Exhibit R-2, RDT&E Budget Item Justification: PB 2022 Defense Advanced Research Projects Agency	Date: May 2021
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 2020	FY 2021	FY 2022 Base	FY 2022 OCO	FY 2022 Total	FY 2023	FY 2024	FY 2025	FY 2026	Cost To Complete	Total Cost
Total Program Element	-	57.721	53.730	76.018	-	76.018	-	-	-	-	-	-
MED-01: *BASIC OPERATIONAL MEDICAL SCIENCE*	-	57.721	53.730	76.018	-	76.018	-	-	-	-	-	-

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 overcoming DoD challenges. Programs in this Program Element address the Department's identified medical gaps in warfighter care related to, restorative function of the body, blood loss, 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 Program Element will explore multiple diagnostic and therapeutic approaches, including developing techniques to protect against emerging pathogens; exploring methods to prevent pathological infection or traumatic injury; and leveraging fundamental and engineered biological mechanisms to enhance tolerance to insults such as pain and altitude. This Program Element 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. This Program Element includes FY 2020 CARES Act Funding in the amount of $5.0 million to identify Food and Drug Administration (FDA)-approved drugs that could be repurposed as effective treatments for COVID-19.

B. Program Change Summary ($ in Millions)	FY 2020	FY 2021	FY 2022 Base	FY 2022 OCO	FY 2022 Total
Previous President's Budget	54.122	53.730	62.181	-	62.181
Current President's Budget	57.721	53.730	76.018	-	76.018
Total Adjustments	3.599	0.000	13.837	-	13.837
• Congressional General Reductions	0.000	0.000			
• Congressional Directed Reductions	0.000	0.000			
• Congressional Rescissions	0.000	0.000			
• Congressional Adds	5.000	0.000			
• Congressional Directed Transfers	0.000	0.000			
• Reprogrammings	4.984	0.000			
• SBIR/STTR Transfer	-6.385	0.000			
• TotalOtherAdjustments	-	-	13.837	-	13.837

Change Summary Explanation

FY 2020: Increase reflects COVID response CARES Act add and reprogrammings offset by the SBIR/STTR transfer.
FY 2021: N/A
FY 2022: Increase reflects scale up of the Combatting Anti-Microbial Resistant Pathogens and Physiological Overmatch programs.

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2020	FY 2021	FY 2022
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 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 animal reservoirs. - Demonstrate scalability of preemptive approaches for suppressing virus jump from one species to another in relevant animal models. - Demonstrate broad-spectrum preemptive approaches for suppressing virus transmission from vectors to animal models. ***FY 2022 Plans:*** - Demonstrate safety, efficiency, and efficacy of scalable countermeasure delivery platform in vitro and in animal models. - Adapt phylodynamic and multi-scale modeling to other host species and diseases. - Demonstrate efficacy of a vaccine to prevent Lassa fever virus spillover in controlled laboratory tests. - Demonstrate efficacy of ecological countermeasures to protect against spillover of henipaviruses and coronaviruses from animal reservoirs in controlled laboratory tests. ***FY 2021 to FY 2022 Increase/Decrease Statement:*** The FY 2022 decrease reflects minor program repricing.	11.848	5.664	5.382
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 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	14.348	13.957	17.650

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2020	FY 2021	FY 2022
area may be applied to the development of both prophylactic and therapeutic medical countermeasures to forward-deployed service members. ***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. - Demonstrate efficacy of biostasis intervention to reversibly slow processes in biological systems of increasing complexity. - Optimize delivery protocols and formulations of biostasis interventions for biological uptake and distribution, and characterize molecular mechanisms of interventions. ***FY 2022 Plans:*** - Observe the effects of biostasis-inducing agents on cell function (e.g., toxicity, metabolism, DNA damage, etc.), and evaluate mechanisms of biostasis. - Validate intervention approaches to focus on inducing and reversing biostasis in increasingly complex, multicellular systems. - Evaluate biological uptake and distribution of biostasis interventions, and characterize molecular mechanisms of interventions. - Begin to characterize time course of biostasis induction and reversibility of cellular stasis. ***FY 2021 to FY 2022 Increase/Decrease Statement:*** The FY 2022 increase reflects the need to demonstrate the ability to preserve a complex biological system (tissue, organoid) with 98% or greater cell survival.			
Title: Outpacing Infectious Disease	13.144	5.850	6.139
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. 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 2021 Plans:***			

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2020	FY 2021	FY 2022
- Prepare and submit pre-Investigational New Drug (IND) regulatory package for clinical trial for therapeutic interfering particles (TIPs). - Demonstrate TIP-based medical countermeasures rapid response platform proof-of-concept. - Prepare Good Manufacturing Practice (GMP) TIP product in quantities sufficient for IND-enabling studies and clinical trial. - Validate predictive mathematical models for viral shedding, symptom severity, and effective interventions. ***FY 2022 Plans:*** - Initiate clinical safety trial for TIPs. - Determine spatial distribution and co-localization of TIPs and viruses in vivo. - Identify alternative methods for discovery and development of prophylactics to increase the longevity of protection for known, new, or emerging diseases. ***FY 2021 to FY 2022 Increase/Decrease Statement:*** The FY 2022 increase reflects minor program repricing.			
Title: Improved Interventions	18.381	13.737	15.733
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. ***FY 2021 Plans:*** - Employ a multi-tissue biological system to characterize indications of DoD relevance (e.g., pain/inflammation or metabolic stress under hypoxia). - Predict and optimize drug activity profiles using computational approaches. - Begin synthesis, testing, and exploration of predicted chemical compounds for indications of DoD interest. - Begin validation of computational pipelines to determine highest-value targets without relying on previous knowledge. ***FY 2022 Plans:*** - Begin validation of novel drug target network by predicting and testing drug combinations in a complex model system. - Collect molecular response profiles to target drugs developed for the indications of interest. - Test novel chemical compounds in appropriate animal models and compare to current single drug therapy.			

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- Accelerate the timeline to network assembly and drug synthesis platform. ***FY 2021 to FY 2022 Increase/Decrease Statement:*** The FY 2022 increase reflects the need for a capability demonstration that establishes the ability to generate a drug target network within 60 days of data collection and validate the proposed network in an appropriate animal model.			
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:*** - Initiate cell engineering and begin to assess engineered cellular viability in vitro. - Initiate development of ex vivo synthetic biology circuit components to enable the delivery of a beneficial biomolecule at a clinically relevant level (e.g., medical countermeasure). - Initiate development of ex vivo engineered cells that can implement a therapeutic purification or detoxification process, such as removing viral, bacterial, or toxin threats. - Begin development of biocompatible carrier devices that control engineered cells in the body. ***FY 2022 Plans:*** - Demonstrate inducible biosynthesis enabling the delivery of a beneficial biomolecule at a clinically relevant level. - Test biosynthesis of at least one therapy in vivo. - Demonstrate communication with the carrier in vivo or through realistic models (e.g., phantom tissue). - Validate biocompatibility of the carrier device in vivo. ***FY 2021 to FY 2022 Increase/Decrease Statement:*** The FY 2022 increase reflects the cost of demonstrating each technical area in small and large animal models.	-	8.817	15.115
Title: Combatting Anti-Microbial Resistant Pathogens ***Description:*** Building upon technologies developed under the Outpacing Infectious Disease program, the Combatting Anti-Microbial Resistant Pathogens program will investigate fundamental methods for using innate host machinery as a technology to create medical countermeasures that degrade or deactivate pathogen targets. The DoD has long recognized the warfighter's	-	5.705	15.999

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2020	FY 2021	FY 2022
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 and bacterial biothreats. This approach represents a significant departure from conventional antibiotics, 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 bacterial pathogens that impact military readiness and pose a global health threat. ***FY 2021 Plans:*** - Begin development of novel ligands to bind microbial and toxin targets using biochemical and computational discovery methods. - Identify pathways for in-host microbe and toxin degradation or deactivation and begin identification of ligands to engage these pathways. - Begin development of linkers to bridge threat-binding and host-engaging ligands using experimental and computational methods. ***FY 2022 Plans:*** - Investigate the ability of chimeric molecules to inhibit DoD-relevant pathogen threats in vitro. - Develop methods to model the kinetics and outcomes of chimeric molecules against pathogens. - Investigate the mechanism of action for chimeric molecules engaging new host machinery. - Develop rapid ligand identification and screening approaches for pathogen targets and host machinery. ***FY 2021 to FY 2022 Increase/Decrease Statement:*** The FY 2022 increase reflects integration of multiple components of the medical countermeasures required to demonstrate their efficacy for capability demonstrations and development of the rapid response platform that will be required for forthcoming pressure tests.			
Accomplishments/Planned Programs Subtotals	57.721	53.730	76.018

D. Other Program Funding Summary ($ in Millions)

N/A

Remarks

E. Acquisition Strategy

N/A