Exhibit R-2, RDT&E Budget Item Justification: PB 2015 Defense Advanced Research Projects Agency	Date: March 2014
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 2013	FY 2014	FY 2015 Base	FY 2015 OCO #	FY 2015 Total	FY 2016	FY 2017	FY 2018	FY 2019	Cost To Complete	Total Cost
Total Program Element	-	37.143	49.500	49.848	-	49.848	44.700	44.100	50.260	41.094	-	-
MED-01: *BASIC OPERATIONAL MEDICAL SCIENCE*	-	37.143	49.500	49.848	-	49.848	44.700	44.100	50.260	41.094	-	-

The FY 2015 OCO Request will be submitted at a later date.

A. Mission Description and Budget Item Justification

The Basic Operational Medical Science Program Element is budgeted in the Basic Research Activity because it 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 taking care of the warfighter such as blast-induced traumatic brain injury. Efforts will draw upon the information, computational modeling and physical sciences 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. This project will establish a fundamental understanding of brain function, short-term memory and the mechanism(s) of injury induced by exposure to blast. Basic research that aims at new methods and medical devices includes the ability to perform in-theater, continuous analysis of a warfighter's health as a preventative measure to mitigate widespread disease and development of biomaterials that allow long-term interfaces with neural tissue, electronics that provide sound attenuation, and processes to remove harmful bacteria and their toxins in blood to prevent sepsis.

B. Program Change Summary ($ in Millions)	FY 2013	FY 2014	FY 2015 Base	FY 2015 OCO	FY 2015 Total
Previous President's Budget	39.676	49.500	51.500	-	51.500
Current President's Budget	37.143	49.500	49.848	-	49.848
Total Adjustments	-2.533	-	-1.652	-	-1.652
• Congressional General Reductions	-0.052	-			
• Congressional Directed Reductions	-3.281	-			
• Congressional Rescissions	-	-			
• Congressional Adds	-	-			
• Congressional Directed Transfers	-	-			
• Reprogrammings	1.824	-			
• SBIR/STTR Transfer	-1.024	-			
• TotalOtherAdjustments	-	-	-1.652	-	-1.652

Change Summary Explanation

FY 2013: Decrease reflects Congressional reductions for Sections 3001 & 3004, sequestration adjustments, and the SBIR/STTR transfer offset by reprogrammings.

FY 2015: Decrease reflects minor program repricing.

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2013	FY 2014	FY 2015
Title: Human Assisted Neural Devices	10.810	9.000	9.936

Description: The Human Assisted Neural Devices program will develop the scientific foundation for understanding the language of the brain for application to a variety of emerging DoD challenges, including improving performance on the battlefield and returning active duty military to their units after injury. This will require an understanding of neuroscience, significant computational efforts, and new material design and implementation. Key advances expected from this research include determining the nature and means through which the brain utilizes sensory inputs to plan and execute behavioral outputs, and discovering the mechanisms and dynamics underlying neural computation and reorganization. These advances will enable restoration of sensorimotor function through the use of devices programmed to bridge gaps in the injured brain. Further, modeling of the brain will progress to an unprecedented level with this novel approach. A key aspect of this effort will be to develop non-destructive neuronal imaging and control techniques that are capable of rapid analysis and interpretation of brain tissue alterations at the cellular scale. Additional research under this effort will generate new methodologies to understand the structural and functional relationships between individual neurons through direct, high-resolution, optical imaging of neuron populations of interest as well as the entire brain.

FY 2013 Accomplishments:
- Expanded the suite of tools and methods to enable optogenetic neuromodulation of specific, diverse neural populations in animal models.
- Demonstrated the ability of non-human primates to perform a dexterous sensorimotor task using only auxiliary sensory information provided through a neural interface.
- Developed models that predict the evolution of neural firing patterns following brain injury, and following the introduction of artificial neural connections aimed at facilitating recovery.

FY 2014 Plans:
- Demonstrate the ability of non-human primates to perform a dexterous sensorimotor task through the use of a neural interface, without the use of neural spike recordings.
- Explore initial models of the brain driven by understanding of the physical connections between individual neurons of highly trained animals conducting a specific task.
- Generate initial, high-resolution, optical connectivity activity data and corresponding very-large neural data sets.
- Identify novel technologies that have potential for measuring the functional dynamics of cortical columns at spatiotemporal resolution consistent with individual neurons.
- Investigate novel technologies that allow for the control of neurons within a cortical column at single neuron spatiotemporal resolution.

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2013	FY 2014	FY 2015
- Develop circuitry models and methods of data analysis that allow for the mathematical characterization and prediction of normal and abnormal cellular processes in the brain. ***FY 2015 Plans:*** - Demonstrate the ability to non-destructively image neural communication between distant cerebral neural circuits in real time. - Demonstrate the ability to simultaneously detect the functional dynamics of multiple individual neurons in the brain over extended periods of time. - Validate the predictive potential of new neural circuitry models by stimulating specific neurons within the circuit to alter behavior and/or function.			
Title: Autonomous Diagnostics to Enable Prevention and Therapeutics (ADEPT) ***Description:*** The Autonomous Diagnostics to Enable Prevention and Therapeutics (ADEPT) program will develop the underlying technologies to rapidly respond to a disease or threat and improve individual readiness and total force health protection by providing capabilities which are currently available only in centralized laboratories in the U.S. to non-tertiary care and individual settings. ADEPT will develop and exploit synthetic biology for the in vivo creation of nucleic acid circuits that continuously and autonomously sense and respond to changes in physiologic state and for novel methods to target delivery, enhance immunogenicity, or control activity of vaccines, potentially eliminating the time to manufacture a vaccine ex vivo. ADEPT advancements to control cellular machinery include research to optimize orthogonality and modularity of genetic control elements; identify methods to increase sensitivity and specificity; and demonstrate methods to control cellular machinery in response to changes in physiological status. ADEPT will develop methodologies for measuring health-specific biomarkers from a collected biospecimen to enable diagnostics at the point-of-need or resource limited clinical facilities (point-of-care), in-garrison or deployed. Additionally, ADEPT will develop techniques that will enable the rapid establishment of transient immunity through stimulation of the production of components of the immune system to impart effective but temporary protection. This transient immunity would bridge the time gap between the delivery of a vaccine and the development of a long term protective immune response. Applied research efforts are budgeted in PE 0602115E, Project BT-01. ***FY 2013 Accomplishments:*** - Demonstrated development of modular and orthogonal nucleic acid-based elements for application within a sense-and-respond circuit that operates within the context of a mammalian cell. - Demonstrated controlled expression in mammalian cells of synthetic circuit that responds to physiological biomarkers associated with health status. - Quantified sensitivity and specificity of developed molecular approaches designed for deployable diagnostics using physiological concentrations of clinically relevant analytes in complex biospecimens. - Quantified performance of biostabilization reagents/materials demonstrating analytical recovery of clinically relevant molecules equivalent to traditional stabilization methods that require cold-chain storage.	21.620	40.500	39.912

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2013	FY 2014	FY 2015
- Quantified performance of methods for room temperature analyses and reagent stabilization demonstrating analytical results with similar-to-enhanced performance as compared to current laboratory methods for clinical diagnostics. - Quantified detection limits achieved with signal amplification methods, demonstrating performance superior to current state of the art methods for quantification of low abundance biomarkers in an actionable timeframe. - Developed new sample preparation methods suitable for simple and multiplexed analysis of biospecimens that are either self-collected under low-resource settings or collected by trained professionals at the physician-office settings. - Determined materials properties and fluidic control requirements for integration of diagnostic methodologies. - Quantified the level of antibody and immunoadhesin production directed by the administration of synthetic oligonucleotides in comparison to standard vaccine delivery. - Investigated the impact of the Ribonucleic Acid (RNA) sequence on the therapeutic strength of immune response in vivo. ***FY 2014 Plans:*** - Demonstrate in mammalian cells the function of a synthetic circuit that can integrate multiple signals associated with health status and respond with a targeted change in cell function. - Demonstrate the ability to generate synthetic nucleic acid and protein circuit components that respond to an exogenously supplied small molecule drug trigger. - Demonstrate biostabilization reagents/materials with biospecimen types and physical formats appropriate for integration into devices for collection and transport of patient samples for diagnostic analysis, and integration into on-person diagnostic devices. - Demonstrate signal amplification methods in conjunction with processing/assay methods. - Optimize developed sample preparation methods and test efficacy using biospecimens representative of those either self-collected under low-resource settings or collected by trained professionals at the physician-office settings to assist the diagnosis of an individual. - Develop advanced materials for incorporation in disposable diagnostic devices. - Optimize advanced microfluidic methods for no/low power flow control. - Demonstrate delivery of synthetic oligonucleotide constructs to cells appropriate to produce an antibody response. - Demonstrate antibody and immunoadhesin production targeted to specific disease classes. - Optimize antibody sequence for maximal therapeutic strength of immune response in vivo. ***FY 2015 Plans:*** - Demonstrate ability to administer nucleic acid encoding multiple antibodies to protect against existing, unmet, clinical targets; emerging global infectious diseases; and known, engineered biothreats. - Demonstrate onset of protection within hours after delivery and duration of therapeutic response greater than IV administered antibodies. - Demonstrate optimized, high sensitivity assay methods for protein and nucleic acid biomarkers, suitable for incorporation in deployable devices.			

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2013	FY 2014	FY 2015
- Demonstrate advanced materials properties and incorporation of developed materials into disposable assay formats. - Demonstrate advanced methods for reagent stabilization and delivery for assays developed for deployable devices. - Demonstrate sample preparation methods in conjunction with developed assays and quantify performance metrics. - Demonstrate performance of developed assays using advance no/low power microfluidic methods. - Measure performance of developed diagnostic methods and demonstrate capability to measure clinically relevant analyte levels in appropriate biospecimen matrices. - Demonstrate in mammalian cells the function of a synthetic circuit that can control the timing and level of expression of a protein when expressed from an RNA-based expression vector. - Demonstrate in mammalian cells the function of a synthetic circuit that can integrate at least two physiological signals associated with a change in health status and respond to at least two exogenously added small molecules, and respond with a targeted change in cell state. - Demonstrate the ability to generate a synthetic antibody via continuous evolution that can specifically bind to a defined target in mammalian cells.			
Title: Dialysis-Like Therapeutics	4.713	-	-
Description: Sepsis, a bacterial infection of the blood stream, is a significant cause of injury and death among combat-injured soldiers. The goal of this program was to develop a portable device capable of controlling relevant components in the blood volume on clinically relevant time scales. Reaching this goal required significant advances in sensing in complex biologic fluids, complex fluid manipulation, separation of components from these fluids, and mathematical descriptions capable of providing predictive control over the closed loop process. The envisioned device would save the lives of thousands of military patients each year by effectively treating sepsis and associated complications. Additionally, the device may be effective as a medical countermeasure against various chemical and biological (chem-bio) threat agents, such as viruses, bacteria, fungi, and toxins. Initial basic research developed the component technologies that will ultimately make up the integrated device. Included in this effort was the development of non-fouling continuous sensors for complex biological fluids; design of high-flow microfluidic structures that do not require the use of anticoagulation; development of intrinsic separation technologies that do not require pathogen specific molecular labels or binding chemistries; and predictive modeling and control (mathematical formalism) with sufficient fidelity to enable agile adaptive closed-loop therapy. Applied research efforts are budgeted in PE 0602115E, Project BT-01. ***FY 2013 Accomplishments:*** - Improved sensing technologies to achieve continuous detection of pathogens, toxins, and other biomolecules in blood and blood components.			

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2013	FY 2014	FY 2015
- Refined microfluidic architectures and coatings for continuous blood flow at high rates of 1.8 L/hour without platelet activation or clotting. - Enhanced label-free separation technologies to successfully remove pathogens, toxins, and select bioagents from blood or blood components by more than 90%. - Validated the sepsis predictive modeling using data from small animal testing within the program.			
Accomplishments/Planned Programs Subtotals	37.143	49.500	49.848

D. Other Program Funding Summary ($ in Millions)

N/A

Remarks

E. Acquisition Strategy

N/A

F. Performance Metrics

Specific programmatic performance metrics are listed above in the program accomplishments and plans section.