Exhibit R-2, RDT&E Budget Item Justification: PB 2024 Defense Advanced Research Projects Agency	Date: March 2023
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 2022	FY 2023	FY 2024 Base	FY 2024 OCO	FY 2024 Total	FY 2025	FY 2026	FY 2027	FY 2028	Cost To Complete	Total Cost
Total Program Element	-	75.071	76.874	50.430	-	50.430	58.058	69.169	67.752	74.426	-	-
MED-01: *BASIC OPERATIONAL MEDICAL SCIENCE*	-	75.071	76.874	50.430	-	50.430	58.058	69.169	67.752	74.426	-	-

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 2022	FY 2023	FY 2024 Base	FY 2024 OCO	FY 2024 Total
Previous President's Budget	77.518	80.874	67.204	-	67.204
Current President's Budget	75.071	76.874	50.430	-	50.430
Total Adjustments	-2.447	-4.000	-16.774	-	-16.774
• Congressional General Reductions	0.000	-4.000			
• 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	0.000	0.000			
• SBIR/STTR Transfer	-2.447	0.000			
• TotalOtherAdjustments	-	-	-16.774	-	-16.774

Congressional Add Details ($ in Millions, and Includes General Reductions)	FY 2022	FY 2023
Project: MED-01: *BASIC OPERATIONAL MEDICAL SCIENCE*		
Congressional Add: *Novel Analytical and Empirical Approaches for Prediction and Monitoring of Disease Transmission - Congressional Add*	1.500	-
Congressional Add Subtotals for Project: MED-01	1.500	-
Congressional Add Totals for all Projects	1.500	-

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Change Summary Explanation

FY 2022: Decrease reflects SBIR/STTR transfer.

FY 2023: Decrease reflects a Congressional reduction for Prior Year Underexecution.

FY 2024: Decrease reflects completion of the Outpacing Infectious Disease, Preventing the Emergence of Disease (PED) and Early Battlefield Interventions (EBI) programs in FY 2023.

C. Accomplishments/Planned Programs ($ in Millions)	FY 2022	FY 2023	FY 2024
Title: Physiological Overmatch	16.754	16.695	14.922

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, receive adequate nutrition and hydration, and maintain a high capacity for teaming and operational synchronization. This program will seek to understand the biological mechanisms of fatigue, and teaming to enable improvements to warfighter health and operational performance. Advances in engineered cells, bioelectronics, and cellular feedback circuits will be investigated to provide controlled, in vivo release of therapies as needed by the warfighter. This approach represents a significant enhancement to warfighter performance by providing protection and resilience from variables that impact operational readiness.

FY 2023 Plans:

- Demonstrate localization of the carrier device within a realistic model, such as phantom tissue.
- Validate that a beneficial biomolecule can be delivered in vivo.
- Confirm biocompatibility of the carrier device for at least 30 days in a large animal model.
- Develop a prototype sensor for tracking circadian rhythm.
- Assess stability of volatile organic compounds (VOCs) in breath samples stored for >12 hours.
- Explore experimental approaches to assess physiological factors contributing to the impact of sleep loss on health and performance.

FY 2024 Plans:

- Confirm that the carrier device remains active and localized for at least 60 days in vivo.
- Develop secure software to signal therapy activation in vivo.
- Demonstrate decontamination of five bacterial pathogens in vivo.
- Begin data collection to assess the contribution of gut-derived biomolecules and metabolites in regulating sleep and arousal states.

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2022	FY 2023	FY 2024
- Identify neurophysiological biomarkers of team coordination and synchrony. ***FY 2023 to FY 2024 Increase/Decrease Statement:*** The FY 2024 decrease reflects finalization of the integrated carrier design in preparation for the clinical studies.			
Title: Combatting Anti-Microbial Resistant Pathogens	15.388	14.375	9.423
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 research include identifying methods to discover and develop new classes of 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 2023 Plans:*** - Investigate the ability of chimeric molecules to inhibit DoD-relevant pathogen threats in vitro. - Demonstrate generalizable therapeutic candidate discovery and optimization approaches. - Develop chimeric molecules showing specificity and efficacy against DoD-relevant pathogen threats in cell culture. - Define mechanisms of degradation for targets captured using chimeric medical countermeasures. - Refine rapid drug identification and screening approaches for degradation or deactivation of novel pathogen targets. ***FY 2024 Plans:*** - Demonstrate in vivo safety and specificity of chimeric-molecule-based medical countermeasures against selected pathogens. - Demonstrate chimeric molecules with greater than five-times the efficacy of state-of-the-art treatment against selected pathogens. - Demonstrate rapidly formulated and assembled chimeric molecules with greater than five-times the efficacy of 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 2023 to FY 2024 Increase/Decrease Statement:***			

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2022	FY 2023	FY 2024
The FY 2024 decrease reflects the completion of discovery efforts and movement towards optimization and validation of selected approaches.			
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. Progress in this area will lead to new pharmacological discovery and design principles that will lead to interventions that can be used to augment physical fitness training and maintenance for military populations, and novel battlefield-ready anesthetics to safely treat and support battlefield causalities. ***FY 2023 Plans:*** - Analyze drug combination effects and compare to single drug therapy. - Optimize novel multi-target drugs for activity based on response profiles. - Identify protein targets and synthesize drugs in less than 60 days. - Use biological model systems to validate multi-target drug actions for therapeutic use. ***FY 2024 Plans:*** - Demonstrate that the optimized novel multi-target drug has greater effectiveness than standard of care. - Determine therapeutic index (i.e., 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. - Establish methods to evaluate neural circuitry underlying the desired state of anesthesia. ***FY 2023 to FY 2024 Increase/Decrease Statement:*** The FY 2024 decrease reflects late-stage platform validation and a decrease in early-stage discovery work.	15.122	15.912	6.461
Title: Assessing Immune Memory (AIM) ***Description:*** Warfighter defense against pathogens is reliant on multiple vaccinations administered repeatedly to maintain effective protection. Building upon initial discoveries and technology development under the Outpacing Infectious Disease program, 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	-	11.757	12.124

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2022	FY 2023	FY 2024
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 2023 Plans:*** - Initiate studies to uncover host mechanisms that lead to the production of long-lasting immune memory cells after antigen presentation. - Determine immune system challenge and appropriate biological model for profiling approaches. - Initiate characterization of established immune responses to selected antigens. - Begin to collect and compare molecular profiles of stimulated immune response. - Begin developing computational frameworks required for analyzing large collections of molecular and phenotypic data. ***FY 2024 Plans:*** - 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 2023 to FY 2024 Increase/Decrease Statement:*** The FY 2024 increase reflects minor program repricing.			
Title: Preventing Blood Stream Infections in Warfighters After Trauma	-	-	7.500
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 design particles that 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 carriers that can circulate in the bloodstream for up to three days. - Evaluate the binding affinity of pathogen-agnostic recognition sequences to different types of fungi and bacteria.			

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2022	FY 2023	FY 2024
- Measure the ability for newly designed prophylactic to bind, clear, and destroy target pathogens. ***FY 2023 to FY 2024 Increase/Decrease Statement:*** The FY 2024 increase reflects program initiation.			
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 is investigating 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 include identifying methods to discover and develop new classes of dynamic therapeutics for fast-mutating viruses. Additionally, methodologies to predict the duration of immune protection are being explored. This approach 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. ***FY 2023 Plans:*** - Submit Investigational New Drug (IND) package for clinical trials for therapeutic interfering particles (TIPs). - Complete current Good Manufacturing Practice (cGMP) production of TIPs for clinical trial. - Initiate clinical safety trial for TIPs. ***FY 2023 to FY 2024 Increase/Decrease Statement:*** The FY 2024 decrease reflects program completion.	6.889	2.501	-
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 is investigating how animal pathogens are transmitted to humans and exploring novel approaches to prevent these events. Tools such as detailed molecular analysis and bioinformatics will be leveraged. Researchers will develop models to quantify the probability of pathogen disease transmission from animals to humans. Promising intervention approaches will be 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. ***FY 2023 Plans:***	4.882	2.716	-

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2022	FY 2023	FY 2024
- Demonstrate vaccine stability and efficacy via Independent Verification and Validation (IV&V). - Validate phylodynamic and multi-scale modeling for multiple host species and diseases. ***FY 2023 to FY 2024 Increase/Decrease Statement:*** The FY 2024 decrease reflects program completion.			
Title: Early Battlefield Interventions (EBI) ***Description:*** The Early Battlefield Interventions (EBI) program is exploring 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 will apply 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 will be 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. ***FY 2023 Plans:*** - Demonstrate biostasis induction at observable and molecular levels in complex, multicellular biological systems. - Evaluate the time course of biostasis induction and reversibility in multicellular systems. - Detail mechanisms underlying biostasis, as well as potential negative effects (e.g., toxicity, DNA damage, etc.) in multicellular biological systems. ***FY 2023 to FY 2024 Increase/Decrease Statement:*** The FY 2024 decrease reflects program completion.	14.536	12.918	-
Accomplishments/Planned Programs Subtotals	73.571	76.874	50.430

	FY 2022	FY 2023
Congressional Add: Novel Analytical and Empirical Approaches for Prediction and Monitoring of Disease Transmission - Congressional Add ***FY 2022 Accomplishments:*** - Initiated research in novel analytical and empirical approaches for prediction and monitoring of disease transmission.	1.500	-
Congressional Adds Subtotals	1.500	-

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D. Other Program Funding Summary ($ in Millions)

N/A

Remarks

E. Acquisition Strategy

N/A