown that in addition to affecting intestinal permeability, claudin-2 interacts with sodium ions to activate a mucosal immune response and mediate pathogen clearance and therefore may also contribute to other intestinal diseases. With support from an FY18 IIRA to Brigham and Women's Hospital and Harvard Medical School, Dr. Turner and his team are conducting mechanistic studies to determine how claudin-2 interacts with sodium ions to regulate mucosal immunity and microbial pathogenesis and how dietary intake of sodium impacts these processes. Using claudin-2 knockout and claudin-2 transgenic mice, the researchers have made significant progress toward defining the mechanisms by which dietary sodium ions impact mucosal immunity. This will form a foundation for continuing work to determine the contributions of claudin-2 to IBD pathogenesis.

Small intestine of a murine model stained for the tight junction proteins claudin-2 (green) and ZO-1 (red). Nuclei (cyan) and epithelial cell lateral membranes (grey) are also shown.

Identifying Rare Genetic Variants in Systemic Sclerosis

Maureen Mayes, M.D., M.P.H., University of Texas Health Science Center at Houston
Brendan Lee, M.D., Ph.D., Baylor College of Medicine

Systemic sclerosis (SSc, scleroderma), a systemic autoimmune disease with high mortality, results from a combination of external triggers and genetic susceptibility; however, specific physiological pathways and genetic contributions to disease progression remain unknown. Current treatments usually involve general immunosuppression rather than addressing the underlying disease-causing abnormalities, which may be specific to different patient populations. With funding from an FY17 IIRA – Partnering PI Option (IIRA-PPIO) to the University of Texas Health Science Center at Houston and Baylor College of Medicine, Drs. Maureen Mayes and Brendan Lee aim to identify causal genetic variants in multiple pathways associated with SSc susceptibility through the largest whole genome sequencing cohort in SSc to date: 300 individuals and their parents. As of September 2020, the sequencing data for 300 samples had been generated and uploaded to the Dynamic Read Analysis for GENomics (DRAGEN) platform at Baylor College of Medicine for preparation and identification of rare variants in individual cases as well as those common among SSc cases. Both inherited and de novo mutations will be identified. Identification of these genetic variants and the metabolic pathways they influence may provide insight into the genetic susceptibility and pathogenic mechanisms of scleroderma and determine the role of these variants in disease causation and severity of outcome.

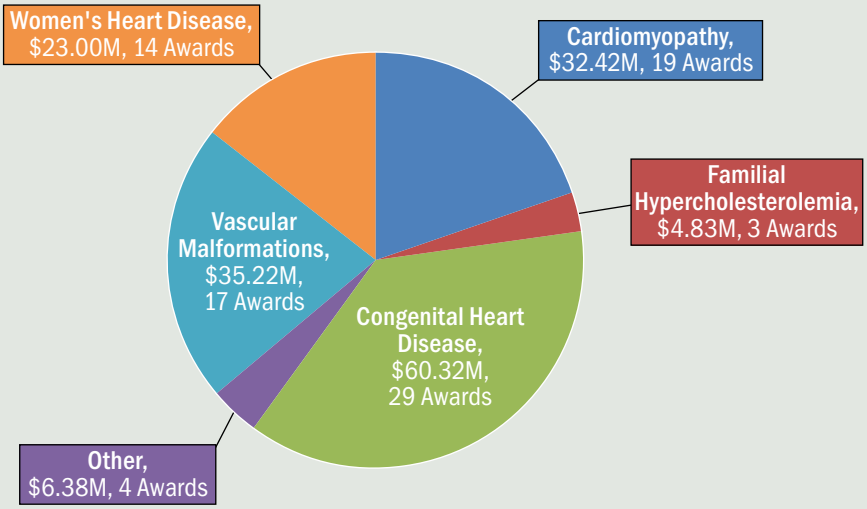
CARDIOVASCULAR HEALTH

FY16–FY20 Topic Areas Funded

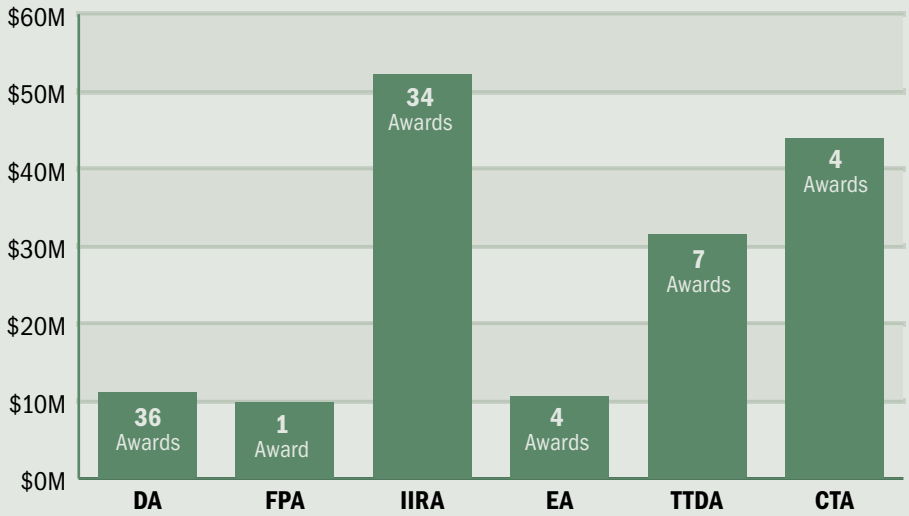
- Cardiomyopathy
- Congenital Heart Disease
- Familial Hypercholesterolemia
- Vascular Malformations
- Women's Heart Disease

FY21 Topic Areas Offered

- Cardiomyopathy
- Congenital Heart Disease
- Familial Hypercholesterolemia
- Hypertension
- Vascular Malformations
- Women's Heart Disease



FY16–FY20 Cardiovascular Health Funding by Topic Area



FY16–FY20 Cardiovascular Health Funding by Award Mechanism

Cardiovascular disease is one of the leading causes of death in the United States, totaling approximately 2,300 fatalities daily, or one death every 38 seconds.[1] Cardiovascular health conditions are a major concern for U.S. Service Members, Veterans and their beneficiaries and contribute to increasing healthcare costs and reduced military readiness. Research focusing on understanding the physiology of disease and development of therapeutics has the potential to improve Warfighter readiness and health. The PRMRP Cardiovascular Health portfolio supports research in a variety of chronic and inherited cardiovascular diseases and conditions. During FY16–FY20, the PRMRP funded 86 awards related to cardiovascular health totaling $162.2M.

[1] https://tristarhealth.com/util/documents/2019/Heart-Disease-and-Stroke-Statistics-2018.pdf

RESEARCH HIGHLIGHTS

Optimizing Cardiovascular Disease Diagnosis for Mobile Deployment Using Advanced Machine Learning

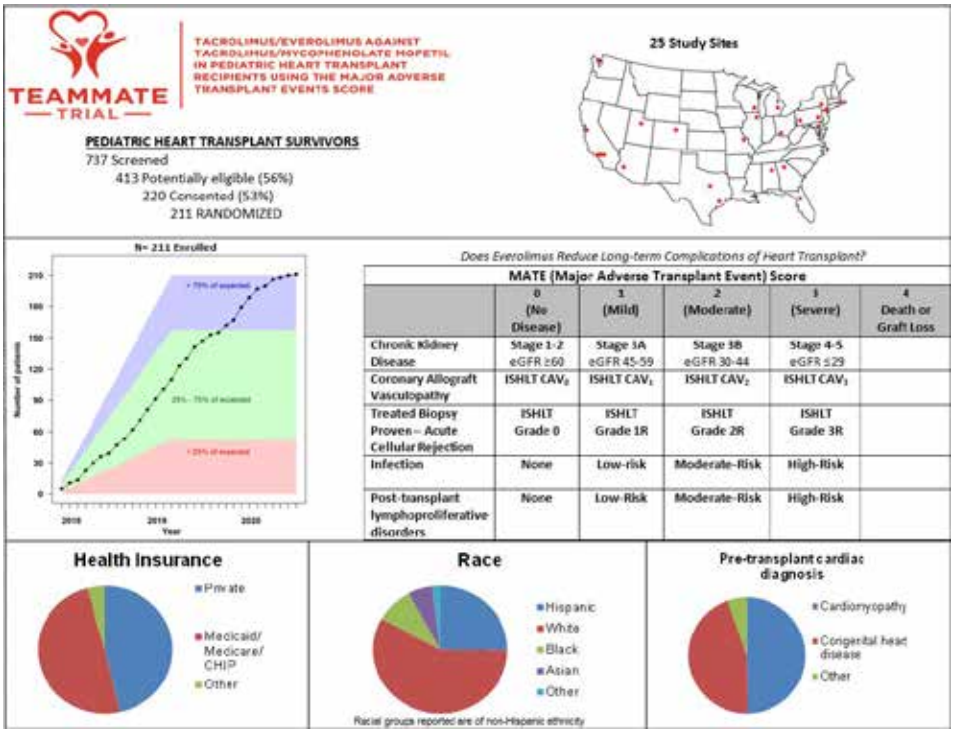
Rima Arnaout, M.D., University of California, San Francisco

Congenital heart disease (CHD) is a serious birth defect classified by one or more structural cardiac abnormalities that develop in utero and can cause significant morbidity and mortality after birth. Although CHD prenatal screenings are routinely performed, the diagnosis rate remains low. With support from an FY18 TTDA to the University of California, San Francisco, Dr. Rima Arnaout proposes to improve the rate of accurate CHD diagnosis by developing a mobile diagnostic platform that uses deep learning programs to assist non expert sonographers in more accurately detecting and diagnosing CHD from ultrasound images. Currently, Dr. Arnaout's team is developing algorithms for pattern recognition. The deep learning algorithms will continue to be refined to enhance the robustness of the platform, which may even allow for detection of CHD subtypes. Furthermore, Dr. Arnaout's team will receive additional data from other medical centers for extensive validation of the technology. If successful, the device would be the first to use state-of-the-art machine learning techniques to guide ultrasound image acquisition and interpretation for improving CHD diagnosis.

Everolimus for Preventing Rejection after Pediatric Heart Transplantation

Lynn Sleeper, Sc.D., Boston Children's Hospital

Through an FY16 CTA to Boston Children's Hospital, Dr. Lynn Sleeper is evaluating everolimus and low-dose tacrolimus, a new rejection treatment for children who have undergone recent heart transplant, in a randomized phase 3 clinical trial. The results from this study will be used to determine whether this new treatment can reduce or prevent complications of transplant, including rejection, coronary artery disease, and kidney disease, when compared to usual care (tacrolimus and mycophenolate mofetil). The ultimate goals are to improve the long-term safety and survival of children after heart transplant and to obtain U.S. Food and Drug Administration (FDA) approval for the first antirejection medicine for pediatric heart transplant. If successful and approved by the FDA, everolimus plus low-dose tacrolimus could improve median survival after pediatric heart transplant beyond the current 15 years post-transplantation. Further, the major adverse transplant event (MATE) score would be validated as a surrogate endpoint and improve clinical trial design for future studies of pediatric heart transplant and other rare diseases.



FY16–FY20 Topic Areas Funded

- Hemorrhage Control
- Pathogen-Inactivated Blood Products
- Pathogen-Inactivated Dried Plasma

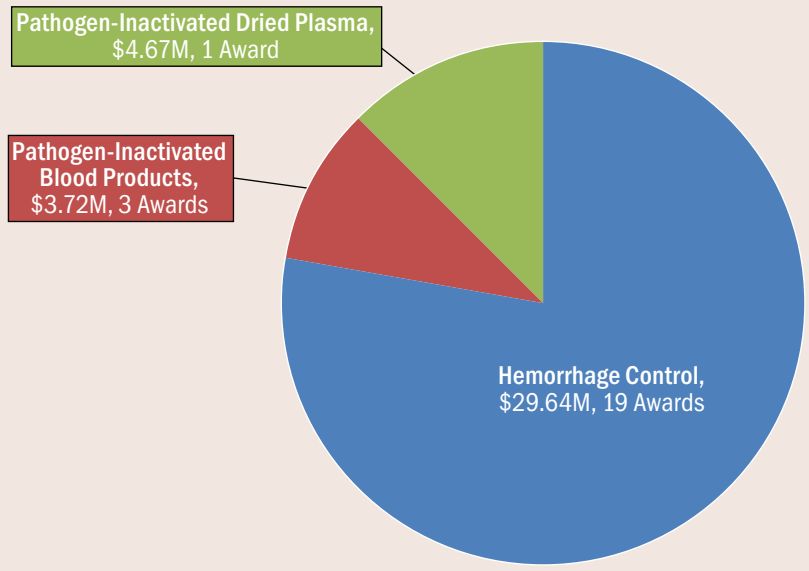
FY21 Topic Areas Offered

- Hemorrhage Control
- Pathogen-Inactivated Blood Products
- Platelet-Like Cell Production

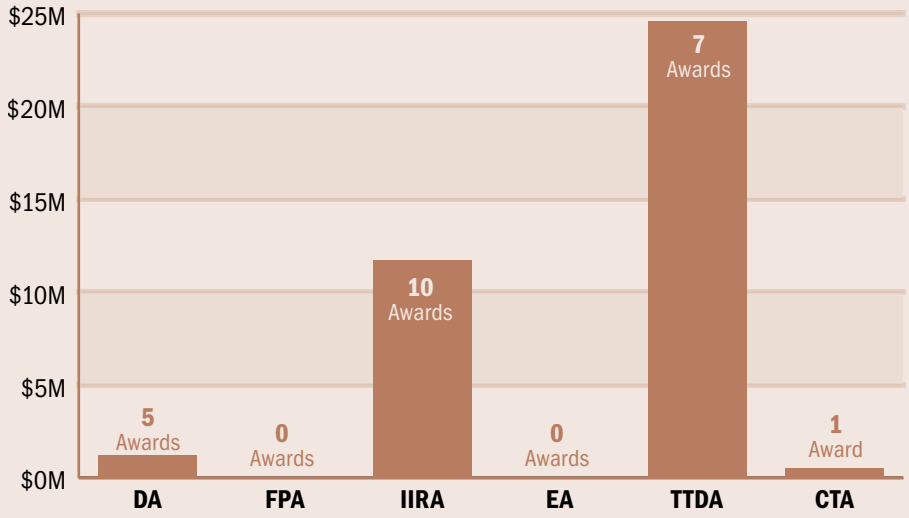
"There are numerous lessons to be learned from any military conflict or domestic health event. We must continue to learn and grow to meet these challenges to health care head on, if not proactively prevent them altogether. The healthcare delivery paradigm is shifting and our nation must remain pro-active, vigilant, and agile to meet the dynamic nature of our healthcare needs. The PRMRP process allows for innovation with military relevance beyond that of the Service Member, as it affects families, Veterans, and all those who deal with complex medical issues. By prioritizing research, we can ensure a better future for health care and wellness to provide everyone the opportunity live better lives."

COL Alicia Madore, R.N., M.S.N., C.C.R.N., C.C.N.S., W.C.C.
Keller Army Community Hospital
PRMRP FY21 Ad Hoc Programmatic Reviewer

HEMORRHAGE CONTROL AND BLOOD PRODUCTS



FY16–FY20 Hemorrhage Control Funding by Topic Area



FY16–FY20 Hemorrhage Control Funding by Award Mechanism

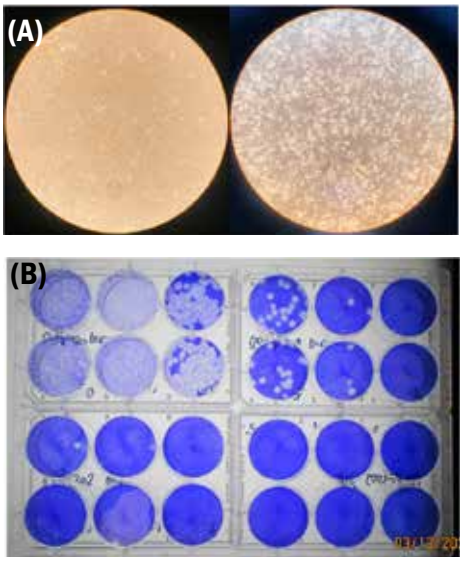
Hemorrhage following trauma or injury is a leading cause of mortality among Service Members and is a serious concern for civilians following events such as car accidents and mass shootings. Research on rapid interventions at the point of injury is essential for military use due to limited medical care in remote deployment areas and may provide additional treatment options for civilian healthcare facilities with limited resources. The PRMRP Hemorrhage Control and Blood Products portfolio includes topic areas that aim to reduce mortality from hemorrhage and aid in the creation of a safe blood supply. During FY16–FY20, the PRMRP funded 23 awards spanning a diverse range of hemorrhage control strategies and blood products totaling $38.0M.

RESEARCH HIGHLIGHTS

Indications Against Highly Pathogenic Agents for a Transportable Pathogen Reduction and Blood Safety System for Whole Blood

Raymond P. Goodrich, Ph.D., Colorado State University

In combat situations, it is not always possible to screen blood donors or perform standard viral testing prior to fresh whole blood transfusion, risking potential transmission of infectious diseases. In FY18, Colorado State University received a PRMRP TTDA for Dr. Raymond Goodrich to demonstrate the effectiveness of the Mirasol system, which uses riboflavin (R) and ultraviolet (UV) light to inactivate viruses, bacteria, parasites, and donor white blood cells and significantly decrease the risk of transmission. When the coronavirus disease 2019 (COVID-19) outbreak began, Dr. Goodrich and his team proved that use of the Mirasol system is also important for the civilian population.[1] Nine plasma products prepared from whole blood and three non-leukoreduced whole blood products were collected from an accredited blood bank. Whole blood products were shipped at room temperature, while plasma products were frozen within 24 hours and then shipped. The plasma and whole blood products were inoculated with SARS-CoV-2, the causative agent of COVID-19. Products had riboflavin solution added and were then treated with UV light, with dosage calculated by volume for the plasma and by hematocrit and volume for whole blood. Mean log reductions in viral titers, determined by comparing pre- and post-treatment samples, were ≥ 4.79 ± 0.15 in plasma and 3.30 ± 0.26 in whole blood, indicating that the Mirasol system is effective in reducing SARS-CoV-2 infectivity. Data from this study was used to inform blood handling guidelines globally. In further research, Dr. Goodrich and his team plan to elucidate mechanisms of inactivation by the Mirasol system for different pathogens to implement specific enhancements.



SARS-CoV-2 Cultures and Plaque Assay for Titer Determinations. (A) Left – Vero cells at confluency, uninfected; Right – SARS-CoV-2 infection in Vero cells. Three days after inoculation. Cytopathic effect (CPE) present. Cells at 40x magnification. (B) Plaque assay results from SARS-CoV-2 in media with R + UV treatment. Top left and right – Virus titration, pre-pathogen reduction; Bottom left – Pathogen reduction at 50 joules (J); Bottom right – Pathogen reduction at 100 J.

Development of a Highly Efficient Adsorber to Remove Anti-A and Anti-B Antibodies from Blood and Plasma for Transfusion

Maryann Gruda, Ph.D., CytoSorbents, Inc.

With support from an FY19 TTDA to CytoSorbents, Inc., Dr. Maryann Gruda is leading an effort to advance a novel blood group antibody (BGA) adsorption technology, HemoDefend-BGA, to a commercial device for FDA submission. Uncontrolled hemorrhage is a leading cause of trauma-related deaths, especially within the first 24 hours of injury, underscoring the critical need for universal plasma, which is not readily available in all military or civilian emergency settings. The most in-demand, universal plasma products are low titer O whole blood and plasma from individuals with AB blood, because they do not contain anti-A and anti-B antibodies that can bind to the recipient's red blood cells and potentially cause fatal hemolytic reactions. The HemoDefend-BGA adsorber filters and purifies blood by removing anti-A and anti-B antibodies while maintaining essential components like albumin, coagulation factors, red blood cells, and platelets. The commercialization of HemoDefend-BGA will allow for stabilization of and prolonged care for Warfighters with life-threatening hemorrhagic injuries without the need for blood typing.

HemoDefend-BGA Device.

[1] Ragan I, Hartson L, Pidcoke H, Bowen R, et al. 2020. Pathogen reduction of SARS-CoV-2 virus in plasma and whole blood using riboflavin and UV light. PLoS One 15(5):e0233947.

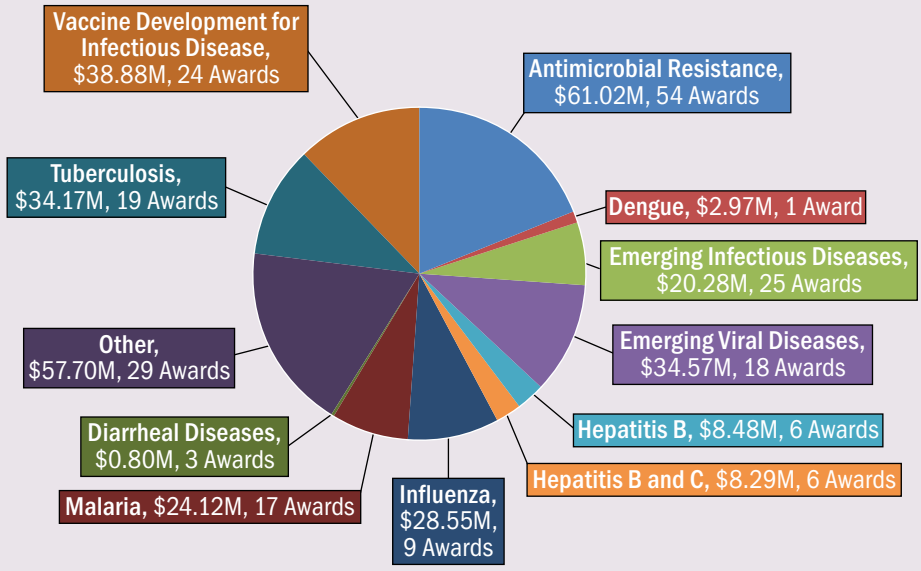
FY16–FY20 Topic Areas Funded

- Antimicrobial Resistance
- Dengue
- Diarrheal Diseases
- Emerging Infectious Diseases
- Emerging Viral Diseases
- Hepatitis B
- Hepatitis B and C
- Influenza
- Malaria
- Tuberculosis
- Vaccine Development for Infectious Disease

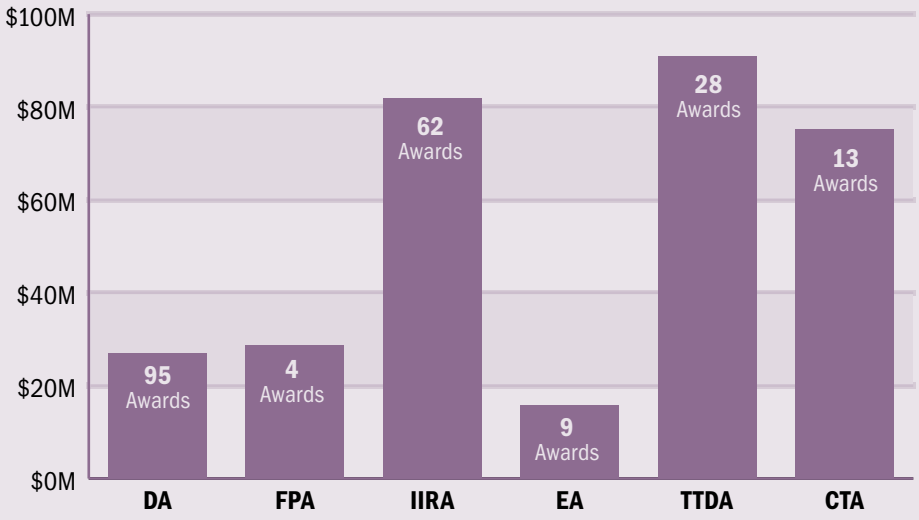
FY21 Topic Areas Offered

- Emerging Viral Diseases
- Hepatitis B
- Malaria
- Plant-Based Vaccines

INFECTIOUS DISEASES



FY16–FY20 Infectious Diseases Funding by Topic Area



FY16–FY20 Infectious Diseases Funding by Award Mechanism

Deployment-related exposures to pathogens can strain the immune defenses of Soldiers, making infectious diseases a major threat to the operational readiness of U.S. military forces. Civilian populations are vulnerable to local pathogens and are at risk of exposure to infectious diseases as a result of regional outbreaks and global pandemics. Research focusing on prevention, treatment, and diagnosis of infectious diseases is essential to maintaining the health of the military force and civilians. During FY16–FY20, the PRMRP funded 211 awards focused on infectious disease research ranging from foundational studies to clinical trials in a variety of bacterial, parasitic, and viral diseases totaling $319.8M.

RESEARCH HIGHLIGHTS

Development of Compounds That Expand the Spectrum of Antibacterial Agents against Multidrug-Resistant Gram-Negative Pathogens

Dr. Michael Pucci, Ph.D., Spero Therapeutics

To address the emergence of multidrug resistance related to infections caused by Gram-negative bacteria, Spero Therapeutics previously identified a class of novel polymixin analogs with bacterial membrane-disrupting properties that were shown to enhance the use of antibiotics against these pathogens. In FY15, Spero Therapeutics was awarded a TTDA for Dr. Michael Pucci to investigate the therapeutic potential of several polymyxin analogs to potentiate potent Gram-positive antibiotics to address Gram-negative pathogen multidrug resistance. Pharmacodynamic studies of a top antibiotic potentiator, SPR741, in combination with azithromycin (AZM) against Gram-negative pathogens revealed enhanced efficacy of AZM against Gram-negative bacteria. Dr. Pucci's team also characterized SPR206, another polymyxin analog, which acted not only as an antibiotic potentiator but also had direct antibacterial activity against Gram-negative pathogens, such as *Pseudomonas aeruginosa*. This eliminated the need for a partner antibiotic. Furthermore, potency studies revealed that SPR206 is more potent than traditionally administered polymyxins and displayed reduced toxicity. Dr. Pucci and his team are continuing the clinical development of SPR206 with funds from the Joint Warfighter Medical Research Program (JWMRP), which involves two phase 1 clinical trials and toxicity studies involving non-human primates (NHP).

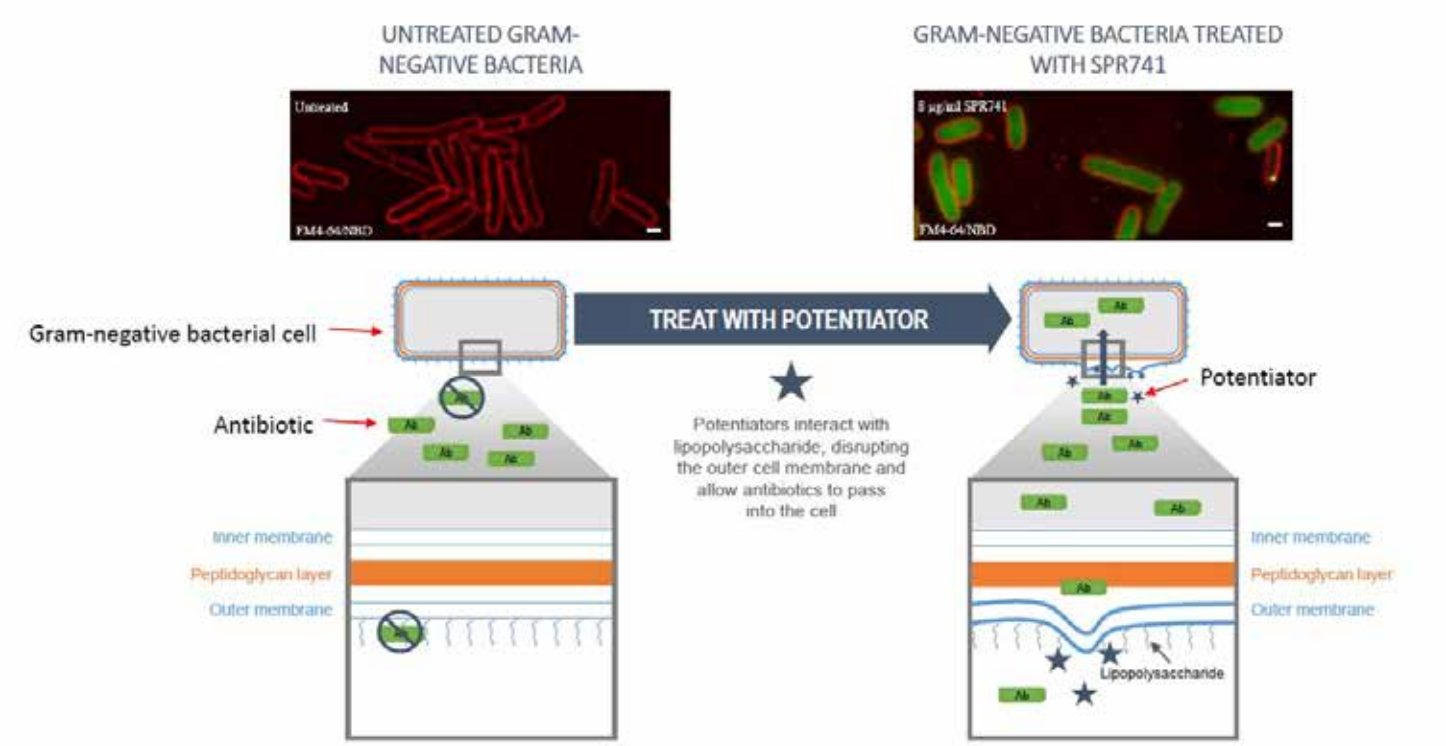
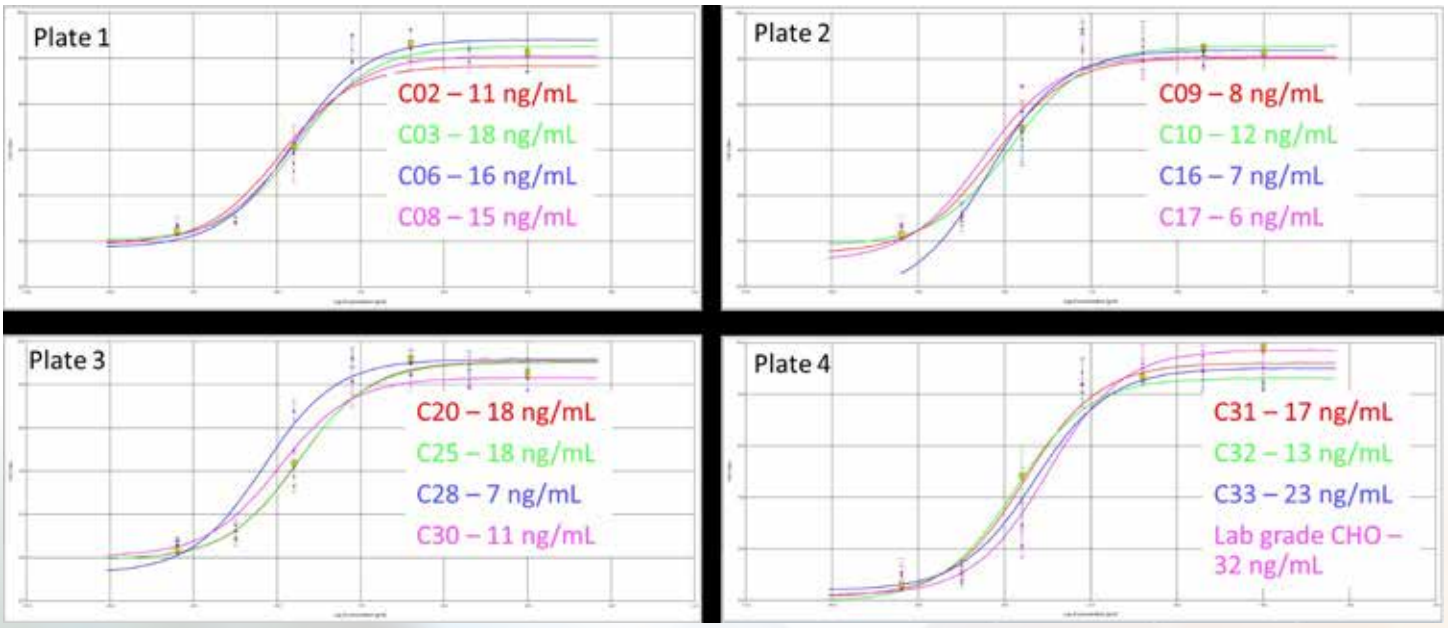


Diagram of potentiator mechanism of action: drug alone (left) and drug plus potentiator (right).

Development of a Monoclonal Antibody for the Prevention and Treatment of Zika Virus Infection

Charles Haines, Ph.D., IDBiologics, Inc.

Zika virus (ZIKV) infection can cause symptoms lasting days to weeks and is most notably known to cause debilitating and lifelong birth defects due to infection during pregnancy. Currently, there are no effective vaccines or protective strategies against ZIKV infection. Through an FY18 TTDA to IDBiologics, Inc., Dr. Charles Haines is conducting preclinical studies using a human monoclonal antibody (mAb), IDB002, which has previously shown neutralizing activity against ZIKV and protection in pregnant mouse and NHP challenge models. The goal of this study is to develop Good Manufacturing Practices (GMP)-quality material for pharmacokinetic and toxicology testing in a small animal model to determine safety and dosing. Dr. Haines' team verified in vitro binding of Chinese hamster ovary cell clone-derived IDB002 and confirmed its neutralization activity. The efficacy of GMP-like manufactured IDB002 will be tested in a ZIKV challenge mouse model, and its ability to protect against infection will be investigated through dose range studies. The results from this study may indicate that IDB002 can be used as a medical countermeasure that can be administered prophylactically or at the very early stages of infection, which would provide protection to Service Members, travelers, and populations in endemic regions.

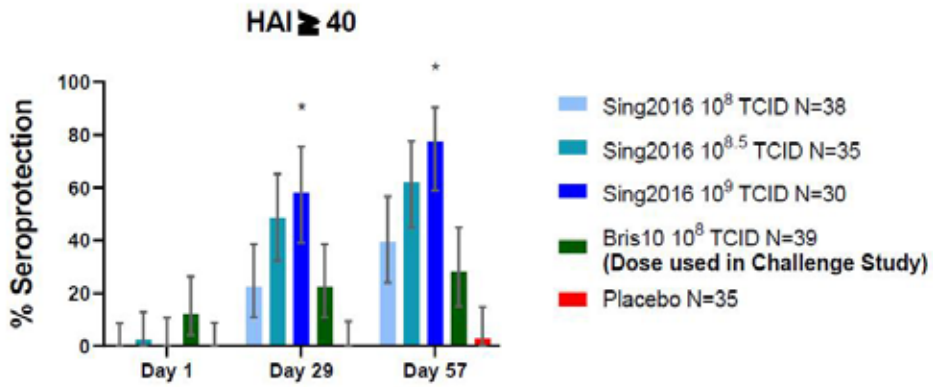


Results from Zika virus neutralization assay, which confirm the functional activity of Chinese hamster ovary (CHO) cell-derived IDB002 antibody material.

Live Influenza Vaccine with Universal Attributes

Pamuk Bilsel, Ph.D., FluGen, Inc.

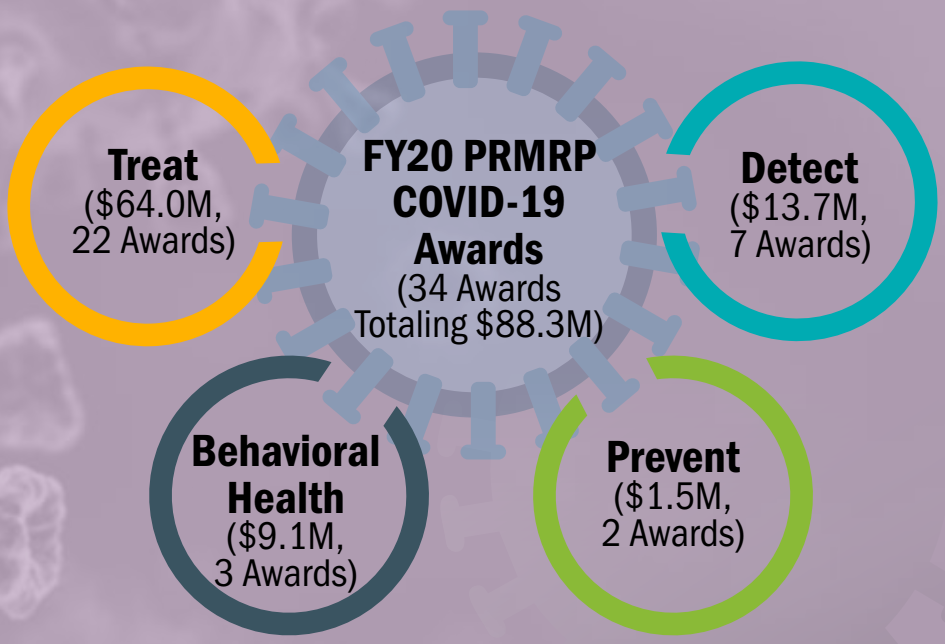
FluGen has developed an alternative live attenuated influenza vaccine to address efficacy issues with current, seasonal influenza vaccines and potentially generate universal protection against disease. Their M2-deficient single replication (M2SR) vaccine platform initiates infection similar to a wild-type influenza virus, and thus induces a full immune response, without the ability to replicate or spread. An FY16 CTA to FluGen, Inc., naming Dr. Pamuk Bilsel as the Principal Investigator (PI), supported a double-blind, placebo controlled phase 2 challenge study in healthy adults. The trial showed that a single intranasal dose of M2SR vaccine produced serum antibody responses in more than half of the treated (i.e., non-placebo) participants. Responders who developed cross-reactive serum microneutralization titers showed reduced viral loads and symptoms after a highly mismatched viral challenge (2007 flu season strain vaccine versus 2014 flu season strain challenge). In a subsequent phase 1b trial, a higher dose level of M2SR induced protective immune responses in a significantly greater proportion of adults as shown in the figure below, indicating the potential for greater protection than that observed in the challenge study. FluGen also received an FY20 CTA to support a randomized double-blind, placebo-controlled phase 1b clinical trial (again led by Dr. Bilsel) of H3N2 M2SR in adults 65 years and older to evaluate cross-reactive immune responses in comparison to standard vaccines commonly used in older adults.

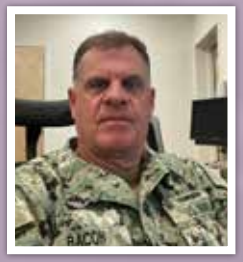


Serum hemagglutination-inhibition (HAI; i.e., seroprotection) responses following 1 (Day 1) and 2 (Day 29) intranasal doses of M2SR or placebo.

COVID-19 RESPONSE

In response to the COVID-19 pandemic, the PRMRP invested $78.3M using FY20 funding opportunities specifically targeted to support COVID-19 research under the topic areas of Emerging Viral Diseases and Respiratory Health. These COVID-19-targeted funding opportunities are supporting 24 awards that include clinical trials, advanced development of targeted drugs for potential treatments, and drugs to treat the life-threatening lung injuries associated with COVID-19. The PRMRP invested an additional $10.0M into 10 COVID-19-related awards that were funded through its traditional FY20 funding opportunities.





"The PRMRP supports basic through applied research across a number of topics areas that directly impacts the welfare of the active-duty Warfighter, retirees, and beneficiaries. Without this support, many of the medical needs would go unmet. As the battlefield of the future and medical requirements change, the ability of PRMRP to shape the research priorities and invest in new areas of encouragement will allow for the development of devices, new therapies, and monitoring systems that will be ready to support the forces immediately. The agility of the program will save lives on the battlefield and provide better quality of life to those most affected."

CAPT David Bacon, Ph.D.,
Military Infectious Diseases Research Program
FY21 PRMRP Programmatic Panel Member

RESEARCH HIGHLIGHTS

Development and Advancement of Broad-Spectrum Respiratory Antivirals

Sumit Chanda, Ph.D., Sanford Burnham Prebys Medical Discovery Institute

With support from an FY19 FPA to Sanford Burnham Prebys Medical Discovery Institute, Dr. Sumit Chanda is leading an effort toward the Development and Advancement of Broad-Spectrum Respiratory Antivirals (DABRA) that target host cell factors for viral replication or activate components of the innate immune response. Four early-stage small molecules with broad-spectrum antiviral activity will be investigated with the hope of rapidly moving several candidates into clinical studies. The overall goal of DABRA is the development of broad-spectrum inhibitors, creating a new, paradigm-shifting standard of care. These antivirals will effectively treat infections caused by multiple respiratory viruses that impact military readiness, including influenza, coronaviruses, human rhinoviruses, respiratory syncytial virus, and adenoviruses. Dr. Chanda and his team are also testing lead compounds for activity against SARS-CoV-2 replication both in vitro and in vivo. If successful, these efforts would lead to the development of a groundbreaking new class of antiviral therapeutics for a wide range of infectious diseases, including those with pandemic potential.

Development of BIO 300 Oral Powder: An Encapsulated Nanogenistein Therapy

Michael Kaytor, Ph.D., Humanetics Corporation

BIO 300 is a current countermeasure that has demonstrated efficacy against the long-term damaging effects of radiation exposure in cancer patients and is currently used by those patients as an orally administered drug. Lung injury due to COVID-19, which has been reported in as many as 50% of patients at the time of hospital discharge, appears similar to lung injury caused by radiation therapy. An FY16 PRMRP TTDA to Humanetics Corporation, led by Dr. Michael Kaytor, resulted in the identification of a dry, solid dosage form that is amenable to a solid dosing form (tablet, capsule, etc.) to better suit the needs of deployed Warfighters. This project received additional funding from the Joint Warfighter Medical Research Program for the continued development and scaling-up of BIO 300. Additionally, Dr. Kaytor has overseen the development of BIO 300 as a therapy for COVID-19 with a clinical trial supported by the National Institute of Allergy and Infectious Diseases, as well as an FY20 PRMRP EA in response to the COVID-19 targeted program announcements. These studies by Dr. Kaytor and his team highlight the progress toward essential treatments for lung fibrosis, especially due to emerging threats such as COVID-19 infection, which could ultimately benefit both U.S. military personnel and the American public.

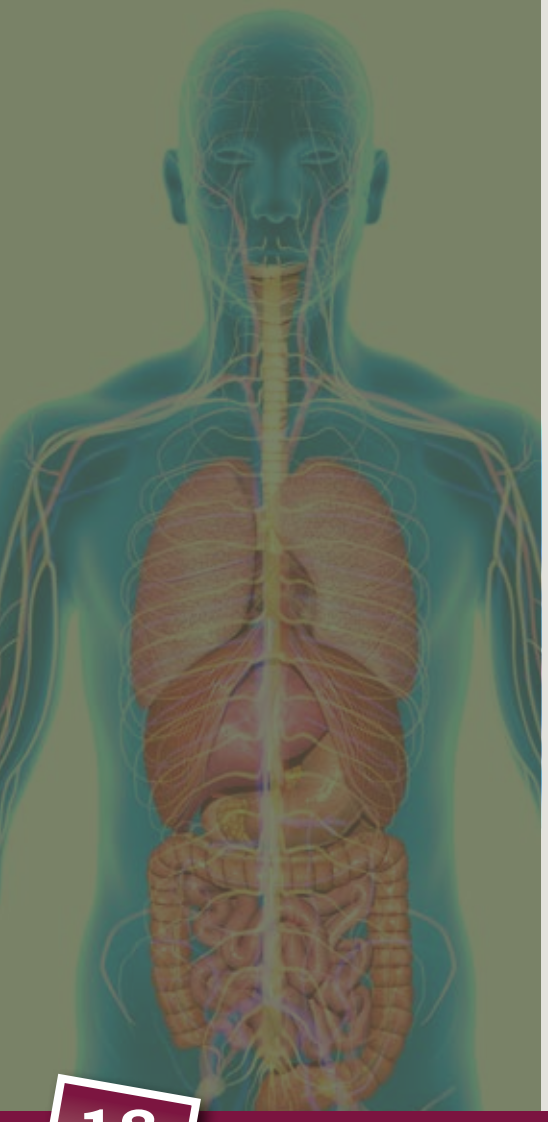
BIO 300 Oral Suspension.

FY16–FY20 Topic Areas Funded

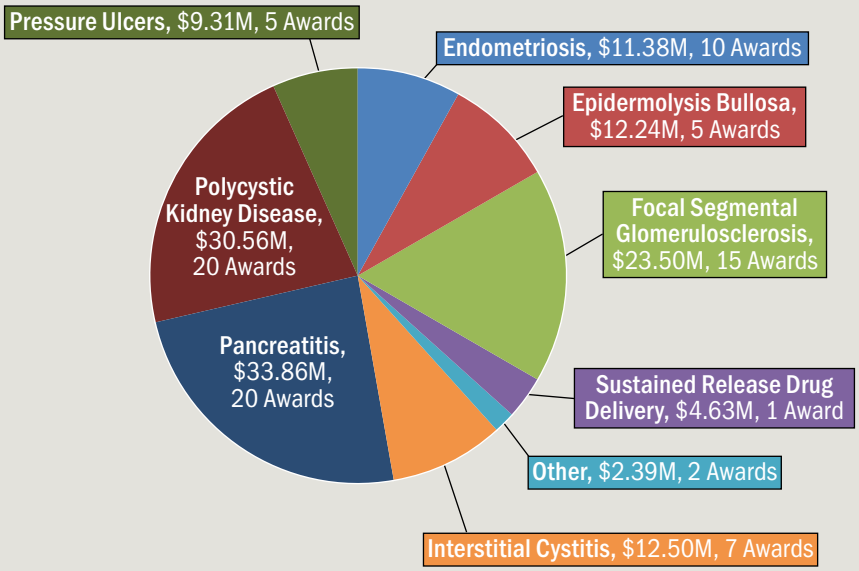
- Endometriosis
- Epidermolysis Bullosa
- Focal Segmental Glomerulosclerosis
- Interstitial Cystitis
- Pancreatitis
- Polycystic Kidney Disease
- Pressure Ulcers

FY21 Topic Areas Offered

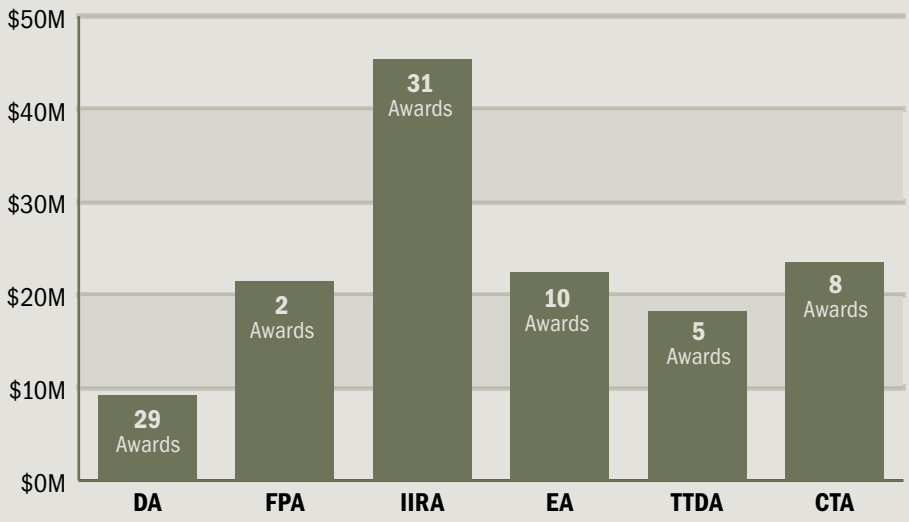
- Endometriosis
- Epidermolysis Bullosa
- Focal Segmental Glomerulosclerosis
- Polycystic Kidney Disease
- Pressure Ulcers



INTERNAL MEDICINE



FY16–FY20 Internal Medicine Funding by Topic Area



FY16–FY20 Internal Medicine Funding by Award Mechanism

The PRMRP's Internal Medicine portfolio spans research addressing diseases and conditions that are disqualifying for service in the U.S. military and represent a major threat to the operational readiness and health of Warfighters and Veterans. These diseases affect the families and dependents of Service Members and Veterans, can impact Warfighter morale, and are a major contributor of Military Health System spending. To address the influence of this diverse group of diseases and conditions on military and civilian populations, the PRMRP Internal Medicine portfolio supports research across the continuum of care. During FY16–FY20, the PRMRP funded 85 awards that will aid in the understanding, diagnosis, and treatment of these diseases totaling $140.4M.

RESEARCH HIGHLIGHTS

Using Affinity-Based Proteomics to Identify Diagnostic and Plasma Biomarkers for Endometriosis

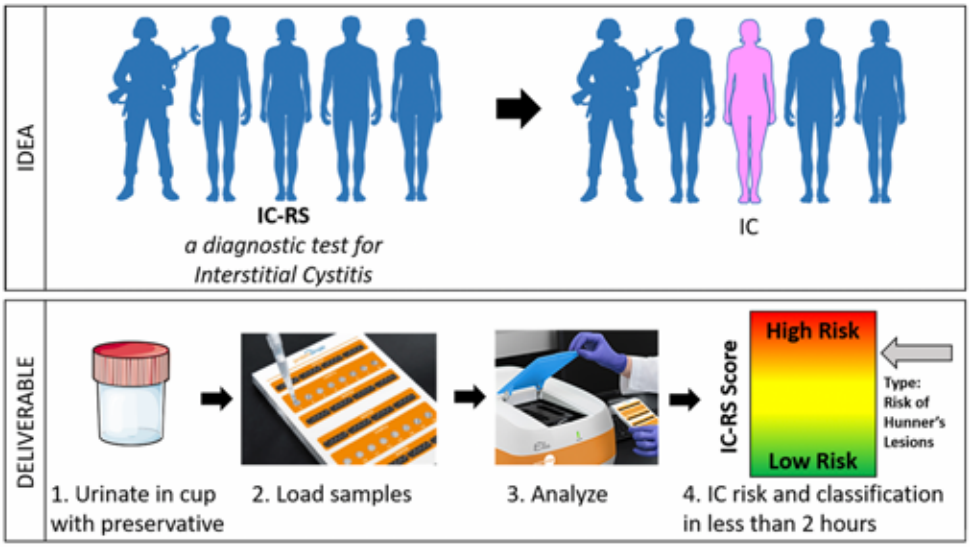
Kathryn Terry, Sc.D., Brigham and Women's Hospital
Towia Libermann, Ph.D., Beth Israel Deaconess Medical Center

On average, it takes 7 years from the onset of symptoms for women to receive an endometriosis diagnosis. Identification of non-invasive diagnostic and prognostic biomarkers of endometriosis has been challenging due to the heterogeneity of the disease and limited access to prospectively collected samples. Drs. Kathryn Terry and Towia Libermann, with support from an FY18 IIRA-PPIO to Brigham and Women's Hospital and Beth Israel Deaconess Medical Center, respectively, are addressing this diagnostic gap by utilizing SOMAscan®, a novel proteomics technology, and specimens collected from two sources: the Nurses' Health Study II, a prospective cohort study, and the Women's Health Study: Adolescent to Adulthood (A2A), a deeply phenotyped longitudinal cohort of endometriosis patients. In the A2A samples, Drs. Terry and Libermann have identified 155 proteins that are differentially expressed in women with endometriosis compared to matched healthy controls. Principal Component Analysis demonstrated that the top 20 differentially expressed proteins could reliably differentiate women with endometriosis from healthy controls. Future work will include analyses of plasma proteins that are candidate biomarkers for early diagnosis of endometriosis and identification of proteins capable of distinguishing endometriosis subtypes. If successful, this project will identify non-invasive diagnostic and prognostic clinical biomarkers that will reduce time to diagnosis of endometriosis as well as provide a biological insight into the heterogeneity of the disease.

Deployable Interstitial Cystitis Urine Diagnostic Technology Development

Bernadette Zwaans, Ph.D., William Beaumont Hospital Research Institute

With support from an FY18 TTDA to the William Beaumont Hospital Research Institute, Dr. Laura Lamb is optimizing and validating a novel diagnostic tool, the Interstitial Cystitis Risk Score (IC-RS). This tool utilizes a machine learning algorithm to identify and classify Interstitial Cystitis (IC) disease based solely on urine samples and patient symptom scores. Dr. Lamb hypothesizes that IC represents an inflammatory disease etiology that presents with pain symptoms and can be detected through specific biomarkers in the urine. Using machine learning, the IC-RS was developed to serve as a valid clinical test for detection of IC urine biomarkers and may provide valuable measurements for therapy evaluation. The team plans to test urine samples from as many people as possible, in both the civilian and military communities across the country. Dr. Lamb and colleagues have begun recruitment, utilizing social media as well as patient advocacy groups, and clinical collection of urine samples from IC patients. If successful, the IC-RS will have the potential to accurately diagnosis IC at an early stage, leading to better prognosis and improved physical and psychological well-being for patients.

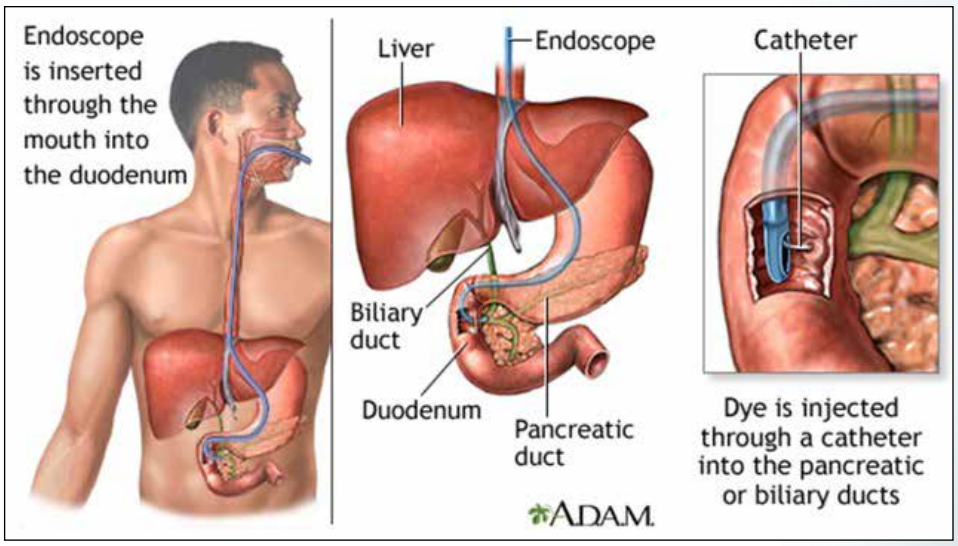


Idea, approach, and deliverable of the deployable IC urine diagnostic technology.

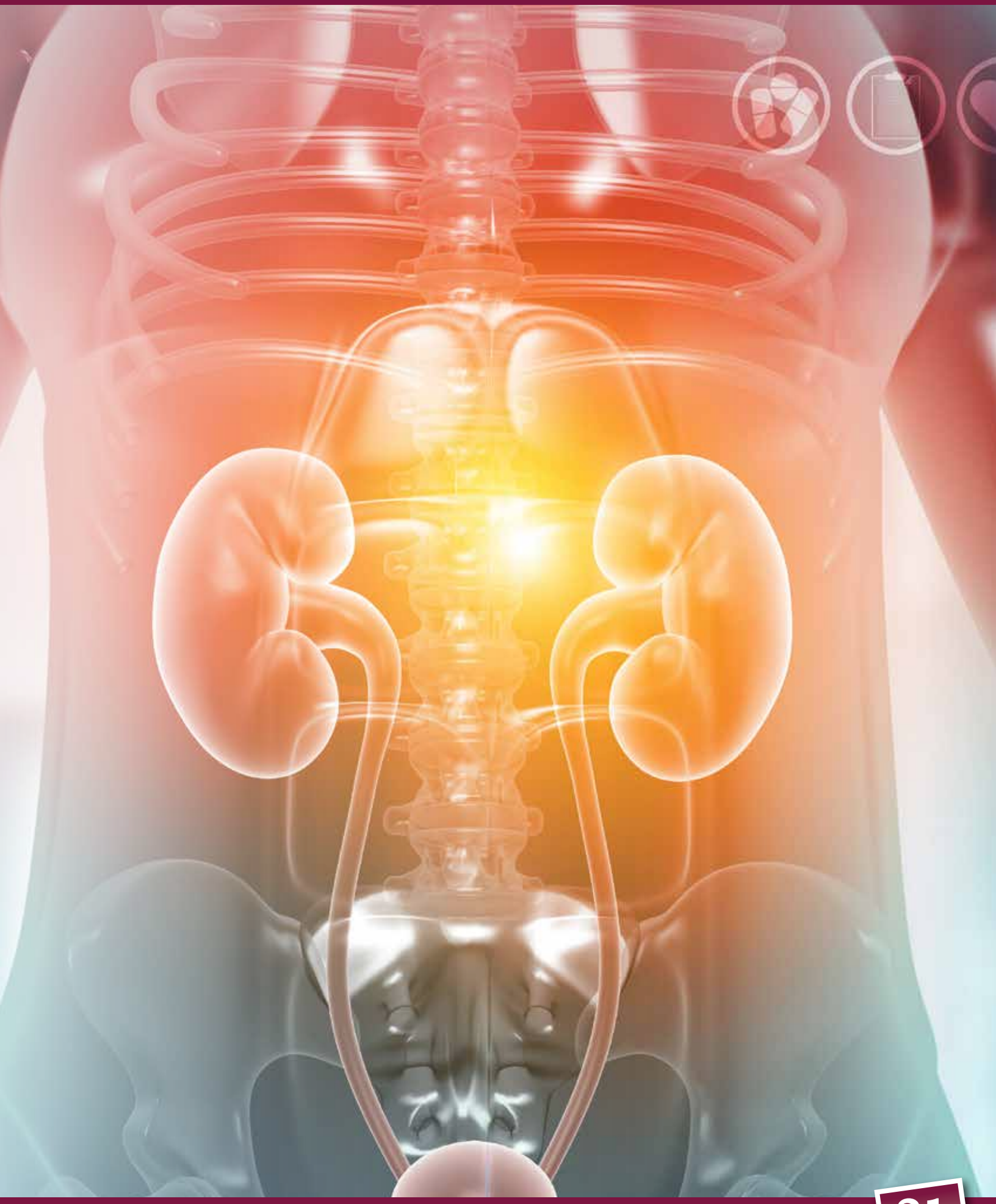
Optimizing a Novel Intraductal Delivery of Calcineurin Inhibitors as a Radiocontrast Infusion Formulation to Prevent Post-ERCP Pancreatitis

Sohail Husain, M.D., The Leland Stanford Junior University

While endoscopic retrograde cholangiopancreatography (ERCP) can be a life-saving emergency gastrointestinal procedure, the patient may develop a painful, potentially lethal inflammatory disorder called post-ERCP pancreatitis (PEP). Researchers speculate that pressure buildup within the pancreatic duct after the ERCP is likely the primary cause of PEP. Current prevention measures, such as excess hydration, anti-inflammatory agents, and stents, cannot fully inhibit the development of PEP. The PRMRP awarded an FY18 TTDA to The Leland Stanford Junior University, naming Dr. Sohail Husain as the PI, to formulate a novel preventative formulation for ERCP that can inhibit the calcineurin (CaN) signaling pathway, thereby preventing the development of PEP at a molecular level. Systemic safety studies of two CaN inhibitor formulations, Tacrolimus radiocontrast (Tac-RC) and Cyclosporin A (CsA)-RC, have been conducted in mice, and results showed that neither formulation caused endocrine toxicity. The investigators also found that the Tac formulation did not cause acute or subacute systemic toxicity. These early results provide evidence to support testing of the CaN inhibitor formulations in additional preclinical models and novel routes of administration. If proven safe and effective, Dr. Husain and colleagues hope that these novel formulations could become the new standard of care for preventing PEP.



Schematic of ECRP: Electric current is injected into the pancreatic duct or common bile duct.



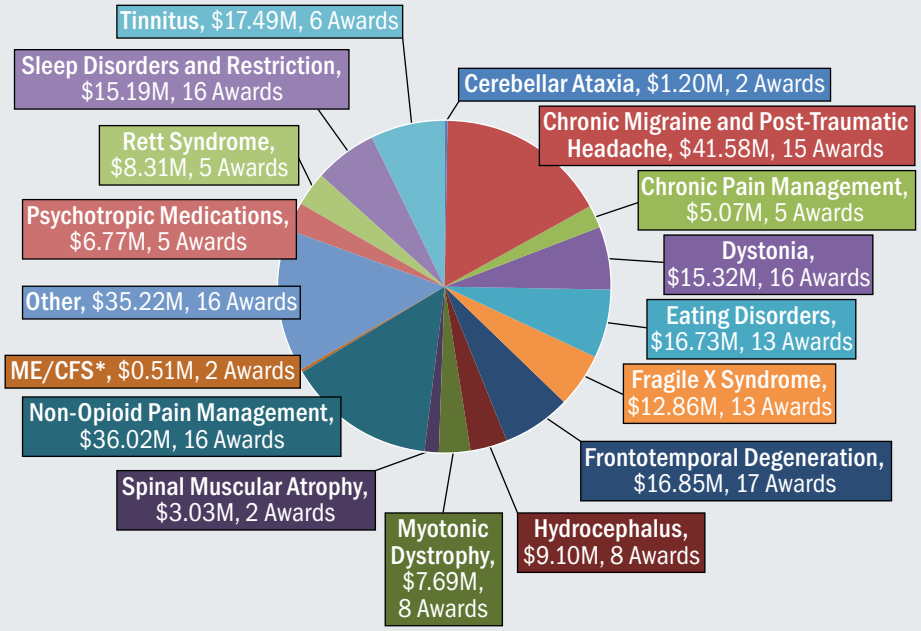
FY16–FY20 Topic Areas Funded

- Cerebellar Ataxia
- Chronic Migraine and Post-Traumatic Headache
- Chronic Pain Management
- Dystonia
- Eating Disorders
- Fragile X
- Frontotemporal Degeneration
- Hydrocephalus
- Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome
- Myotonic Dystrophy
- Non-Opioid Pain Management
- Psychotropic Medications
- Rett Syndrome
- Sleep Disorders and Restriction
- Spinal Muscular Atrophy
- Tinnitus

FY21 Topic Areas Offered

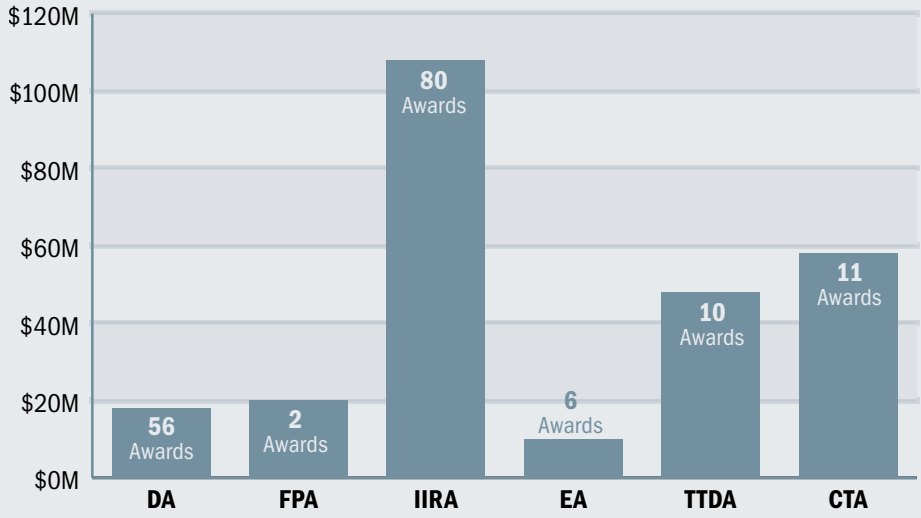
- Dystonia
- Eating Disorders
- Fragile X
- Frontotemporal Degeneration
- Hydrocephalus
- Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome
- Myotonic Dystrophy
- Non-Opioid Therapy for Pain Management
- Peripheral Neuropathy
- Sleep Disorders and Restriction
- Suicide Prevention

NEUROSCIENCE



FY16–FY20 Neuroscience Funding by Topic Area

* Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)



FY16–FY20 Neuroscience Funding by Award Mechanism

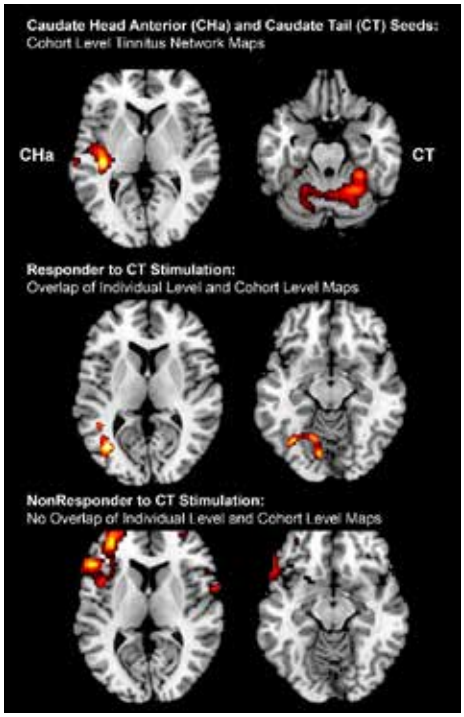
Deployed Service Members are at an increased risk of neurological injuries, with traumatic brain injury (TBI) becoming a signature injury of modern military conflicts. Additionally, the unique and extreme mental challenges Service Members endure during deployment places their psychological health at risk. The PRMRP Neuroscience portfolio supports research focusing on understanding, preventing, and treating neurological and psychological diseases and conditions that can lead to improvements in the health and quality of life of Service Members, Veterans, and civilian populations. During FY16–FY20, the PRMRP funded 165 awards addressing neurological and psychological health issues totaling $248.9M.

RESEARCH HIGHLIGHTS

Neuroimaging-Based Objective Diagnostic Tool to Detect Subjective Tinnitus

Steven W. Cheung, M.D., University of California, San Francisco

Tinnitus is an auditory medical condition defined by the perception of ringing, buzzing, hissing, and other sounds in one or both ears, despite the absence of an actual external sound. Although tinnitus is the most prevalent Service-connected disability for Veterans, there are no objective tools to detect, diagnose, or guide treatment. With support from an FY17 TTDA, Dr. Steven Cheung and collaborators at the University of California, San Francisco and the University of Minnesota are developing a multimodal neuroimaging-based tool to detect and monitor subjective tinnitus that would be suitable for broad clinical deployment. By using resting-state functional magnetic resonance imaging (fMRI) connectivity maps of caudate nucleus subdivisions, brain modulation treatment for tinnitus can be enhanced. Dr. Cheung and his team are currently developing the non-invasive brain imaging tool and have been recruiting participants since April 2019. They have demonstrated proof-of-principle results that support using this tool in individual tinnitus patients. Once fully validated, this technology could be used to confirm a tinnitus diagnosis, monitor response to treatment, guide preclinical studies, and personalize therapeutics.



Striatal-based tinnitus neuromodulation treatment response differences arise from individual level variations in striatal network as detected by resting-state fMRI.

Optimization of Selective M4 Muscarinic Receptor Antagonists for Treatment of Dystonia

P. Jeffrey Conn, Ph.D., Vanderbilt University

Dystonia is a debilitating brain disorder causing painful, disabling movements for which there are few available treatments. Among the few effective pharmacological treatments for dystonia are antagonists that inhibit the function of receptors for acetylcholine (Ach), a neurotransmitter in the brain. These receptors, specifically muscarinic acetylcholine receptors (mAChR), are critical for the communication between brain cells in the regions of the brain that control motor function. Unfortunately, current mAChR antagonists block mAChRs in virtually all brain regions and in other body systems. Because of this, no current treatments for dystonia achieve symptom relief without inducing severe adverse effects. Recent research indicates that a specific subtype of mAChR, involving the M4 receptor, may play a dominant role in regulating motor function specific to dystonia. Dr. P. Jeffrey Conn has successfully identified a lead series of M4-specific mAChR antagonists with promising pharmaceutical properties that could potentially avoid the adverse effects of other non-specific mAChR antagonists. Through an FY18 TTDA to Vanderbilt University, Dr. Conn is optimizing these compounds and testing them in a new, validated mouse model of dystonia. His research team has made significant progress in optimizing new M4 antagonists and establishing their molecular pharmacology and pharmacokinetic profiles. They hope to further optimize the lead candidate and receive Investigational New Drug (IND) approval by the FDA to begin clinical testing.

Targeting Food Cue Reactivity and Satiety Sensitivity to Decrease Binge Eating and Weight

Kerri Boutelle, Ph.D., University of California, San Diego

Binge eating disorder and obesity affect both Service Members and Veterans, impairing military readiness and increasing medical costs both during and after military Service. While binge eating disorder can be treated effectively with cognitive behavioral therapy, patients with comorbid obesity rarely have significant weight loss following reductions in binge eating. Dr. Kerri Boutelle and her team developed a new treatment model specifically targeted toward treatment of binge eating disorder and comorbid obesity: Regulation of Cues (ROC). ROC treatment targets improving responsiveness to internal hunger cues as well as decreasing responsiveness to external food cues, and preliminary studies demonstrated feasibility and acceptability of ROC in adults as well as in children. With support from an FY17 CTA to the University of California, San Diego, Dr. Boutelle and her team are evaluating the feasibility, acceptability, and efficacy of ROC in reducing binge eating and weight in Veterans as compared to cognitive behavioral therapy. They are also evaluating moderators and mediators of treatment outcomes, such as responding to food cues and reward-based eating. If proven acceptable and efficacious, ROC would become the first treatment for treatment of binge eating disorder and comorbid obesity.

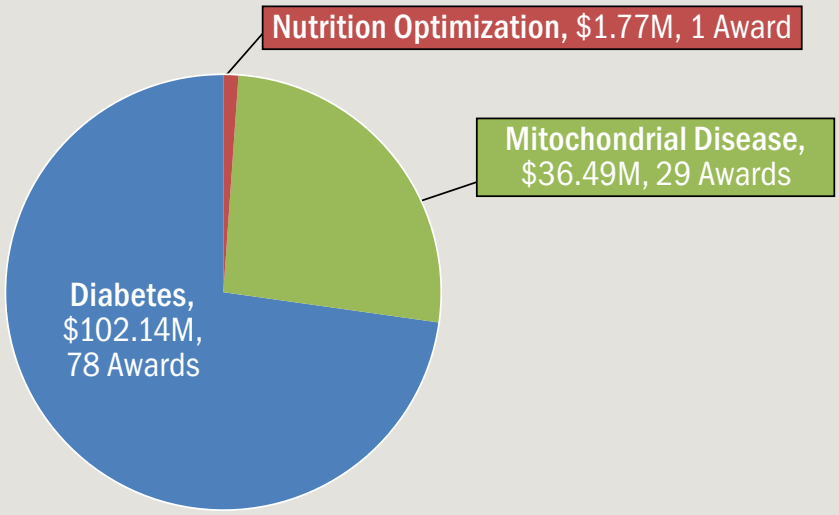
NUTRITION AND METABOLISM

FY16–FY20 Topic Areas Funded

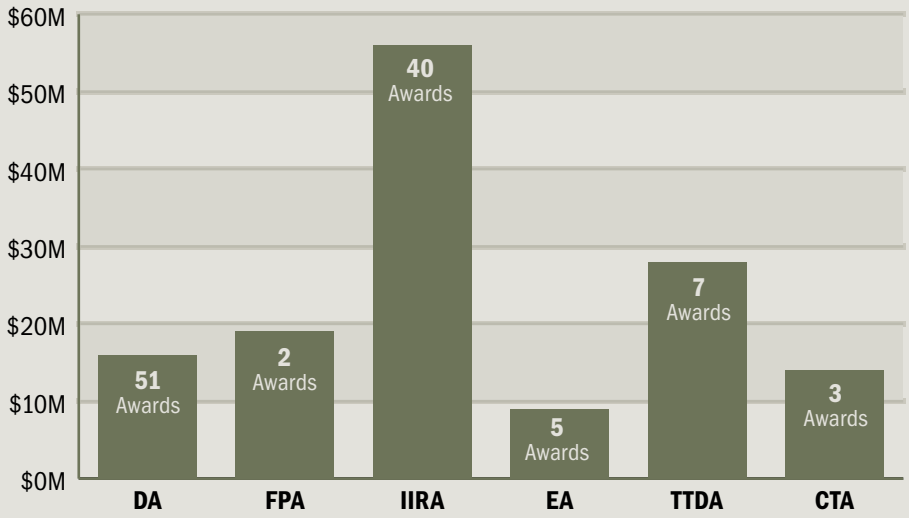
- Diabetes
- Mitochondrial Disease
- Nutrition Optimization

FY21 Topic Areas Offered

- Diabetes
- Mitochondrial Disease
- Nutrition Optimization

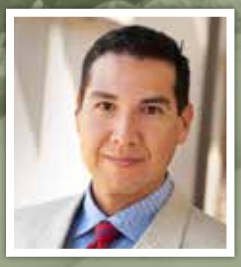


FY16–FY20 Neuroscience Funding by Topic Area



FY16–FY20 Neuroscience Funding by Award Mechanism

The PRMRP Nutrition and Metabolism portfolio covers chronic diseases and conditions, such as diabetes, one of the most common forms of prolonged disease in the United States, and mitochondrial diseases, which can result in significant functional declines for diagnosed individuals. Additionally, Service Members and Veterans are at a higher risk of injury and illness during deployments, making nutrition optimization that enhances recovery and rehabilitation an integral part of increasing operational readiness. During FY16–FY20, the PRMRP funded 108 awards related to nutrition and metabolism totaling $140.4M.



"To know that there are so many brilliant minds across the nation working on a goal of eradicating diabetes makes me feel humbled yet proud to be a part of something that is so vitally important for everyone."

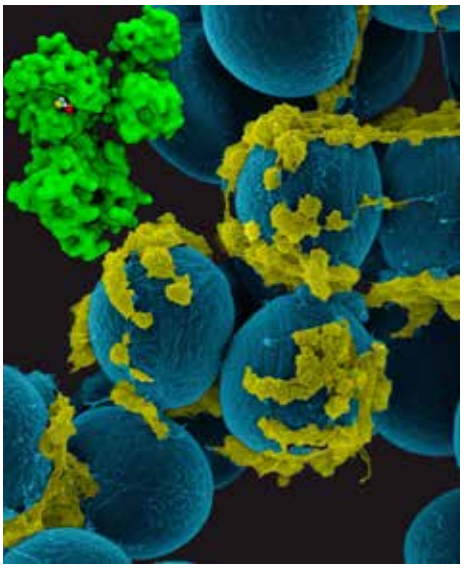
Dr. Lancer Stephens,
American Diabetes Association
FY21 PRMRP Consumer Peer Reviewer

RESEARCH HIGHLIGHTS

(R)-ND-336 for the Treatment of Diabetic Foot Ulcers

Mayland Chang, Ph.D., University of Notre Dame

Diabetes affects more than 30 million individuals in the United States. Approximately 25% of Veterans receiving care from the Department of Veterans Affairs (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. Dr. Mayland Chang is supported by an FY18 TTDA to the University of Notre Dame for the 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. 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.



The selective matrix metalloproteinase 9 (MMP-9) inhibitor, (R)-ND-336, bound to a computational model of active MMP-9 with scanning electron microscopy image of Staphylococcus epidermidis in the background (magnification 100,000). DFUs are recalcitrant to healing due to the presence of upregulated active MMP-9, which increases with infection and wound severity. (R)-ND-336 accelerates wound healing in S. epidermidis-infected diabetic mice.

Treatment Strategies for Mitochondrial Disease

Michio Hirano, M.D., Columbia University Medical Center

Mitochondrial diseases are among the most common inherited metabolic disorders and characteristically present as severe multisystem conditions that can be lethal. However, there are still significant challenges to finding rational treatments for these disorders due to the incomplete understanding of disease pathogenesis and limited number of informative preclinical therapeutic studies. Building upon the strength of the Columbia University Medical Center mitochondrial research team, Dr. Michio Hirano and colleagues aim to advance therapeutic strategies through five integrated and synergistic projects with the support of an FY19 PRMRP FPA to Columbia University Medical Center. Dr. Hirano has assembled a team of skilled investigators to lead these distinct but interconnected projects, ranging from basic biology to a clinical trial, with the ultimate goal of treating mitochondrial disorders. These projects focus on mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), as well as the necessity of preclinical optimization of gene therapies, and the relationship between oxidative energy metabolism and cellular behavior. More specifically, one of the projects will build upon a 20-year effort to document the natural history of MELAS by initiating a clinical trial to assess the role of N-acetyl cysteine in mitigating the severity of this mitochondrial disease and assess biomarkers. This FPA will address important gaps in the understanding of the pathophysiology of mitochondrial diseases and the unmet need for therapies.

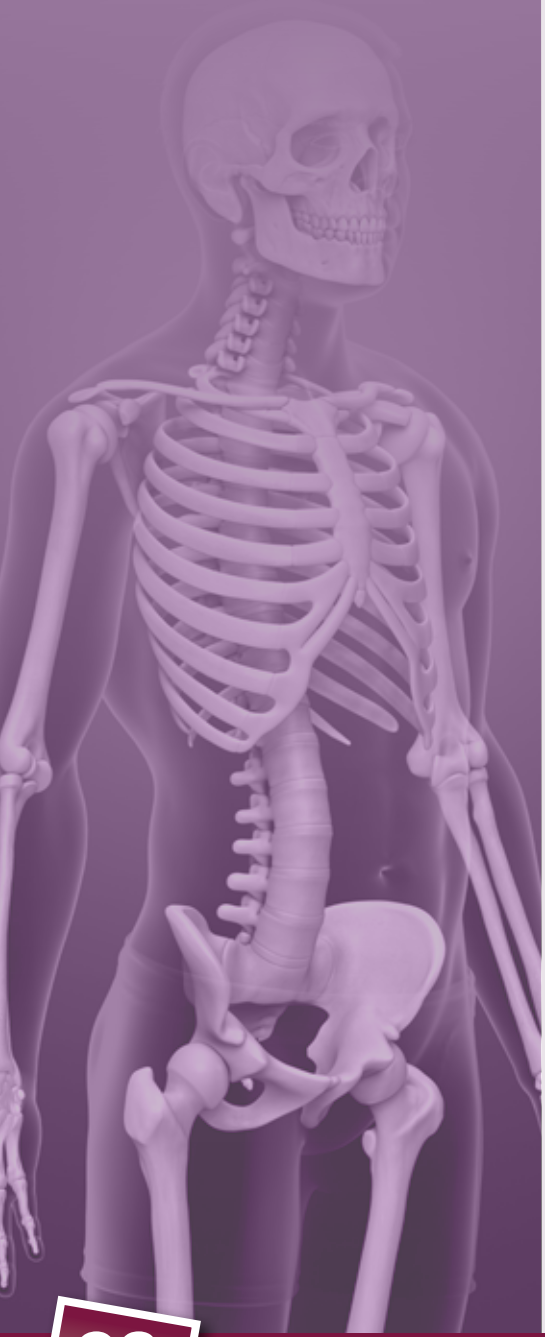
ORTHOPAEDIC MEDICINE

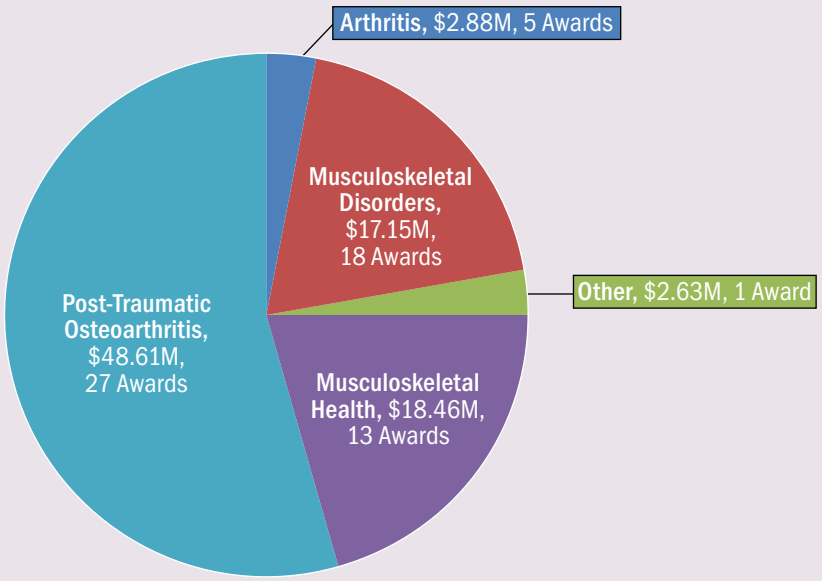
FY16–FY20 Topic Areas Funded

- Arthritis
- Musculoskeletal Disorders
- Musculoskeletal Health
- Post-Traumatic Osteoarthritis

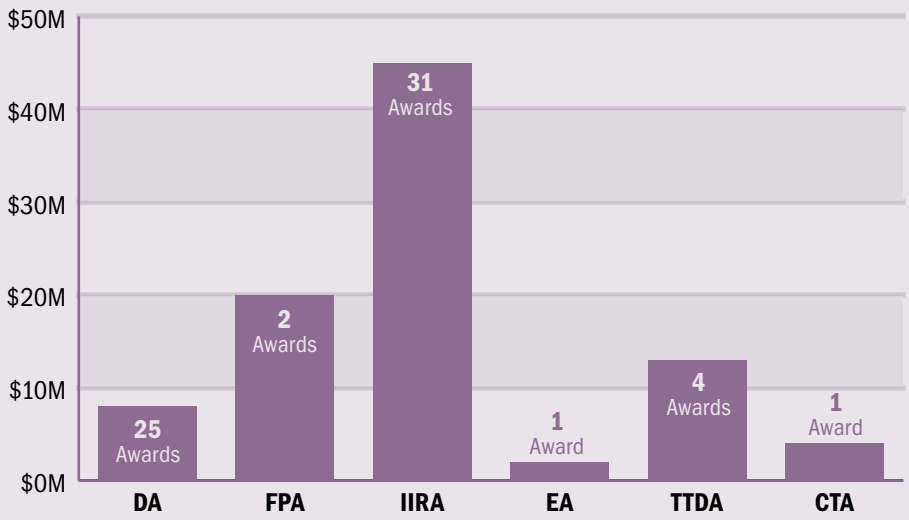
FY21 Topic Areas Offered

- Arthritis
- Fibrous Dysplasia





FY16–FY20 Orthopaedic Medicine Funding by Topic Area



FY16–FY20 Orthopaedic Medicine Funding by Award Mechanism

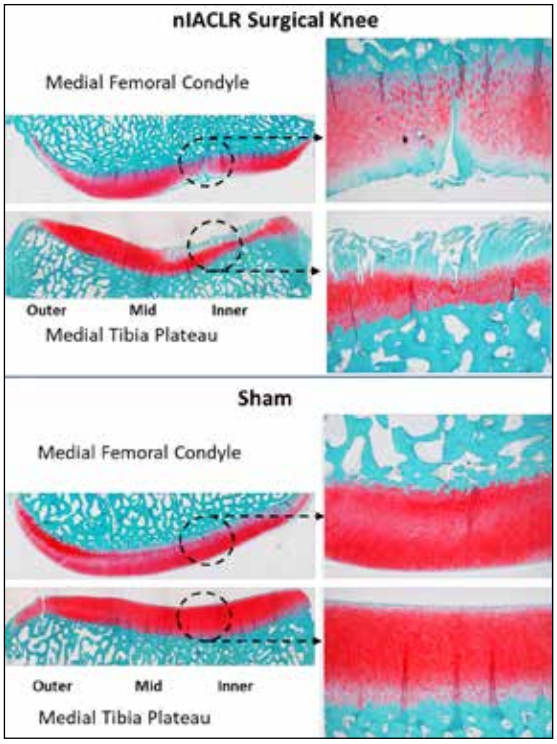
Because of advances in protective gear and deployed field care, high numbers of Service Members are able to survive traumatic injuries sustained in combat. However, Service Members who recover from these injuries are at an increased risk for developing chronic conditions like musculoskeletal disorders and arthritis. The PRMRP Orthopaedic Medicine portfolio supports research in topic areas that focus on reconstruction and definitive care of a spectrum of combat and civilian injuries, with the goal of enhancing recovery, reducing disability, and increasing quality of life for affected individuals and their families. During FY16–FY20, the PRMRP funded 64 awards related to orthopaedic medicine totaling $89.7M.

RESEARCH HIGHLIGHTS

Intra-Articular Injection of Alpha-2-Macroglobulin Prevents Post-Traumatic Osteoarthritis

Lei Wei, M.D., Rhode Island Hospital

According to the U.S. Centers for Disease Control and Prevention, osteoarthritis (OA) is one of the leading causes of disability in the United States, affecting over 32.5 million U.S. adults. OA is caused by damage and eventual loss of cartilage in the joints, and post-traumatic osteoarthritis (PTOA) is OA that develops after joint injury. PTOA accelerates the degeneration of the cartilage (within 3 years) following military-relevant joint injuries. Through an FY18 IIRA to Rhode Island Hospital, Dr. Lei Wei is studying the translation of an Alpha-2-Macroglobulin (A2M) injectable therapy for the prevention of PTOA. Dr. Wei and his team are conducting studies using a mini-pig model of PTOA to determine whether early administration of A2M injections attenuates PTOA pathogenesis after an intra-articular joint injury involving anterior cruciate ligament and improves joint function determined by gait assessment. The research team will also explore the mechanism through which A2M inhibits cartilage catabolism in vitro. This study's success could be the next step toward a therapy to improve the quality of life for active-duty military personnel by allowing in-field administration of an injectable at the time of injury to prevent PTOA.



Safranin O-fast green staining reveals significantly more cartilage degeneration of the medial tibial plateau in the surgically-induced OA group (top) compared to the sham group (bottom).

Nuclear Pore Complexes in the Maintenance of Skeletal Muscle Integrity and Function

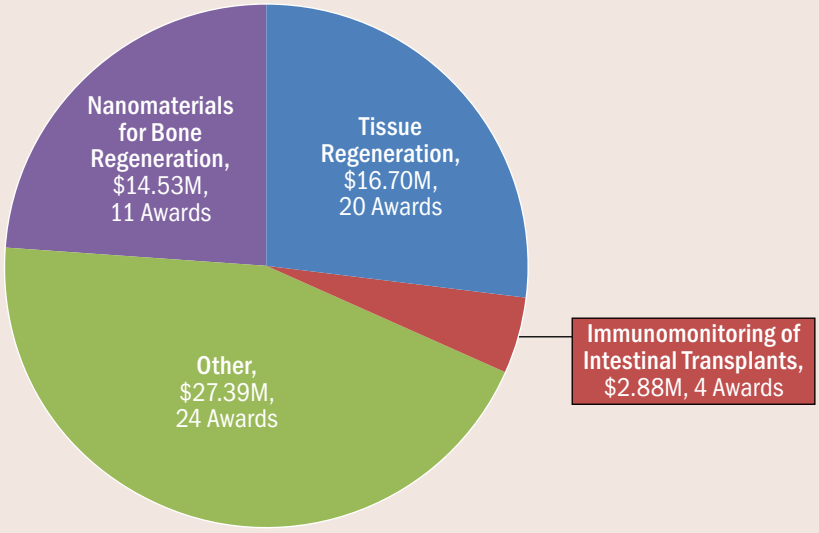
Maximiliano D'Angelo, Ph.D., Sanford Burnham Prebys Medical Discovery Instituter

Dr. Maximiliano D'Angelo and his colleagues have identified nuclear pore complex component (Nup210) as an important regulator of muscle physiology and showed progressive deterioration of muscle structure and function associated with a lack of Nup210 in small animal model studies. With the support of an FY19 IIRA to Sanford Burnham Prebys Medical Discovery Institute, he now conducts mechanistic studies to characterize the role of Nup210 in muscle maintenance and to determine if upregulation can promote muscle repair and function in mouse models with Duchenne muscular dystrophy. Dr. D'Angelo and his team will characterize how skeletal muscle deteriorates in a Nup210 knockout mouse model by using immune profiling and functional analysis to understand the alterations in the muscle. They will also define the origins of $Nup210^{-/-}$ muscle alterations and subsequently investigate if Nup210 upregulation can stimulate muscle regeneration. If successful, this could provide a novel clinical approach to enhance muscle function and repair, prevent muscle loss with age, and lead to novel therapeutic strategies to treat muscle dystrophies.

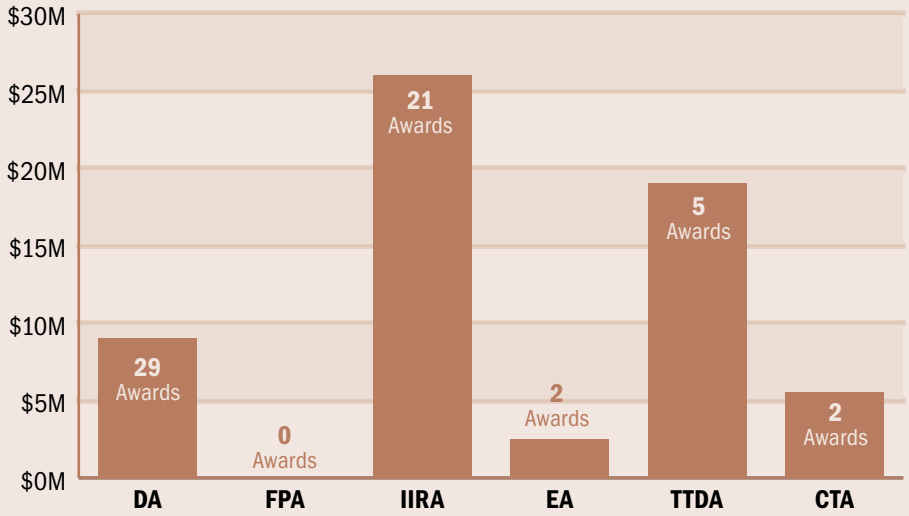
REGENERATIVE MEDICINE

FY16–FY20 Topic Areas Funded

- Immunomonitoring of Intestinal Transplants
- Nanomaterials for Bone Regeneration
- Tissue Regeneration



FY16–FY20 Regenerative Medicine Funding by Topic Area



FY16–FY20 Regenerative Medicine Funding by Award Mechanism

Traumatic injuries sustained as a result of accidents, acts of violence, and natural disasters can leave survivors with chronic pain, tissue damage, and other comorbid conditions that are a significant and costly cause of chronic disability. The PRMRP Regenerative Medicine portfolio supports research in topic areas that focus on reconstruction and regeneration along a spectrum of combat and civilian injuries, with the goal of improving the long-term health and quality of life of survivors of traumatic injuries. Regenerative medicine projects focus on a variety of musculoskeletal health, bone health, and tissue and organ regeneration. During FY16–FY20, the PRMRP funded 59 awards related to regenerative medicine efforts totaling $61.5M.

"Consumer advocates have a lot to gain and contribute to the research community, by sharing their insights as to which proposals will improve lives of people with the conditions that are being targeted. Their suggestions are valued and they can learn more about the research process and meet researchers and learn more about how research proposals are evaluated in determining which ones are funded. It is very fulfilling to participate as a consumer advocate in research panels."

Valerie Chang,
American Association for Respiratory Care
FY20 PRMRP Consumer Peer Reviewer

RESEARCH HIGHLIGHTS

Development of a Novel AAV Vector Capsid Optimized for OA Gene Therapy

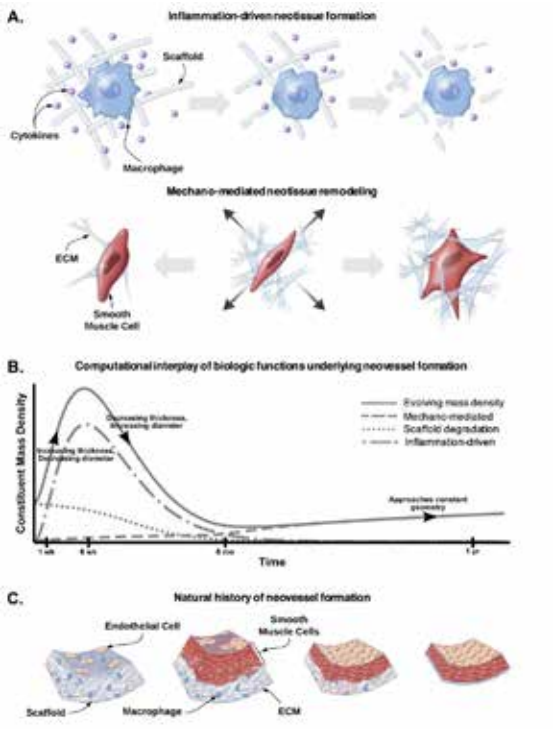
Steven Ghivizzani, Ph.D., University of Florida

With support from an FY18 TTDA to the University of Florida, Dr. Steven Ghivizzani and colleagues are optimizing for clinical use a gene therapy-based technology that drives expression of anti-arthritic proteins directly from the diseased tissue. Investigators have demonstrated in both small and large animal models that this potential therapeutic remained active for more than a year after a single dose. The therapeutic prevented development of OA after acute injury as well as prevented disease progression and reduced symptoms in joints with established OA. However, the previous platform required high doses to achieve efficacy and could be thwarted by innate immunity in the target population. Current efforts are focused on improving targeted delivery to OA joints, increasing gene expression efficacy, lowering the dose needed for treatment efficacy, and avoiding potential immune resistance to the therapy. These advancements will lead to improved safety profiles, reduced production costs, and greater response rates in more patient populations.

Development and Preclinical Validation of an Improved Tissue-Engineered Vascular Graft for Use in Congenital Heart Surgery

Christopher Breuer, M.D., Research Institute at Nationwide Children's Hospital

Dr. Christopher Breuer leads efforts supported by an FY17 TTDA to the Research Institute at Nationwide Children's Hospital to construct a second-generation tissue-engineered vascular graft (TEVG) composed of patient-derived bone marrow mononuclear cells seeded onto a biodegradable tubular scaffold. The grafts have been implanted in juvenile sheep and monitored over a 12-month period for safety and performance. Angiographic assessments, including angiograph, three-dimensional (3D) rotational angiograph, pressure tracing, and intravascular ultrasound, have been performed to evaluate the maintenance and growth capacity of the TEVGs. Interim analysis of the first 24 implanted grafts demonstrate a survival rate of more than 90%. Furthermore, Dr. Breuer has developed a novel 3D fluid-solid-growth model that describes and predicts neovessel formation, including narrowing. Catheterization data from the implanted animals will be used to inform this computational model. The TEVG has the capacity to grow as the patient matures and would improve outcomes for children undergoing congenital heart surgery by preventing the need for reoperation.



Computationally inferred mechanistic insights into the transient early TEVG stenosis. (A) Implantation of the polymeric scaffold induces a foreign body reaction and macrophages infiltrate the scaffold to stimulate neotissue formation. As the polymer disappears, smooth muscle cells remodel the extracellular matrix to establish mechanical homeostasis. (B) The computational model shows the interplay of scaffold degradation on inflammation-driven and mechano-mediated neotissue formation. During the first 6 months after implantation, neotissue formation occurs through signaling that drives cellular migration and extracellular matrix production; after the scaffold degrades, formation rates are mediated by the ability of vascular cells to sense and respond to their local mechanical environment. (C) The schematic demonstrates neovessel formation at 1 week, 6 weeks, 6 months, and 1 year after implantation of the TEVG.

RESPIRATORY HEALTH

FY16–FY20 Topic Areas Funded

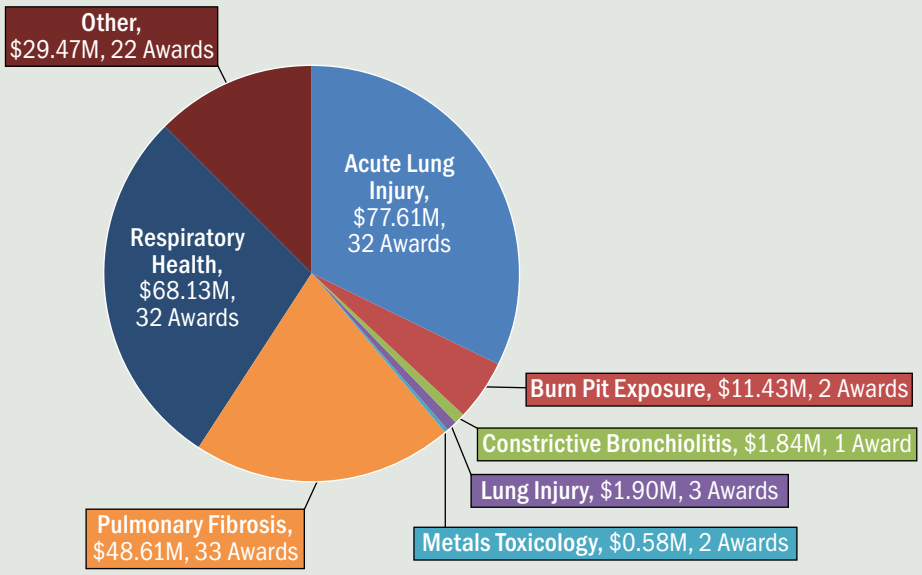
- Acute Lung Injury
- Burn Pit Exposure
- Constrictive Bronchiolitis
- Lung Injury
- Metals Toxicology
- Pulmonary Fibrosis
- Respiratory Health

FY21 Topic Areas Offered

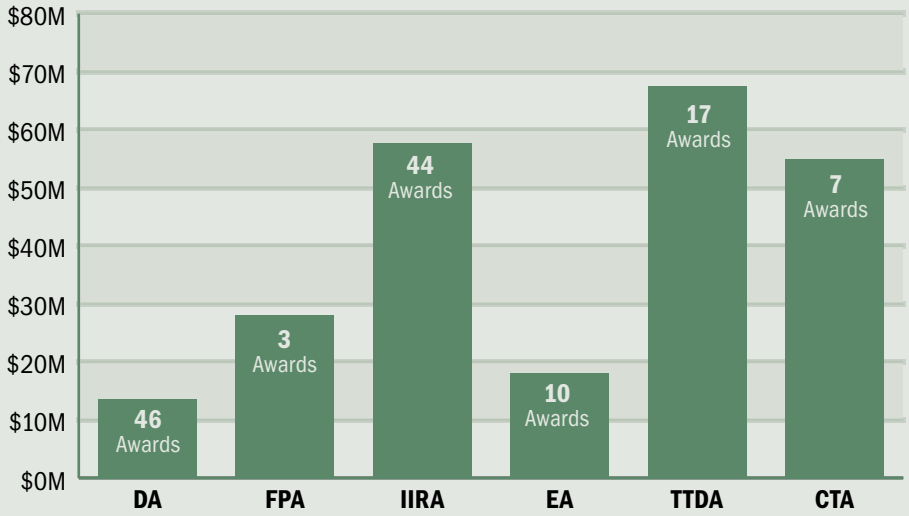
- Burn Pit Exposure
- Metals Toxicology
- Pulmonary Fibrosis
- Respiratory Health

"Research in our laboratory that is supported by the PRMRP has advanced new solutions to unmet needs, including the translation of innovation toward practice. Our DA created a unique interdisciplinary research team and trained multiple young scientists. One of these trainees received her Ph.D. in biomedical engineering and leads a startup company based on the results of this award that is focused on removing pathogens from blood for treatment of sepsis. The feasibility of a novel nanotechnology to sense toxic metals is advancing with resources from a DA. This work aims to provide early detection of harmful consequences from embedded fragments resulting from blast injuries. Both projects directly address critical gaps in military health. Few other programs support novel ideas from which innovation and new solution paradigms are forged. We are grateful to have the opportunity to work with the PRMRP to train emerging experts and establish novel solutions that are focused on military medicine."

Dr. Todd Giorgio,
Vanderbilt University
FY17 PRMRP DA Recipient



FY16–FY20 Respiratory Health Funding by Topic Area



FY16–FY20 Respiratory Health Funding by Award Mechanism

Chronic pulmonary diseases are major threats to U.S. military Service Members, as well as to the general population. From 2010 to 2019, these diseases affected 226,668 active-duty Service Members and an additional 2.57 million beneficiaries.[1] The diseases and conditions in the PRMRP Respiratory Health portfolio can be caused by trauma, critical illness, or exposure to airborne hazards during deployments, such as toxic metals, hazardous particulates, and burn pits. All of these factors place deployed Service Members at an increased risk for respiratory complications. Thus, research focusing on understanding, preventing, and treating pulmonary disease addresses an important military need. During FY16–FY20, the PRMRP funded 127 awards related to respiratory health totaling $239.6M.

[1] Data provided by the Armed Forces Health Surveillance Branch based on electronic records within the Defense Medical Surveillance System.

RESEARCH HIGHLIGHTS

Characterization of Acute Exposure to Toxic Metals in Military Environments and Personnel

Todd Giorgio, Ph.D., Vanderbilt University

Currently no technology exists to detect and quantify human contact with toxic metals during peak exposure. Dr. Todd Giorgio, with the support of an FY17 DA to Vanderbilt University, is investigating the health effects of metal exposure in Service Members resulting from explosions and inhalation near burn pits in the battlefield. Dr. Giorgio hypothesized that a zinc oxide (ZnO) nanowire substrate functionalized with gold nanoparticles and chelating ligands could sensitively detect toxic metals via surface-enhanced Raman spectroscopy (SERS). Dr. Giorgio and his lab created two types of masks to localize ZnO seed layer deposition as well as to localize metal nanoparticle deposition so that users can compare SERS with non-SERS measurements. The investigators grew nanowire forests on polydimethylsiloxane substrates, which showed that growing a nanowire is possible inside a microchannel, and they also developed crystalline ZnO nanowires. Ongoing studies suggest that fluorescence could also be used to improve SERS sensitivity. Dr. Giorgio and his team further demonstrated that improved Raman spectra could be developed through controlling the microchannel wall thickness. One research article from this project was published in 2021, another is currently in progress, and Dr. Giorgio's lab continues to work on this important subject.

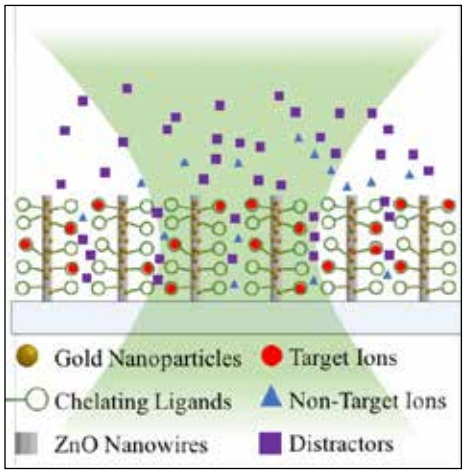


Illustration of the proposed advanced sensor. ZnO nanowires functionalized with gold nanoparticles amplify the changes in Raman spectra resulting from toxic metals.

Mesenchymal Stromal Cells for Treatment of ARDS Following Trauma or Pneumonia

Michael Matthay, M.D., University of California, San Francisco

Acute respiratory distress syndrome (ARDS) is a life-threatening respiratory condition that causes damage and inflammation in the lungs and can lead to critically low blood oxygen levels. ARDS is brought on by factors released after severe traumatic injury or primary lung infections from pneumonia and is a leading cause of death in the United States. There is no proven therapy for ARDS other than supportive care. With support from an FY16 CTA to the University of California, San Francisco, Dr. Michael Matthay is assessing the therapeutic efficacy of donated bone marrow-derived mesenchymal stromal cells (MSCs) for treating ARDS in a randomized phase 2b clinical trial (STAT). A previous phase 2a trial showed that MSCs were safe in patients with moderate and severe ARDS. Recruitment and treatment for the phase 2b trial has begun at the University of California, San Francisco, Zuckerberg San Francisco General Hospital, UC Davis Medical Center and Trauma Center, Oregon Health Science Center, and the University of Texas Health Science Center at Houston (see figure). This clinical trial includes COVID-19 patients who may also benefit from the MSC therapy. If this treatment shows therapeutic potential, then a pivotal multi-center phase 3 trial will investigate the impact of MSCs on mortality and duration of mechanical ventilation in ARDS patients.

Participating clinical sites for the STAT phase 2b trial of MSCs for ARDS: University of California, San Francisco and Zuckerberg San Francisco General Hospital (PIs – Michael Matthay, Carolyn Hendrickson, and Lucy Kornblith); Oregon Health Science Center (PIs – Marty Schreiber and Akram Khan); University of Texas Health Science Center at Houston (PIs – Bela Patel, Charles Cox, and Laura Moore); Vanderbilt University (PIs – Lorraine Ware and Oscar Guillamondegui); University of Washington/Harborview Hospital (PI – Bryce Robinson); and University of California Davis Medical Center and Trauma Center (PIs – Rachael Callcutt and Tim Albertson).

PRMRP CLINICAL PIPELINE

The PRMRP has invested in the development and testing of multiple therapies and technologies since its inception in 1999, many of which have continued to advance through further phases of clinical testing. The PRMRP is currently supporting preclinical technology development efforts, as well as clinical trials ranging from phase 1 to phase 3.

Current Clinical Phase	Agent/Technique	PI (Organization)	Award Mechanism	Description
AUTOIMMUNE DISEASES AND IMMUNOLOGY				
Preclinical	Oral microbiome biomarkers for rheumatoid arthritis	Edward Chan (University of Florida)	DA	Patients with and without rheumatoid arthritis may exhibit different oral microbiomes based on associations with periodontal disease. This study will classify microbes to identify oral biomarkers specifically associated with rheumatoid arthritis.
Preclinical	Biomarkers for response to lupus nephritis therapy	Tamara Nowling (Medical University of South Carolina)	IIRA	Glycosphingolipids may serve as a urinary biomarker to identify patients less likely to respond to traditional lupus nephritis treatments and identify additional drug targets for new treatments.
Phase 1	ARA-LAMP-vax	Teri Heiland (Immunomic Therapeutics, Inc.)	TTDA	The PRMRP supported the preclinical development of ARA-LAMP-vax, a DNA plasmid vaccine for treating peanut allergies. This vaccine is now being tested in a phase 1 clinical trial for pediatric use and the platform was licensed to Astellas in 2016.
CARDIOVASCULAR HEALTH				
Preclinical	AAV9-GFP-AIP	William Pu (Children's Hospital, Boston)	TTDA	A cardiomyocyte-targeted adeno-associated virus (AAV) gene therapy vector, AAV9-GFP-AIP, that expresses autocamtide-2-related inhibitory peptide in cardiomyocytes is being developed as a potential novel therapy for Catecholaminergic Polymorphic Ventricular Tachycardia.
Preclinical	Low-force Expanding-Adaptable Pediatric (LEAP) Valve	Corin Williams (Charles Stark Draper Laboratory, Inc.)	TTDA	The LEAP Valve is a cardiac valve prosthetic that can be appropriately sized for infants and toddlers with CHD and serves as an adaptive stent that passively expands with growth.
Preclinical	Syndecan-4 proteoliposomes	Aaron Baker (University of Texas at Austin)	TTDA	Syndecan-4 proteoliposomes are being developed to enhance the effectiveness of angiogenic growth factors, such as fibroblast growth factor-2 (FGF-2) and platelet derived growth factor BB (PDGF-BB), using co-therapy with the goal of restoring blood flow to ischemic tissues.
Preclinical	Platelet-like particles (PLPs)	Thomas Barker (University of Virginia)	TTDA	PLPs specifically target wound environments through high affinity binding to the matrix protein fibrin and are being developed to induce clotting in congenital heart defect patients at high risk for bleeding following cardiac surgery and cardiopulmonary bypass.

Current Clinical Phase	Agent/Technique	PI (Organization)	Award Mechanism	Description
Preclinical	CAP-2003	Linda Marban (Capricor, Inc.)	TTDA	A scalable manufacturing process for cardiosphere-derived exosomes, CAP-2003, is being established. CAP-2003 is intended to induce reductions in scar size and improvements in cardiac function that translate into improved quality of life and longer survival for patients with heart disease.
Preclinical	Infrared light (IRL) therapy	Maik Huttemann (Wayne State University)	TTDA	A non-invasive IRL therapy utilizing novel wavelengths is being developed to modulate mitochondrial function in vivo, thus limiting the production of reactive oxygen species (ROS) and protecting against ischemia-reperfusion injury of the heart and brain.
Preclinical	Fontan Circulation Assist Device (FCAD)	William Weiss (Pennsylvania State University, Milton S. Hershey Medical Center)	TTDA	FCAD is a small, implantable blood pump to provide long-term mechanical right heart support for patients who have had the Fontan surgical palliation (primarily for single ventricle congenital heart defects) and who exhibit progressive Fontan failure.
Preclinical	A deep machine learning platform to detect CHD	Rima Arnaout (University of California, San Francisco)	TTDA	This tool is a scalable, mobile diagnostic that can assist a non-expert sonographer obtain diagnostic-quality ultrasound images of the fetal heart through real-time acquisition guidance, detect and present key images to the clinician for interpretation, and provide a screening triage of the heart as normal or abnormal.
Preclinical	PediaFlow	James Antaki (Cornell University)	TTDA	PediaFlow is a miniature implantable ventricular assist device with external hardware components that is being developed for infants and children with CHD that uses magnetic levitation technology.
Preclinical	Ectonucleotide Pyrophosphatase-1 (ENPP1) Monoclonal Antibody	Arjun Deb (University of California, Los Angeles)	TTDA	ENPP1 pro-inflammatory changes in the infarcted heart contribute to adverse cardiac remodeling. Preclinical testing and validation in NHPs and humanized mouse models will determine whether ENPP1 can prevent the development of ischemic cardiomyopathy after myocardial infarction.
Preclinical	Coversin and/or CX-01 therapies	Yansong Li (U.S. Army Institute of Surgical Research)	TTDA	Coversin (a complement inhibitor to reduce inflammation) and CX-01 (a low anticoagulant heparin derivative) are being studied for their ability to attenuate morbidity and mortality following severe hemorrhage.
Preclinical	BioPace	Hee Cheol Cho (Emory University)	TTDA	BioPace, consisting of a natural human gene and a small molecule drug with Tgfβ inhibition, is being developed in a large animal model of complete heart block to restore native heart rhythm and transform native myocardial tissue to natural pacemaker tissue by focal gene transfer, thus preventing the need for risky and invasive operations.

Current Clinical Phase	Agent/Technique	PI (Organization)	Award Mechanism	Description
Phase 2b	Mesenchymal stem cells (MSCs) by transendocardial injection	Joshua Hare (University of Miami, Coral Gables)	CTA	In a phase 1/2 trial, MSCs demonstrated safety and efficacy in treating non-ischemic dilated cardiomyopathy (NIDCM), although some data suggested that patient genotype could influence response to MSC treatment. This phase 2b trial will evaluate the role of patient genotype in response to autologous (i.e., self) versus allogeneic (i.e., donor) MSC treatments for NIDCM.
Phase 3	Everolimus and low-dose tacrolimus	Lynn Sleeper (Boston Children's Hospital)	CTA	Everolimus and low-dose tacrolimus, a new rejection treatment for children who have undergone recent heart transplant, is being evaluated in a randomized phase 3 trial to determine whether this new treatment can reduce or prevent complications of transplant, including rejection, coronary artery disease, and kidney disease, when compared to usual care.
HEMORRHAGE CONTROL AND BLOOD PRODUCTS				
Preclinical	HemoDefend-BGA	Maryann Gruda (CytoSorbents, Inc.)	TTDA	The HemoDefend-BGA Adsorber, which reduces blood group antibodies, is being scaled up and preclinically validated to expand the availability of universal blood products and resources for hemorrhage control for treating life-threatening battlefield injuries.
Preclinical	Lyophilized SynthoPlate (Lyo-SP)	Anirban Sen Gupta (Case Western Reserve University)	TTDA	SynthoPlate, liposome-templated synthetic platelet surrogate technology for hemorrhage control, has safety and efficacy in animal trauma models. Lyo-SP is being developed as a lyophilized, deployable, rapidly aqueous-reconstitutable “synthetic platelet” technology.
Preclinical	Self-Sensing Hemorrhage Control and Resuscitative Catheter (SHARC)	David Baer (Prytime Medical Devices, Inc.)	TTDA	A next-generation resuscitative endovascular balloon occlusion of the aorta catheter to control non-compressible torso hemorrhage in prehospital environments. A built-in electronic blood pressure monitoring system will be combined in the same device with a precision-control occlusion balloon to temporize hemorrhage in combat casualties.
Preclinical	Mirasol System for Whole Blood	Terry Cussen (Terumo BCT, Inc.)	TTDA	The Mirasol System is a blood safety device that reduces the potential infectious pathogen load and inactivates white blood cells in whole blood intended for transfusion or separation into blood components. A next-generation device was developed and optimized to better suit the production needs of military and civilian blood centers.

Current Clinical Phase	Agent/Technique	PI (Organization)	Award Mechanism	Description
Preclinical	Mirasol System for Whole Blood	Raymond Goodrich (Colorado State University)	TTDA	The Mirasol System performance is being evaluated with fresh whole blood against emerging infectious agents and potential bioterrorism threats arising from genetic modification or design, making it suitable for use in combat casualty care and civilian settings.
INFECTIOUS DISEASES				
Preclinical	Oxaborale compounds for cutaneous Leishmaniasis	Karl Werbovetz (Ohio State University) and Brian Vesely (The Geneva Foundation)	IIRA-PPIO	A 2018 patent was filed for the use of small molecule oxaborale compounds for the treatment of cutaneous Leishmaniasis.
Preclinical	AAK1 and GAK inhibitors	Shirit Einav (The Leland Stanford Junior University) and John Dye (U.S. Army Medical Research Institute of Infectious Diseases)	IIRA-PPIO	Novel selective inhibitors of two major regulators of viral infection, AP2-associated protein kinase 1 (AAK1) and cyclin G-associated kinase (GAK), have shown broad-spectrum activity against dengue, Ebola, and chikungunya viruses.
Preclinical	A-Blocks Surgical Hydrogel	Micael Bevilacqua (Amicrobe, Inc.)	TTDA	The A-Blocks Surgical Hydrogel is intended for direct, local application to exposed tissues to broadly protect against microbial contamination and infection after surgery and/or trauma. Initial Good Laboratory Practices toxicology studies and pre-IND communications with the FDA have been initiated.
Preclinical	ImmunoPoC™	Eran Eden (MeMed Diagnostics, Ltd.)	TTDA	ImmunoPoC™ interprets a patient's immune response to provide insight into whether an infection is viral or bacterial. The ImmunoPoC™ blood test will help military clinicians decide which patients require antibiotic treatment (and which do not), leading to improved health outcomes as well as reduced antibiotic misuse, and ultimately, will help curb the rise of antibiotic resistance.
Preclinical	Locked Nucleic Acid 14 (LNA14)	Jeffrey Glenn (The Leland Stanford Junior University)	TTDA	LNA14, an inhibitor that targets a universally conserved packaging signal in influenza A virus, is undergoing preclinical evaluation and IND-enabling studies. LNA14 may be developed into a single-dose therapeutic with broad-spectrum activity against influenza A virus.
Preclinical	GEO-LM01	Mark Newman (GeoVax, Inc.)	TTDA	GEO-LM01 is a novel vaccine against Lassa virus that has demonstrated proof of concept in a lethal mouse challenge model. Currently, immunogenicity and efficacy data are being generated for GEO-LM01 in guinea pig and NHP animal models.

Current Clinical Phase	Agent/Technique	PI (Organization)	Award Mechanism	Description
Preclinical	Shigella flexneri WRSf3G2 Vaccine	Akamol Suvarnapunya (Walter Reed Army Institute of Research)	TTDA	A phase 1-compliant lot of S. flexneri 3a WRSf3G2 is being manufactured under GMP conditions following the established processes previously used to successfully manufacture WRSs2 (a second-generation S. sonnei vaccine) and its isogenic equivalent WRSf2G12 (an S. flexneri serotype 2a vaccine candidate). The research seed of WRSf3G2 has undergone extensive preclinical characterization using in vitro and in vivo (guinea pig) models.
Preclinical	CoagCare	Ramkumar Abhishek (Abram Scientific)	TTDA	CoagCare is a point-of-care viscoelastic coagulation diagnostic system comprised of plastic-laminated test strips that interface with a hand-portable, wirelessly connected meter, to detect coagulopathy in 5-10 minutes. This device is being prototyped, manufactured, and tested as a diagnostic tool to detect coagulopathy early in COVID-19 patients and help triage care accordingly.
Preclinical	Pan-Group 2 Influenza A Virus Vaccines	Florian Krammer (Icahn School of Medicine at Mount Sinai)	TTDA	A strategy based on sequential vaccination with chimeric hemagglutinins (HA) that redirects the immune response is being used to develop and characterize group 2 influenza vaccine candidates. GMP seed viruses for the manufacturing of clinical-grade, live-attenuated chimeric HA vaccines are being manufactured for preclinical and toxicology studies.
Preclinical	mRNA vaccine for Lassa Virus	Alexander Bukreyev (University of Texas, Galveston Medical Branch)	TTDA	This vaccine uses a 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.
Preclinical	Clofazimine	Sumit Chanda (Sanford Burnham Prebys Medical Discovery Institute)	FPA	Upon investigating early-stage small molecules for activity against SARS-CoV-2 replication both in vitro and in vivo, an FDA-approved anti-leprosy drug, clofazimine, was found to exhibit potent antiviral activity and prevented the exaggerated inflammatory response observed in COVID-19 patients. A phase 2 clinical trial is planned.
Phase 1/2a	VLPM01, vaccine candidate	Wataru Akahata (VLP Therapeutics, LLC)	TTDA	A malaria vaccine candidate, VLPM01, was developed using a proprietary vaccine platform based on virus-like particle (VLP) technology, resulting in IND submission to the FDA. A phase 1/2a study is currently evaluating the safety, tolerability, immunogenicity, and experimental efficacy of VLPM01 in healthy, malaria-naïve adult volunteers.

Current Clinical Phase	Agent/Technique	PI (Organization)	Award Mechanism	Description
Phase 1/2a	Schistosoma mansoni tetraspanin (Sm-TSP)-2/ Alhydrogel®	David Diemert (George Washington University)	CTA	A phase 1/2a trial is ongoing to evaluate the safety and immunogenicity of the Sm-TSP-2/ Alhydrogel schistosomiasis vaccine in adults in Uganda. A Safety Monitoring Committee reviewed the safety and interim immunogenicity results from phase 1 of the trial and recommended that phase 2 proceed.
Phase 2a, Phase 1b	M2 Deficient Single Replication (M2SR) Influenza Vaccine	Pamuk Bilsel (FluGen)	CTA	The M2SR vaccine carries a mutation that results in no influenza M2 protein production with no subsequent cell-to-cell spread or virus shedding. Two ongoing phase 2a clinical trials are investigating the ability of M2SR to generate immunity via intranasal inoculation. Additionally, an integrated phase 1b study is planned to evaluate the ability of H3N2 M2SR to induce broad immunity in adults 65 years and older.
Phase 2a	Mirasol Pathogen Reduction Technology (PRT)	Aaron Tobian (Johns Hopkins University)	CTA	A phase 2a trial is ongoing to evaluate the dependability, quality, reproducibility, ease of operation, and sustainability of the Mirasol PRT for reducing the risk of transfusion-transmitted infections in fresh whole blood and blood components. Participants are being enrolled from four different sites in Uganda.
Phase 2	Prebiotic Inulin	Daniel Freedberg (Columbia University Medical Center)	CTA	Inulin is a vegetable-derived non-digestible polysaccharide that is a key nutrient source for short-chain fatty acid (SCFA)-producing bacteria. A phase 2 clinical trial aims to collect feasibility and safety data on inulin and will determine the efficacy of inulin for the prevention of multidrug-resistant infections in intensive care unit patients.
Phase 1b/2a	MTBVAC	Dagna Laufer (International AIDS Vaccine Initiative, Inc.)	CTA	MTBVAC is a novel, live-attenuated Mycobacterium tuberculosis (Mtb) vaccine that presents a more complete array of Mtb-specific antigens to the host immune system. A phase 1b/2a, double-blind, randomized, Bacille Calmette-Guérin controlled, dose-escalation safety and immunogenicity study in healthy adults with and without latent tuberculosis infection is underway.
Phase 2	Convalescent Plasma for COVID-19 Patients	Michele Donato (Hackensack University Medical Center)	CTA	A randomized single-institution phase 2 trial will assess the efficacy and safety of treatment with convalescent plasma infusion versus without convalescent plasma infusion in patients with early COVID-19 infection at high risk of admission.

Current Clinical Phase	Agent/Technique	PI (Organization)	Award Mechanism	Description
INTERNAL MEDICINE				
Preclinical	Alivio Microparticle-Based Hydrogel	Gregory Zugates (Alivio Therapeutics, Inc.)	TTDA	The Alivio microparticle-based hydrogel technology selectively targets inflamed tissue and releases an encapsulated therapeutic agent directly to the bladder in response to inflammation levels. The goal is to utilize this technology to deliver lidocaine via urinary catheter for prolonged pain relief in interstitial cystitis.
Preclinical	COL7A1-Corrected iPSC-Derived Keratinocyte Stem Cell Sheets	Dennis Roop (University of Colorado)	TTDA	This stem cell therapy is based on a previously developed induced pluripotent stem cell (iPSC) therapy for recessive dystrophic epidermolysis bullosa (RDEB). The COL7A1-corrected iPSC-derived keratinocyte stem cell sheets, when grafted onto wounds, may adhere tightly and provide long-term wound closure with reduced rejection potential in RDEB patients.
Pilot	Pancreatic Islet Extraportal Transplantation	Gregory Beilman (University of Minnesota, Twin Cities)	CTA	This pilot study will determine if the addition of extrahepatic islet infusion to intrahepatic islet infusion after total pancreatectomy with islet autotransplant is safe and will lead to improved αcell function with preservation of αcell function, which could lead to improved long-term function of pancreatic islets and improved glucose regulation for diabetes control.
Phase 2	Metformin (repurposed)	Kyongtae Bae (University of Pittsburgh)	CTA	This phase 2 study will evaluate the safety and tolerability of metformin as a novel therapy for treating early-stage autosomal dominant polycystic kidney disease (ADPKD) by activating AMP-activated protein kinase.
Phase 2	Granexin Gel	Gautaum Ghatnekar (FirstString Research, Inc.)	CTA	A phase 2 clinical trial will evaluate a Granxin gel treatment to temper excessive inflammatory responses that worsen tissue damage. This treatment is meant to reduce pressure ulcers and improve overall patient quality of life.
Phase 2	Cabergoline	Amy DiVasta (Boston Children's Hospital)	CTA	A phase 2 clinical trial will assess the efficacy of a commercially available angiogenesis inhibitor shown to reduce pelvic pain, cabergoline, to treat endometriosis.
Phase 3	Rituximab combined with Plasmapheresis	Michelle Rheault (University of Minnesota, Twin Cities)	CTA	A phase 3 clinical trial will test to determine whether the combination of rituximab and plasmapheresis prior to kidney transplant in patients with focal segmental glomerulosclerosis can predict risk factors for recurrent kidney disease.
Phase 4	Pravastatin	Michel Chonchol (University of Colorado at Denver)	CTA	Pravastatin is being evaluated in a phase 4 clinical trial for efficacy in decreasing kidney growth and improving kidney function in adult ADPKD patients with results expected to be the first insights into the use of statins to improve renal function.

Current Clinical Phase	Agent/Technique	PI (Organization)	Award Mechanism	Description
NEUROSCIENCE				
N/A	Light Pulses as a Countermeasure for Circadian Desynchrony	Jamie Zeitzer (Palo Alto Institute of Molecular Medicine)	CTA	This trial is assessing the efficacy of light pulses for re-regulating circadian rhythm – most applicable for jet lagged or shift workers. The trial consists of multiple phases to examine different conditions and treatment lengths. If successful, this study will inform guidelines to optimize usage of light pulses to counteract circadian desynchrony.
Preclinical	nStrada™	Mitchell Greenberg (NanoMedical Systems, Inc.)	TTDA	nStrada™ is an implanted capsule that acts as a reservoir for drug molecules to diffuse out at a constant rate. The device is being developed and optimized to release buprenorphine formulated for long-term stability to treat opioid addiction and help prevent relapse.
Preclinical	Contulakin G	Baldomero Olivera (University of Utah)	FPA	Contulakin G is a highly pure, synthetic, and biologically active peptide toxin isolated from cone snail venom and known to have anesthetic or analgesic effects. Contulakin G is being preclinically evaluated as a novel pain therapeutic and will soon move to clinical trials for anti-nociceptive activity in cancer patients.
Preclinical	XT-203	Raymond Chavez (Xalud Therapeutics)	TTDA	XT-203 is a toll-like receptor 4 antagonist that does not block opioid analgesia and can be used in combination with opioids to increase their efficacy and reduce their abuse potential. XT-203 is undergoing IND-enabling studies and may also have stand-alone analgesic effects, reducing the need for opioids entirely.
Phase 2	Losartan	Murray Stein (University of California San Diego)	CTA	This randomized controlled trial will determine if the angiotensin type 1 receptor, losartan, is superior to placebo for reducing posttraumatic stress disorder (PTSD) symptom severity and if genetic polymorphisms in angiotensin converting enzyme inhibitors/angiotensin receptor blockers predict response.
Phase 2	Prazosin	Murray Raskind (Seattle Institute for Biomedical and Clinical Research)	CTA	This phase 2 clinical trial is evaluating the effect of the alpha-1 adrenoreceptor antagonist drug, prazosin, on sleep disturbance, PTSD symptoms, depressive symptoms, alcohol consumption, global cognitive function, health-related quality of life, and global clinical status.
Phase 2	Percutaneous Peripheral Nerve Stimulation (PNS)	Joseph Boggs (SPR Therapeutics, Inc.)	CTA	Percutaneous PNS is being evaluated in a phase 2 randomized clinical trial for its ability to reduce pain, reduce opioid use, and improve function in patients with lower back pain from overuse injuries.

Current Clinical Phase	Agent/Technique	PI (Organization)	Award Mechanism	Description
Phase 2	Etanercept	Jinsheng Zhang (Wayne State University)	CTA	Etanercept blocks tumor necrosis factor alpha, which is believed to contribute to autoimmune cochleovestibular disorders including hearing loss and tinnitus by upregulating inflammatory responses. A phase 2 clinical trial will test the therapeutic effect and time course of effect of etanercept on blast-induced tinnitus.
Phase 2	Doxazosin	Anne Richards (Northern California Institute for Research and Education)	CTA	This ongoing phase 2, randomized clinical trial is assessing the effectiveness of doxazosin compared to placebo for treating posttraumatic stress (PTS) nightmares, sleep disturbance, and non-nightmare PTS symptoms in Veterans with full and partial syndromal PTS.
Market	Banyan Brain Trauma Indicator	Ronald Hayes (Banyan Biomarkers, Inc.)	IIRA Existing Program Project	Alongside the initial discovery and validation studies, a semi-quantitative assay kit, known as the Bayan Brain Trauma Indicator, was developed and ultimately became the first blood test approved by the FDA to evaluate mild TBI as part of its Breakthrough Devices Program in 2018 (DEN170045).
Market	Hu3F8	Nai-Kong Cheung (Sloan Kettering Institute for Cancer Research)	CTA	A phase 1 clinical trial evaluated the monoclonal antibody humanized 3F8 (hu3F8) to treat patients with neuroblastoma or other ganglioside G2-positive tumors with relapsed or refractory disease. The FDA approved hu3F8 for treating an orphan disease (neuroblastoma) in children.
NUTRITION AND METABOLISM				
Preclinical/ Phase 1	N-acetyl cysteine (NAC)	Michio Hirano (Columbia University Medical Center)	FPA	NAC, an antioxidant, is being examined as a treatment strategy for mitochondrial disease through preclinical and clinical approaches. Recently, an IND was cleared by the FDA for a phase 1 dose finding study of NAC in patients with the mitochondrial 3243A>G mutation and low brain glutathione levels.
Preclinical	(R)-ND-336 for the Treatment of DFUs	Mayland Chang (University of Notre Dame)	TTDA	(R)-ND-336, which selectively promotes natural wound healing in diabetic wounds, is undergoing preclinical development in a diabetic mouse wound model to file an IND with the FDA and begin human clinical trials.
N/A	Time-Restricted Feeding and Timed Light Therapy	Courtney Peterson (University of Alabama at Birmingham)	CTA	This clinical trial will assess how early time-restricted feeding and/ or timed light therapy can improve blood sugar control, as well as other chronobiological aspects of health, in adults with type 2 diabetes.

Current Clinical Phase	Agent/Technique	PI (Organization)	Award Mechanism	Description
ORTHOPAEDIC MEDICINE				
Preclinical	Localized Gene Therapy for PTOA	Constance Chu (The Leland Stanford Junior University and Palo Alto VA)	FPA	Pharmacological and cellular treatments are being evaluated acutely and early after anterior cruciate ligament injury in patients and in animal models. Additionally, localized, anti-inflammatory gene therapy is being investigated for sustained administration in an equine model of PTOA, which could lead to treatments to delay or prevent PTOA in patients with joint injuries.
Preclinical	Nanocarrier Treatment for PTOA	Paula Hammond (Massachusetts Institute of Technology)	EA	Nanoparticles assembled specifically to target and treat PTOA cartilage tissue with therapeutic proteins will be tested in rat and dog models.
Phase 1	Interleukin-1 Receptor Antagonist (IL-1Ra) Gene Therapy	Christopher Evans (Mayo Clinic)	CTA	A phase 1 clinical trial is exploring the safety and tolerability of IL-1Ra gene therapy when injected into knee joints of patients that have mild to moderate osteoarthritis. The therapy could mitigate joint inflammation by providing localized and sustained release of the naturally occurring inhibitor for the inflammatory cytokine IL-1.
REGENERATIVE MEDICINE				
Preclinical	Osteo Adapt BVF	Luis Alvarez (Theradaptive)	TTDA	Using a proprietary variant of bone morphogenetic protein-2 (BMP2) called tethered BMP2 (tBMP2) that binds very tightly to ceramic materials, porous ceramic implants were developed and surface-coated with tBMP2. Preclinical studies are underway to test Osteo Adapt BVF, a fully synthetic bone graft material composed of tBMP2 loaded at tunable doses on Vitoss®, an FDA 510(k)-cleared bone filler product.
Preclinical	Tissue-Engineered Vascular Graft (TEVG)	Christopher Breuer (Research Institute at Nationwide Children's Hospital)	TTDA	Initial trials revealed stenosis complications and demonstrated a need for vascular grafts with capacity for growth following congenital heart surgery. Current efforts will characterize the growth capacity of second-generation TEVGs and develop a computational model to further optimize TEVG design.
Preclinical	Gene therapy for PTOA	Steven Ghivizzani (University of Florida)	TTDA	Previous studies demonstrated therapeutic potential of AAV-delivered gene therapy to treat OA. New AAV constructs will increase targeting to the joints, gene expression efficacy, and avoid potential immunoresistance.

Current Clinical Phase	Agent/Technique	PI (Organization)	Award Mechanism	Description
RESPIRATORY HEALTH				
Preclinical	Repair of injured lung epithelium	Gregory Downey (National Jewish Medical and Research Center)	EA	To develop therapies addressing deployment-related lung diseases, this study will identify specific respiratory immune cells causing damage to lung epithelium.
Phase 2	Selective Cytopheretic Device Therapy (SCD Rx)	H. Humes (Innovative BioTherapies, Inc.)	TTDA	SCD Rx to treat acute lung injury/ ARDS was assessed in a combat-relevant porcine model and demonstrated significant therapeutic benefits, providing evidence to advance the technology to clinical trials. The FDA granted Emergency Use Authorization for SCD Rx in COVID-19 patients with acute kidney injury and ARDS and a multicenter clinical trial is underway.
Phase 2	BIO 300 Oral Powder	Michael Kaytor (Humanetics Corporation)	TTDA EA	A nanoparticle oral suspension formulation of genistein, BIO 300, showed promise in reducing pulmonary injury in a phase 1b/2a clinical trial for patients receiving radiation therapy for lung cancer and was formulated into an oral powder for further testing. BIO 300 oral powder is now being tested as a post-infection prophylactic to mitigate pulmonary inflammation leading to COVID-19 complications in a phase 2 trial.
Preclinical	Berzosertib	Brigitte Gomperts (University of California, Los Angeles)	TTDA	Berzosertib, a kinase inhibitor that targets the DNA damage response pathway, demonstrated anti-viral activity against SARS-CoV-2 by limiting viral replication and cell death. Preclinical testing using two different SARS-CoV-2 infected lung models will be performed, along with in vitro and in vivo efficacy testing on SARS-CoV-2 cell toxicity and intracellular replication.
Preclinical	Diaphragm Pacing Therapy System (DPTS)	Matthew Gani (Lungpacer Medical USA, Inc.)	TTDA	A novel neurostimulation technology, DPTS, is being developed to provide temporary minimally invasive transvenous diaphragm pacing to improve respiratory function, increase inspiratory muscle strength, and improve weaning success and survival rates in difficult-to-wean mechanical ventilation patients.
Preclinical	Paracorporeal Pump-Integrated Artificial Lung (pPIAL)	Dongfang Wang (University of Kentucky)	TTDA	pPIAL is being developed as a simple, single device lung support system to enable safe Warfighter transport from combat theaters to regional medical centers. pPIAL allows direct attachment to a patient's body, eliminating the long tubing connection.
Phase 2b	Mesenchymal Stem Cell (MSC) Treatment for ARDS	Michael Matthay (University of California, San Francisco)	CTA	An ongoing multicenter, randomized, blinded, placebo-controlled phase 2b trial is testing the therapeutic potential of allogeneic bone-marrow derived MSCs for treating ARDS, with a major focus trauma patients.

Current Clinical Phase	Agent/Technique	PI (Organization)	Award Mechanism	Description
Phase 2	Vadadustat	Holger Eltzschig (University of Texas, Health Science Center at Houston)	CTA	A phase 2 trial will assess an oral drug, Vadadustat, for the prevention and treatment of ARDS in hospitalized COVID-19 patients. Vadadustat is a hypoxia-inducible factor activator and will be evaluated for its ability to decrease lung inflammation, consequently reducing the necessity of mechanical ventilation due to COVID-19 infection.
Phase 3	Clinical Practice Guideline (CPG) Against the Use of Beta-Blockers in Chronic Obstructive Pulmonary Disease (COPD)	Mark Dransfield (University of Alabama at Birmingham)	CTA	A multicenter phase 3 clinical trial found no difference in risk of COPD exacerbation between metoprolol (a beta blocker) and placebo; however, metoprolol was associated with higher risk of exacerbation leading to hospitalization. Results published in the New England Journal of Medicine in 2019 led to a CPG discouraging use of beta-blockers in COPD patients.

PRMRP TOPIC AREAS OFFERED AND FUNDED FY16–FY21

Topic Area	FY21[1]	FY20	FY19	FY18	FY17	FY16
Acute Lung Injury			✓	✓	✓	✓
Antimicrobial Resistance			✓	✓	✓	✓
Arthritis	✓	✓	✓	✓	✓	
Burn Pit Exposure	✓	✓	✓	✓	✓	
Cardiomyopathy	✓		✓	✓		
Cerebellar Ataxia			✓	✓		
Chronic Migraine and Post-Traumatic Headache		✓	✓	✓	✓	✓
Chronic Pain Management				✓		
Congenital Heart Disease	✓	✓	✓	✓	✓	✓
Constrictive Bronchiolitis		✓	✓	✓	✓	✓
Diabetes	✓	✓	✓	✓	✓	✓
Diarrheal Diseases					✓	
Dystonia	✓	✓	✓	✓	✓	✓
Early Trauma Thermal Regulation					✓	
Eating Disorders	✓	✓	✓	✓	✓	
Emerging Infectious Diseases			✓	✓	✓	✓
Emerging Viral Diseases	✓	✓				
Endometriosis	✓	✓		✓		
Epidermolysis Bullosa	✓	✓	✓	✓	✓	
Familial Hypercholesterolemia	✓	✓				
Fibrous Dysplasia	✓	✓				
Focal Segmental Glomerulosclerosis	✓	✓	✓	✓	✓	✓
Food Allergies	✓	✓				
Fragile X Syndrome	✓	✓		✓	✓	✓
Frontotemporal Degeneration	✓	✓	✓	✓		
Guillain-Barré Syndrome		✓	✓	✓	✓	
Hemorrhage Control	✓	✓	✓			
Hepatitis B	✓	✓	✓			✓
Hepatitis B and C				✓	✓	
Hereditary Angioedema			✓	✓	✓	✓
Hydrocephalus	✓	✓	✓	✓	✓	✓
Hypertension[2]	✓					
Immunomonitoring of Intestinal Transplants		✓	✓	✓	✓	
Inflammatory Bowel Disease	✓	✓	✓	✓	✓	✓
Influenza					✓	✓
Integrative Medicine					✓	✓
Interstitial Cystitis		✓	✓	✓	✓	✓
Lung Injury			✓	✓		
Lupus						✓
Malaria	✓			✓	✓	✓
Metals Toxicology	✓	✓	✓	✓	✓	✓

Topic Area	FY21[1]	FY20	FY19	FY18	FY17	FY16
Mitochondrial Disease	✓	✓	✓	✓	✓	✓
Musculoskeletal Disorders			✓	✓	✓	
Musculoskeletal Health		✓				
Myalgic Encephalomyelitis/Chronic Fatigue Syndrome	✓	✓				
Myotonic Dystrophy	✓	✓	✓	✓		
Nanomaterials for Bone Regeneration			✓		✓	✓
Non-Opioid Therapy for Pain Management	✓			✓	✓	✓
Nutrition Optimization	✓	✓	✓	✓		
Pancreatitis		✓	✓	✓	✓	✓
Pathogen-Inactivated Blood Products	✓	✓	✓	✓		
Pathogen-Inactivated Dried Cryoprecipitate					✓	
Pathogen-Inactivated Dried Plasma						✓
Peripheral Neuropathy[2]	✓					
Plant-Based Vaccines	✓	✓				
Platelet-Like Cell Production[2]	✓					
Polycystic Kidney Disease	✓	✓	✓		✓	✓
Post-Traumatic Osteoarthritis			✓	✓	✓	✓
Pressure Ulcers	✓	✓	✓	✓		
Psychotropic Medications						✓
Pulmonary Fibrosis	✓	✓	✓	✓	✓	✓
Resilience Training		✓	✓			
Respiratory Health	✓	✓	✓	✓	✓	✓
Rett Syndrome			✓	✓	✓	✓
Rheumatoid Arthritis	✓	✓	✓	✓	✓	✓
Scleroderma			✓	✓	✓	✓
Sleep Disorders (and Restriction)	✓	✓	✓	✓	✓	✓
Spinal Muscular Atrophy		✓	✓	✓	✓	
Suicide Prevention[2]	✓					
Sustained Release Drug Delivery	✓	✓		✓	✓	
Tinnitus			✓	✓	✓	✓
Tissue Regeneration			✓	✓		
Trauma				✓		
Tuberculosis			✓	✓	✓	✓
Vaccine Development for Infectious Disease				✓	✓	✓
Vascular Malformations	✓	✓	✓	✓	✓	✓
Women's Heart Disease	✓	✓	✓	✓	✓	✓

✓ Offered — Funded as a primary Topic Area — Funded as a secondary Topic Area only

[1] FY21 awards not finalized at this time. | [2] New in FY21

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