Exhibit R-2, RDT&E Budget Item Justification: PB 2025 Defense Advanced Research Projects Agency	Date: March 2024
Appropriation/Budget Activity 0400: *Research, Development, Test & Evaluation, Defense-Wide* / BA 1: *Basic Research*	**R-1 Program Element (Number/Name)** PE 0601117E / *BASIC OPERATIONAL MEDICAL SCIENCE*

COST ($ in Millions)	Prior Years	FY 2023	FY 2024	FY 2025 Base	FY 2025 OCO	FY 2025 Total	FY 2026	FY 2027	FY 2028	FY 2029	Cost To Complete	Total Cost
Total Program Element	-	73.355	50.430	99.048	-	99.048	113.121	127.305	134.596	139.388	-	-
MED-01: *BASIC OPERATIONAL MEDICAL SCIENCE*	-	73.355	50.430	99.048	-	99.048	113.121	127.305	134.596	139.388	-	-

A. Mission Description and Budget Item Justification

The Basic Operational Medical Science Program Element (PE) will explore and develop basic research in medical-related information and technology leading to fundamental discoveries, tools, and applications critical to overcoming DoD challenges. This PE will address the Department's identified warfighter medical care related to prevention and treatment of infectious disease, real-time healthcare interventions of acute and chronic illness and injury, and interventions for improved warfighter resilience and performance against operational stressors. This PE also supports innovation and robust transition planning in the technology cycle by working with entrepreneurs to increase the likelihood that DARPA-funded technologies take root in the U.S. and provide new capabilities for national defense.

B. Program Change Summary ($ in Millions)	FY 2023	FY 2024	FY 2025 Base	FY 2025 OCO	FY 2025 Total
Previous President's Budget	76.874	50.430	58.058	-	58.058
Current President's Budget	73.355	50.430	99.048	-	99.048
Total Adjustments	-3.519	0.000	40.990	-	40.990
• Congressional General Reductions	0.000	0.000			
• Congressional Directed Reductions	0.000	0.000			
• Congressional Rescissions	0.000	0.000			
• Congressional Adds	0.000	0.000			
• Congressional Directed Transfers	0.000	0.000			
• Reprogrammings	-0.734	0.000			
• SBIR/STTR Transfer	-2.785	0.000			
• TotalOtherAdjustments	-	-	40.990	-	40.990

Change Summary Explanation

FY 2023: Decrease reflects SBIR/STTR transfer and reprogrammings.

FY 2024: N/A

FY 2025: Increase reflects initiation of the Modernized Field Anesthesia program, Accelerated Training and Readiness Assessment program and the Emerging Opportunities in Basic Operational Medical Science thrust as well as the scaling up of efforts in the Preventing Blood Stream Infections in Warfighters After Trauma and Assessing Immune Memory (AIM) programs.

C. Accomplishments/Planned Programs ($ in Millions)	FY 2023	FY 2024	FY 2025
Title: Physiological Overmatch	16.695	12.575	9.131

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2023	FY 2024	FY 2025
Description: Warfighters operate under extreme physiological conditions, sometimes with limited resources and manpower, and must acclimate quickly to changing operational needs. The Physiological Overmatch program is investigating innovative approaches to allow the warfighter to adapt rapidly to operational challenges during deployment by developing novel detection and treatment systems. The program will initiate work in aiding the deployed soldier's ability to defend against biological pathogens, resist fatigue, combat sleep deprivation, and maintain a high capacity for teaming and operational synchronization. This program will seek to develop technology devices for in vivo release of therapies as needed by the warfighter, to understand the biological mechanisms of fatigue, and to evaluate teaming all of which will enable improvements to warfighter health and operational performance. This approach represents a significant enhancement to warfighter performance by providing protection from impacts to operational readiness and provides information related to fatigue states and the ability to operate in optimal teaming constructs. ***FY 2024 Plans:*** - Confirm that the therapy delivery device remains active and localized for at least 60 days in vivo. - Develop secure software to signal therapy activation in vivo. - Demonstrate decontamination of bacterial pathogens in vivo. - Obtain physiological measures across sleep deprived, sleep recovery, and non-sleep deprived states. - Begin biospecimen collection to assess the contribution of gut-derived biomolecules and metabolites in regulating sleep and arousal states. ***FY 2025 Plans:*** - Analyze biospecimens to identify gut-derived biomolecules and metabolites in regulating sleep and arousal states. - Identify potential molecular pathways or mechanisms of host interactions with the gut microbiome that are associated with the restorative effect of sleep on cognitive performance in an animal model. - Demonstrate decontamination of pathogens in a large animal model when released from a fully integrated device. - Demonstrate release of therapy from a fully integrated device to regulate circadian rhythm in a large animal model. ***FY 2024 to FY 2025 Increase/Decrease Statement:*** The FY 2025 decrease reflects finalization of development activities to focus on final device evaluations.			
Title: Combatting Anti-Microbial Resistant Pathogens	12.875	8.423	5.923
Description: The Combatting Anti-Microbial Resistant Pathogens program is investigating fundamental methods for using preexisting host machinery as a technology to create medical countermeasures that degrade or deactivate pathogen targets. The DoD has long recognized the warfighter's outsized risk of exposure to biological threat agents and to infectious disease, including the increasing prevalence of antimicrobial-resistant (AMR) organisms that are ranked as a Tier 1 threat to the U.S. military. Similarly, the danger posed by bacterial biothreats persists with few countermeasures available. Key advances expected from this			

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2023	FY 2024	FY 2025
research include identifying methods to discover and develop new classes of chimeric therapeutics for AMR bacteria, bacterial biothreats, and other DoD-relevant diseases and threats. These approaches represent a significant departure from conventional therapeutics, which typically rely on a limited number of small molecules with a narrow set of targets and mechanism of action. Advances in this area may be applied to the mitigation of known, new, and emerging diseases that impact military readiness and pose a global health threat. ***FY 2024 Plans:*** - Demonstrate in vivo safety and specificity of chimeric-molecule-based medical countermeasures against selected pathogens. - Demonstrate chimeric molecules with greater efficacy of state-of-the-art treatment against selected pathogens. - Demonstrate rapidly formulated and assembled chimeric molecules with increased efficacy over the state-of-the-art treatment against pathogens. - Develop up to four novel chimeric countermeasures for full optimization and potential Investigational New Drug (IND) application submission. ***FY 2025 Plans:*** - Develop Good Manufacturing Practices (GMP) grade versions of chimeric medical countermeasures and production pathways to develop GMP-grade therapeutics for pre-IND testing. - Initiate IND applications on chimeric-molecule-based medical countermeasures. - Establish Good-Laboratory Practice (GLP) compliant in vivo models for pre-IND safety, genotoxicity, pharmacology, and toxicity assessments. ***FY 2024 to FY 2025 Increase/Decrease Statement:*** The FY 2025 decrease reflects the refinement of novel chimeric medical countermeasures for IND submission.			
Title: Assessing Immune Memory (AIM)	11.757	11.624	18.200
Description: Warfighter defense against pathogens is reliant on multiple vaccinations administered repeatedly to maintain effective protection. The Assessing Immune Memory (AIM) program will seek to increase the longevity of infectious disease protection in warfighters by establishing tools that can be employed in new prophylactic development pipelines. Specifically, this program will develop a research and evaluation (R&E) tool to predict vaccine duration through the understanding of critical host factors and immune responses. Further, the tool will evaluate prophylaxis candidates and leverage effective modalities for delivery against emerging, re-emerging, or entirely unknown pathogens. Advances in this program will enable the DoD to increase the number of effective and long-lasting vaccines for warfighters, ensuring broader and consistent immunity in field-forward environments. ***FY 2024 Plans:***			

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2023	FY 2024	FY 2025
- Collect molecular profiles at early and late timepoints following vaccine challenge in relevant biological models. - Define cell and molecular features that correlate with vaccines that provide observably long immune protection. - Perform single cell molecular analyses to categorize cell-type identifiers that contribute to immune memory. - Begin to integrate data to develop a roadmap for immune memory. ***FY 2025 Plans:*** - Quantify single-cell molecular features from immune cell populations captured following vaccination. - Demonstrate immune cell features correlate with immune memory in the chosen model system. - Test mechanistic generalizability across multiple variations of vaccination. - Identify biologically relevant pathways that lead to immune memory cell formation. ***FY 2024 to FY 2025 Increase/Decrease Statement:*** The FY 2025 increase reflects a shift in focus to evaluating a broad range of vaccine models to determine generalizability of critical factors that correlate with immune responses.			
Title: Preventing Blood Stream Infections in Warfighters After Trauma	-	5.500	18.498
Description: Bloodstream infections (BSI) are a significant source of morbidity in service members that sustain combat-related injuries. Trauma temporarily degrades the efficacy of the host immune system thereby increasing the risk of life-threating opportunistic infections from fungi and bacteria that enter into the blood. If unchecked, bloodborne fungi and bacteria lead to debilitating conditions such as invasive fungal infections (IFI), sepsis, and shock. The Preventing Blood Stream Infections in Warfighters After Trauma program will develop a systems-level approach to prevent BSI in warfighters that suffer trauma from blast. Prophylactic systems circulating in the blood will be developed to bind infectious particles in the blood early and label pathogens for clearance and deliver drugs to destroy pathogens and/or restore healthy physiology. Ultimately this program will develop novel technologies that will protect service members from morbidity and mortality associated with BSI. ***FY 2024 Plans:*** - Initiate development of delivery molecules that can circulate in the bloodstream for an extended period of time. - Evaluate the binding affinity of pathogen-agnostic recognition sequences to different types of fungi and bacteria. - Begin to measure the ability for newly designed prophylactic to bind or neutralize target pathogens. ***FY 2025 Plans:*** - Demonstrate developed prophylaxis is non-toxic and non-immunogenic in the host. - Demonstrate prophylactic prevents growth of a single fungal and bacterial pathogen in blood. - Demonstrate developed prophylaxes increase survival in single fungal and bacterial pathogen in blood.			

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2023	FY 2024	FY 2025
- Demonstrate prophylaxes can be produced at scale. ***FY 2024 to FY 2025 Increase/Decrease Statement:*** The FY 2025 increase reflects enhancements in the in vivo trauma care conditions that include burn and blast scenarios.			
Title: Modernized Field Anesthesia* ***Description:*** *Previously part of Improved Interventions The Modernized Field Anesthesia program will aim to produce safe, battlefield-ready anesthetics to reduce the trauma associated with injury and improve combat casualty outcomes. Current therapeutics that enable life-saving interventions and wound stabilization must be used in hospitals or highly-monitored settings due to their lack of safety. Prolonged peer or near-peer conflict could severely impact medical evacuation (MEDIVAC) times, resulting in extended time before patients reach a hospital. The Modernized Field Anesthesia program will seek to uncover mechanisms of anesthesia at multiple biological levels ranging from the molecular to the organismal. Novel treatments developed under the program will exhibit the desirable properties of anesthetics, including calming effects and loss of sensation and consciousness but will have vastly improved safety profiles, making them usable in the field by warfighters with minimal medical training. ***FY 2024 Plans:*** - Develop appropriate biological models for evaluating anesthetic endpoints. - Establish methods to evaluate the biological mechanisms underlying the desired state of anesthesia. ***FY 2025 Plans:*** - Develop appropriate biological models and implement systems and profiling techniques for interrogating multiple model systems of anesthesia. - Initiate studies for anesthetic target discovery associated with analgesia, loss of consciousness, and immobility. - Develop the computational infrastructure required for analysis and prioritization of cellular/molecular target space. - Define target profile effects that are associated with current anesthetic interventions. ***FY 2024 to FY 2025 Increase/Decrease Statement:*** The FY 2025 increase reflects a widening of experimental focus to include multiple length-scales in the development and improvement of biological models of anesthesia.	-	3.000	18.282
Title: Accelerated Training and Readiness Assessment* ***Description:*** *Previously part of Physiological Overmatch	-	3.000	15.419

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2023	FY 2024	FY 2025
The Accelerated Training and Readiness Assessment program will seek to advance technologies to drive efficiency and efficacy of military operator preparation and expertise building. This program will seek to understand fundamental biological processes to support real-time physiological assessment, performance diagnostics, and objective prediction of warfighter and team proficiency, with the ultimate goal of improved DoD mission readiness and execution. Advances in this program will result in a significant enhancement to warfighter team performance by providing methods to determine teaming potential and actionable paths to optimal teaming. ***FY 2024 Plans:*** - Develop custom metrics for assessment of team performance and initiate capture of ground truth data across real-world team training sessions. - Create testbed to identify and validate biobehavioral signatures of team coordination. ***FY 2025 Plans:*** - Collect data and identify candidate biobehavioral signatures of warfighter and team performance. - Demonstrate ability to measure and characterize identified signatures rapidly, reliably, and accurately during team training sessions. - Initiate development of predictive models for biobehavioral signature validation. ***FY 2024 to FY 2025 Increase/Decrease Statement:*** The FY 2025 increase reflects shift from initial discovery of candidate biobehavioral signatures to characterization work across various team training scenarios.			
Title: Emerging Opportunities in Modeling Basic Operational Medical Science	-	-	13.595
Description: The DoD will accelerate discovery and development by leveraging recent advances in computational methods to identify new capabilities and address evolving stressors encountered by warfighters. The Emerging Opportunities in Modeling Basic Operational Medical Science thrust seeks to advance machine learning and artificial intelligence to create physics-based simulation of biological function with undetermined or broad military utility. This thrust will seek to understand fundamental biological processes to accurately simulate, and thus predict biological functions, identify emergent properties, predict antibiotic resistance, and help accelerate biology research. Accurate, extensible, and interpretable physics-based simulations of microbial cell behavior will help maintain domestic competitiveness in biomedical research, increase the resiliency of supply chains, serve as a tool for public health and to ensure biosecurity. Technologies in this effort will be developed to create high-fidelity simulations of fundamental biological processes. ***FY 2025 Plans:*** - Initiate automated experimentation and data collection to create high-quality data sets of biological processes.			

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2023	FY 2024	FY 2025
- Initiate development of initial computational simulation of biological processes. - Create application-specific computational learning models to support the accurate and reliable simulation of biological behavior. - Evaluate initial computational models to assess the ability to simulate, predict, and forecast microbial behavior in DoD-relevant settings. ***FY 2024 to FY 2025 Increase/Decrease Statement:*** The FY 2025 increase reflects thrust initiation.			
Title: Improved Interventions ***Description:*** The Improved Interventions program seeks to develop novel pharmacological interventions to quickly and holistically optimize the performance of the healthy warfighter and improve treatment of the injured warfighter. The status quo for pharmacological intervention is one drug, one target, which often has many undesirable side effects. This program will create a platform to develop pharmacological interventions capable of modulating multiple targets within biological systems of the body, which will reduce side effects and promote safety. Research will focus on the integration of novel bioinformatics approaches, and new chemical synthesis methods to treat the system in order to achieve desired physiological effects. This program will lead to new pharmacological discovery and design principles that will lead to pharmacological interventions that can be used to safely treat and support battlefield causalities. ***FY 2024 Plans:*** - Demonstrate that the optimized novel multi-target drug has greater efficacy than standard of care. - Determine therapeutic index (i.e., ratio of toxic dose/effective dose) of the novel multi-target drug. - Characterize pharmacokinetic properties of the novel multi-target drugs. - Begin Investigational New Drug (IND)-enabling preclinical studies for pharmacology and toxicology. ***FY 2024 to FY 2025 Increase/Decrease Statement:*** The FY 2025 decrease reflects program completion.	13.893	6.308	-
Title: Outpacing Infectious Disease ***Description:*** Military readiness and national security depend on the health and well-being of military service members. Unfortunately, today's antivirals and vaccines are often circumvented by fast-mutating viruses that evolve to develop drug resistance. Military service members often deploy to areas with such diseases that require new protective measures to maintain readiness. The Outpacing Infectious Disease program investigated fundamental methods for using biology as a technology to create adaptive therapeutic response mechanisms to outpace viral diseases such as enabling co-evolution and co-transmission of newly developed therapeutics to ultimately outcompete the pathogen. Key advances expected from this research included identifying methods to discover and develop new classes of dynamic therapeutics for fast-mutating viruses. This approach	2.501	-	-

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2023	FY 2024	FY 2025
represents a significant departure from conventional antiviral therapies, which typically rely on static solutions and continuous re-formulation and re-development in attempt to keep pace with emerging strains and disease variants. Advances in this area may be applied to the mitigation of known, new, or emerging diseases that impact military readiness and pose a national security risk as a potential pandemic.			
Title: Preventing the Emergence of Disease (PED) ***Description:*** Many emerging infectious disease outbreaks have origins in animal reservoirs and occur in areas where DoD personnel are deployed, putting them at high risk of endemic and emerging diseases. The Preventing the Emergence of Disease (PED) program investigated how animal pathogens are transmitted to humans and exploring novel approaches to prevent these events. Tools such as detailed molecular analysis and bioinformatics were leveraged. Researchers developed models to quantify the probability of pathogen disease transmission from animals to humans. Promising intervention approaches were developed to prevent viral species jumps from animal reservoirs to humans. Predicting such jumps is a key capability to mitigating outbreaks originating in animal reservoirs.	2.716	-	-
Title: Early Battlefield Interventions (EBI) ***Description:*** The Early Battlefield Interventions (EBI) program explored new methods to slow and limit damage caused by acute trauma, injury, and bloodstream infection often suffered by warfighters under far forward conditions. Research efforts applied advances in molecular and cellular biology, cell signaling, and biomaterials to develop new tools to alter the time course of pathological processes and prevent bloodstream infections in warfighters that suffer trauma. This tactic is a departure from traditional therapeutic approaches that seek to control symptoms associated with active infections or innate physiological responses to tissue trauma. Therapeutics were developed to rapidly detect infections following trauma and deliver therapeutics to restore healthy physiology. Advances in this area may be applied to the development of both prophylactic and therapeutic medical countermeasures to forward-deployed service members.	12.918	-	-
Accomplishments/Planned Programs Subtotals	73.355	50.430	99.048

D. Other Program Funding Summary ($ in Millions)

N/A

Remarks

E. Acquisition Strategy

N/A