Exhibit R-2, RDT&E Budget Item Justification: PB 2021 Defense Advanced Research Projects Agency	Date: February 2020
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 2019	FY 2020	FY 2021 Base	FY 2021 OCO	FY 2021 Total	FY 2022	FY 2023	FY 2024	FY 2025	Cost To Complete	Total Cost
Total Program Element	-	49.692	54.122	53.730	-	53.730	62.181	61.553	66.511	70.996	-	-
MED-01: *BASIC OPERATIONAL MEDICAL SCIENCE*	-	49.692	54.122	53.730	-	53.730	62.181	61.553	66.511	70.996	-	-

A. Mission Description and Budget Item Justification

The Basic Operational Medical Science Program Element will explore and develop basic research in medical-related information and technology leading to fundamental discoveries, tools, and applications critical to solving DoD challenges. Programs in this project address the Department's identified medical gaps in warfighter care related to health monitoring, restorative function of the body, and prevention and treatment of infectious disease. Efforts will draw upon computational modeling and experimental data to discover properties of biological systems that cross multiple scales of biological architecture and function, from the molecular and genetic level through cellular, tissue, organ, and whole organism levels. To enable in-theater, continuous monitoring, protection, and treatment of warfighters, this project will explore multiple diagnostic and therapeutic approaches, including developing techniques to protect against emerging pathogens; exploring methods to slow damage from pathological infection or traumatic injury; and leveraging fundamental and engineered biological mechanisms to enhance tolerance to insults such as pain and altitude.

B. Program Change Summary ($ in Millions)	FY 2019	FY 2020	FY 2021 Base	FY 2021 OCO	FY 2021 Total
Previous President's Budget	46.575	54.122	51.337	-	51.337
Current President's Budget	49.692	54.122	53.730	-	53.730
Total Adjustments	3.117	0.000	2.393	-	2.393
• 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	3.471	0.000			
• SBIR/STTR Transfer	-0.354	0.000			
• TotalOtherAdjustments	-	-	2.393	-	2.393

Congressional Add Details ($ in Millions, and Includes General Reductions)	FY 2019	FY 2020
Project: MED-01: *BASIC OPERATIONAL MEDICAL SCIENCE*		
Congressional Add: *TBI Treatment for Blast Injuries*	5.000	-
Congressional Add Subtotals for Project: MED-01	5.000	-
Congressional Add Totals for all Projects	5.000	-

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Change Summary Explanation

FY 2019: Increase reflects reprogrammings offset by the SBIR/STTR transfer.
FY 2020: N/A
FY 2021: Increase reflects the initiation of the Physiological Overmatch program.

C. Accomplishments/Planned Programs ($ in Millions)	FY 2019	FY 2020	FY 2021
Title: Preventing the Emergence of Disease (PED)	12.819	12.598	8.449
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 2020 Plans:*** - Refine mathematical models of virus dynamics within and between two host species, and initiate validation with data from the field. - Integrate virus transmission dynamics, environmental data, and viral fitness metrics into spillover risk model for selected viruses. - Demonstrate proof-of-concept preemptive approaches for suppressing virus jump from one species to another in a relevant animal model. ***FY 2021 Plans:*** - Expand mathematical models to predict when viral shedding from animals will lead to spillover at a spatial and temporal scale relevant for intervention. - Using mathematical models, identify bottlenecks for the optimal timing, delivery and scaling of countermeasures to ensure efficacy in reservoir species. - Demonstrate scalability of preemptive approaches for suppressing virus jump from one species to another in a relevant animal model. - Demonstrate broad-spectrum preemptive approaches for suppressing virus transmission from vectors to animal models. ***FY 2020 to FY 2021 Increase/Decrease Statement:*** The FY 2021 decrease reflects completion of development efforts and subsequent focus on those mathematical models and interventions that have been demonstrated most effective in earlier proof-of-concept experiments.			
Title: Early Battlefield Interventions (EBI)	11.744	13.348	13.957

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2019	FY 2020	FY 2021
Description: Based on initial research conducted under the Analysis and Adaptation of Human Resilience program, budgeted in this PE and project, the Early Battlefield Interventions (EBI) program is exploring new methods to slow and limit damage caused by acute trauma, injury, and 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 associated with infection and tissue damage. 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. Advances in this area may be applied to the development of both prophylactic and therapeutic medical countermeasures to forward-deployed service members. ***FY 2020 Plans:*** - Characterize the molecular mechanisms for reversibly slowing biological processes in cells. - Begin to test novel interventions to reversibly slow biochemical processes in multicellular biological systems (e.g., organoids, tissues). - Evaluate protein stabilization induced by interventions in multicellular biological systems. - Characterize intervention formulations to enhance cell penetration and reversibility. - Identify platform technologies to enable controlled systemic delivery of multiple orthogonal interventions to reset or establish healthy biological patterns. ***FY 2021 Plans:*** - Evaluate and optimize computational models for molecular design and prediction to achieve biostasis. - Begin evaluation of effects on cell functions and molecular pathways for biostasis-inducing agents. - Continue testing the ability of biostasis interventions to reversibly slow processes in biological systems of increasing complexity, ranging from single proteins through multicellular systems (e.g., organoids, organ chips, and tissues). - Optimize delivery protocols and formulations of biostasis interventions for biological uptake and distribution, and characterize molecular mechanisms of interventions. ***FY 2020 to FY 2021 Increase/Decrease Statement:*** The FY 2021 increase reflects minor program repricing.			
Title: Outpacing Infectious Disease	14.190	13.894	8.734
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 thrust 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			

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2019	FY 2020	FY 2021
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. 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 2020 Plans:*** - Assess optimal route, dose, and timing of treatment for selected virus therapeutic interfering particle (TIP) candidates in relevant animal models. - Determine the broad-spectrum efficacy of TIPs against multiple viral strains. - Assess TIP transmission dynamics in animal models. - Prepare regulatory package for pre-clinical trial for TIPs. ***FY 2021 Plans:*** - Demonstrate TIP-based medical countermeasures rapid response platform proof-of-concept. - Prepare Good Manufacturing Practice (GMP) TIP product in quantities sufficient for Investigational New Drug (IND)-enabling studies and clinical trial. - Initiate clinical safety trial for TIPs. ***FY 2020 to FY 2021 Increase/Decrease Statement:*** The FY 2021 decrease reflects completion of exploratory research efforts and transition to applied countermeasure development.			
Title: Improved Interventions	-	14.282	13.575
Description: The Improved Interventions program seeks to develop novel pharmacological interventions to quickly and holistically optimize the performance of the healthy 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, high-content physiological model systems, and new bio-orthogonal 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 products that can be used to augment physical fitness training and maintenance for military populations. The Improved Interventions program builds upon the genomic and physiological analyses conducted under the Analysis and Adaptation of Human Resilience program, budgeted in this PE and project. ***FY 2020 Plans:***			

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2019	FY 2020	FY 2021
- Generate preliminary datasets of proteins involved in a complex physiological process. - Begin to build computational tools that model complex physiological processes. - Begin development of informatics pipeline to predict targets regardless of prior knowledge. - Analyze biochemical processes associated with proteins of unknown function. - Identify chemical synthesis methods to build novel small molecules to target any protein or combination of proteins in the human proteome. - Begin identification of targets for modulation and interface with central and peripheral sensory neurons. ***FY 2021 Plans:*** - Employ a multi-tissue biological system to adequately characterize an indication of military operational relevance (e.g., pain/ inflammation or metabolic stress under hypoxia). - Use computational approaches to predict and optimize drug activity profiles. - Begin synthesis, testing, and exploration of predicted chemical compounds for indications of interest (e.g., pain/inflammation and metabolic stress under hypoxia). - Begin validation of computational pipelines to determine highest-value targets without relying on previous knowledge. ***FY 2020 to FY 2021 Increase/Decrease Statement:*** The FY 2021 decrease reflects minor program repricing.			
Title: Physiological Overmatch ***Description:*** Warfighters must operate under extreme physiological conditions with limited resources, acclimating quickly to austere environments. The Physiological Overmatch program will investigate innovative approaches to leverage biological systems to adapt to environmental challenges during deployment. The program will initiate work in aiding the deployed soldier's ability to defend against biological pathogens and chemical contaminants, resist fatigue, and receive adequate nutrition and hydration. Advances in engineered cells, bioelectronics, and cellular feedback circuits will enable the controlled, in vivo release of therapies as needed by the warfighter. This approach represents a significant enhancement to warfighter performance by providing internal protection from novel threats. ***FY 2021 Plans:*** - Demonstrate engineered cellular viability in vitro and the capability of cellular systems to mitigate degraded performance caused by disrupted circadian rhythms or contaminated food or water. - Demonstrate ex vivo synthetic biology circuit components enabling the delivery of a beneficial biomolecule at a clinically relevant level (e.g., medical countermeasure). - Demonstrate ex vivo engineered cells that can implement a therapeutic purification or detoxification process, such as removing viral, bacterial, or toxin threats.	-	-	9.015

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2019	FY 2020	FY 2021
- Begin development of biocompatible devices that control engineered cells in the body. ***FY 2020 to FY 2021 Increase/Decrease Statement:*** The FY 2021 increase reflects program initiation.			
Title: Analysis and Adaptation of Human Resilience ***Description:*** The Analysis and Adaptation of Human Resilience program explored new methods to maintain and optimize warfighter health in response to environmental insults such as new and emerging infectious diseases. Research efforts in this area applied recent advances in comparative biology, genetic sequencing, omics technologies, and bioinformatics to develop new tools for modulating health to ensure warfighter readiness. One approach to achieve the program's goal was to identify the fundamental mechanisms that enable certain species to be tolerant to various environmental insults. Genomic and physiological analyses of a wide array of resilient animal species were combined with sophisticated algorithms to identify important patterns of survival. By analyzing patterns in the underlying variability of host responses for resilient animals, a survival blueprint is being developed to restore and maintain warfighter homeostasis in response to infection. This approach was orthogonal to traditional infectious disease research, which primarily relies on reducing the pathogen load through drug intervention. Research efforts within this program may enable discovery of novel methods to optimize human health against infectious diseases caused by multi-drug resistant pathogens.	5.939	-	-
Accomplishments/Planned Programs Subtotals	44.692	54.122	53.730

	FY 2019	FY 2020
Congressional Add: TBI Treatment for Blast Injuries ***FY 2019 Accomplishments:*** Conduct research in TBI treatment for blast injuries.	5.000	-
Congressional Adds Subtotals	5.000	-

D. Other Program Funding Summary ($ in Millions)

N/A

Remarks

E. Acquisition Strategy

N/A