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Exhibit R-2, RDT&E Budget Item Justification: PB 2023 Defense Advanced Research Projects Agency **Date:** April 2022

Appropriation/Budget Activity 0400: <i>Research, Development, Test & Evaluation, Defense-Wide</i> / BA 1: <i>Basic Research</i>					R-1 Program Element (Number/Name) PE 0601117E / <i>BASIC OPERATIONAL MEDICAL SCIENCE</i>							
COST (\$ in Millions)	Prior Years	FY 2021	FY 2022	FY 2023 Base	FY 2023 OCO	FY 2023 Total	FY 2024	FY 2025	FY 2026	FY 2027	Cost To Complete	Total Cost
Total Program Element	-	57.542	77.518	80.874	-	80.874	67.204	67.738	90.378	80.321	-	-
MED-01: <i>BASIC OPERATIONAL MEDICAL SCIENCE</i>	-	57.542	77.518	80.874	-	80.874	67.204	67.738	90.378	80.321	-	-

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, sleep restriction, 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; increasing the longevity of effective therapeutics against pathogenic threats; and leveraging fundamental and engineered biological mechanisms to enhance tolerance to insults such as pain, altitude, and chronic loss of sleep. 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.

B. Program Change Summary (\$ in Millions)

	<u>FY 2021</u>	<u>FY 2022</u>	<u>FY 2023 Base</u>	<u>FY 2023 OCO</u>	<u>FY 2023 Total</u>
Previous President's Budget	53.730	76.018	0.000	-	0.000
Current President's Budget	57.542	77.518	80.874	-	80.874
Total Adjustments	3.812	1.500	80.874	-	80.874
• Congressional General Reductions	0.000	0.000			
• Congressional Directed Reductions	0.000	0.000			
• Congressional Rescissions	0.000	0.000			
• Congressional Adds	0.000	1.500			
• Congressional Directed Transfers	0.000	0.000			
• Reprogrammings	5.542	0.000			
• SBIR/STTR Transfer	-1.730	0.000			
• Adjustments to Budget Year	-	-	80.874	-	80.874

Congressional Add Details (\$ in Millions, and Includes General Reductions)

Project: MED-01: *BASIC OPERATIONAL MEDICAL SCIENCE*

FY 2021	FY 2022

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Congressional Add Details (\$ in Millions, and Includes General Reductions)	FY 2021	FY 2022
Congressional Add: <i>Novel analytical and empirical approaches to the prediction and monitoring of disease transmission - Congressional Add</i>	-	1.500
Congressional Add Subtotals for Project: MED-01	-	1.500
Congressional Add Totals for all Projects	-	1.500

Change Summary Explanation

FY 2021: Increase reflects reprogrammings offset by SBIR/STTR transfer.
 FY 2022: Increase reflects Congressional add for Project Increase - novel analytical and empirical approaches to the prediction and monitoring of disease transmission.
 FY 2023: FY 2023 funding increase reflects the fact that the FY 2022 President's Budget request did not include out-year funding.

C. Accomplishments/Planned Programs (\$ in Millions)	FY 2021	FY 2022	FY 2023
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Title: Early Battlefield Interventions (EBI)	13.302	15.150	12.918
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 area may be applied to the development of both prophylactic and therapeutic medical countermeasures to forward-deployed service members.			
FY 2022 Plans:			
<ul style="list-style-type: none"> - Observe the effects of biostasis-inducing agents on cell function (e.g., toxicity, metabolism, DNA damage, etc.) and evaluate mechanisms of biostasis. - Establish 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 2023 Plans:			
<ul style="list-style-type: none"> - 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. 			

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C. Accomplishments/Planned Programs (\$ in Millions)		FY 2021	FY 2022	FY 2023
<p>- Detail mechanisms underlying biostasis, as well as potential negative effects (e.g., toxicity, DNA damage, etc.) in multicellular biological systems.</p> <p>FY 2022 to FY 2023 Increase/Decrease Statement: The FY 2023 decrease reflects completion of discovery efforts and movement towards final demonstration experiments to validate candidate effects.</p>				
<p>Title: Improved Interventions</p> <p>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.</p> <p>FY 2022 Plans:</p> <ul style="list-style-type: none"> - 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 biological model systems and compare to current single drug therapy. - Accelerate the timeline to network assembly and drug synthesis platform. <p>FY 2023 Plans:</p> <ul style="list-style-type: none"> - 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. <p>FY 2022 to FY 2023 Increase/Decrease Statement: The FY 2023 increase reflects minor program repricing.</p>		15.137	15.733	15.912
<p>Title: Physiological Overmatch</p> <p>Description: Warfighters must operate under extreme physiological conditions with limited resources, acclimating quickly to austere environments. The Physiological Overmatch program is investigating innovative approaches to leverage biological systems to adapt to environmental challenges during deployment. The program will initiate work in aiding the deployed soldier's</p>		12.262	17.365	18.195

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C. Accomplishments/Planned Programs (\$ in Millions)	FY 2021	FY 2022	FY 2023
<p>ability to defend against biological pathogens, 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.</p> <p>FY 2022 Plans:</p> <ul style="list-style-type: none"> - 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. - Begin high-resolution data collection for characterization of fatigue states. <p>FY 2023 Plans:</p> <ul style="list-style-type: none"> - 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. - Initiate development of approaches to improve resilience to fatigue. <p>FY 2022 to FY 2023 Increase/Decrease Statement: The FY 2023 increase reflects minor program repricing.</p>			
<p>Title: Combatting Anti-Microbial Resistant Pathogens</p> <p>Description: The Combatting Anti-Microbial Resistant Pathogens program is investigating 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 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.</p> <p>FY 2022 Plans:</p>	6.717	15.999	15.875

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<ul style="list-style-type: none"> - 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. <p>FY 2023 Plans:</p> <ul style="list-style-type: none"> - Demonstrate effective host and threat binding ligands and generalizable discovery and design strategies. - Demonstrate generalizable therapeutic candidate discovery and optimization approaches. - Develop chimeric molecules showing specificity and efficacy against DoD-relevant pathogen threats in cell culture. - Refine rapid drug identification and screening approaches for degradation or deactivation of novel pathogen targets. <p>FY 2022 to FY 2023 Increase/Decrease Statement: The FY 2023 decrease reflects minor program repricing.</p>				
<p>Title: Preventing the Emergence of Disease (PED)</p> <p>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.</p> <p>FY 2022 Plans:</p> <ul style="list-style-type: none"> - Demonstrate safety, efficiency, and efficacy of scalable countermeasure delivery platform in vitro and in animal models. - 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 from animal reservoirs in controlled laboratory tests. <p>FY 2023 Plans:</p> <ul style="list-style-type: none"> - Identify optimal thermostabilizing properties, delivery formulations, and storage conditions to ensure vaccine stability, safety and efficacy. - Validate phylodynamic and multi-scale modeling for other host species and diseases. <p>FY 2022 to FY 2023 Increase/Decrease Statement:</p>		5.664	4.882	2.716

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The FY 2023 decrease reflects completion of medical countermeasure and predictive modeling validation, and finalizing independent verification and validation efforts.				
<p>Title: Outpacing Infectious Disease</p> <p>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.</p> <p>FY 2022 Plans:</p> <ul style="list-style-type: none"> - Submit pre-Investigational New Drug (IND) package for clinical trial for therapeutic interfering particles (TIPs). - Initiate studies to facilitate clinical safety trials for TIPs. - Determine spatial distribution and co-localization of TIPs and viruses in animal models. - Identify alternative methods for discovery and development of prophylactics to increase the longevity of protection for known, new, or emerging diseases. <p>FY 2023 Plans:</p> <ul style="list-style-type: none"> - Submit IND package for clinical trials for TIPs. - Complete current Good Manufacturing Practice (cGMP) production of TIPs for clinical trial. - Initiate clinical safety trial for TIPs. <p>FY 2022 to FY 2023 Increase/Decrease Statement: The FY 2023 decrease reflects the completion of cGMP production of TIPs for clinical trial and submission of IND package.</p>		4.460	6.889	2.501
<p>Title: Assessing Immune Memory (AIM)</p> <p>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</p>		-	-	12.757

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C. Accomplishments/Planned Programs (\$ in Millions)	FY 2021	FY 2022	FY 2023
<p>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.</p> <p>FY 2023 Plans:</p> <ul style="list-style-type: none"> - 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. <p>FY 2022 to FY 2023 Increase/Decrease Statement: The FY 2023 increase reflects program initiation.</p>			
Accomplishments/Planned Programs Subtotals	57.542	76.018	80.874

	FY 2021	FY 2022
Congressional Add: Novel analytical and empirical approaches to the prediction and monitoring of disease transmission - Congressional Add	-	1.500
FY 2022 Plans: - Conduct research in novel analytical and empirical approaches to the prediction and monitoring of disease transmission.		
Congressional Adds Subtotals	-	1.500

D. Other Program Funding Summary (\$ in Millions)

N/A

Remarks

E. Acquisition Strategy

N/A