Exhibit R-2, RDT&E Budget Item Justification: PB 2013 Defense Advanced Research Projects Agency	DATE: February 2012
APPROPRIATION/BUDGET ACTIVITY 0400: *Research, Development, Test & Evaluation, Defense-Wide* BA 2: *Applied Research*	R-1 ITEM NOMENCLATURE PE 0602383E: *BIOLOGICAL WARFARE DEFENSE*

COST ($ in Millions)	FY 2011	FY 2012	FY 2013 Base	FY 2013 OCO	FY 2013 Total	FY 2014	FY 2015	FY 2016	FY 2017	Cost To Complete	Total Cost
Total Program Element	35.318	30.421	19.236	-	19.236	27.008	27.076	25.425	23.651	Continuing	Continuing
BW-01: *BIOLOGICAL WARFARE DEFENSE*	35.318	30.421	19.236	-	19.236	27.008	27.076	25.425	23.651	Continuing	Continuing

A. Mission Description and Budget Item Justification

DARPA's Biological Warfare Defense project is budgeted in the Applied Research Budget Activity because its focus is on the underlying technologies associated with pathogen detection, prevention, treatment and remediation. This project funds programs supporting revolutionary new approaches to biological warfare (BW) defense and is synergistic with efforts of other Government organizations.

Efforts to counter the BW threat include countermeasures to stop pathophysiologic consequences of biological or chemical attack, host immune response enhancers, medical diagnostics for the most virulent pathogens and their molecular mechanisms, collection of atmospheric trace constituents to support chemical mapping, tactical and strategic biological and chemical sensors, and integrated defensive systems. This program also includes development of a unique set of platform technologies and medical countermeasures synthesis that will dramatically decrease the timeline from military threat detection to countermeasure availability.

B. Program Change Summary ($ in Millions)	FY 2011	FY 2012	FY 2013 Base	FY 2013 OCO	FY 2013 Total
Previous President's Budget	32.692	30.421	62.736	-	62.736
Current President's Budget	35.318	30.421	19.236	-	19.236
Total Adjustments	2.626	-	-43.500	-	-43.500
• Congressional General Reductions	-0.166	-			
• Congressional Directed Reductions	-	-			
• Congressional Rescissions	-0.003	-			
• Congressional Adds	-	-			
• Congressional Directed Transfers	-	-			
• Reprogrammings	3.636	-			
• SBIR/STTR Transfer	-0.841	-			
• TotalOtherAdjustments	-	-	-43.500	-	-43.500

Change Summary Explanation

FY 2011: Increase reflects internal below threshold reprogrammings offset by the reductions for the Section 8117 Economic Adjustment and the SBIR/STTR transfer.

FY 2013: Decrease reflects the completion of chemical reconnaissance efforts and reduced efforts in medical countermeasures.

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2011	FY 2012	FY 2013
Title: Medical Countermeasures	-	12.919	19.236
Description: To further develop an expedited medical countermeasure capability, emerging technologies will be integrated to address the safety and efficacy considerations in the risk/benefit package necessary to successfully counter naturally emerging or engineered biological warfare threats and new emerging infectious threats. These technologies will also be focused on reduction of time, risk, and cost associated with new therapeutic development. ***FY 2012 Plans:*** - Begin development of in vitro tissue constructs (IVTC) that mimic the functions of human physiological systems. - Demonstrate that individual IVTCs exhibit the physiological functions normally associated with the corresponding intact human physiological system. - Design and prototype a modular platform able to sustain and monitor IVTC function. - Begin development of algorithms that will use the data obtained from the IVTC to predict drug or vaccine health effects in humans. ***FY 2013 Plans:*** - Assemble one or more IVTCs to recapitulate the function of an intact human physiological system. - Demonstrate an integrated set of IVTCs able to reproduce the function of two human physiological systems. - Demonstrate a modular platform able to sustain the integrated IVTCs for 1 week. - Demonstrate that the integrated IVTCs respond and react to test compounds in a manner that corresponds to the known effects of those compounds on human physiological systems. - Demonstrate that the modular platform can be used to predict the kinetics of metabolism and elimination that the test compounds are known to exhibit in human physiological systems. - Develop relevant functional models and technologies to identify products with therapeutic activity. - Develop new technologies to expand access to therapeutically-relevant natural products in the unexplored universe of known and unknown chemicals to expand the space for drug discovery.			
Title: Unconventional Therapeutics	16.626	7.000	-
Description: This thrust is developing unique and unconventional approaches to ensure that soldiers are protected against a wide variety of naturally occurring, indigenous or engineered threats. Past successes in this effort have come from developing therapeutics that are designed to work against broad classes of pathogens. Work in this area has also uncovered new approaches to therapeutics that, rather than attacking specific pathogens, enhance innate human immune mechanisms against broad classes of pathogens. Integral to these efforts is the development of methods that rapidly identify a broad spectrum of pathogens. Not only will these approaches be more effective against known pathogens, they also promise to offer substantial protection against unknown pathogens including engineered and emerging pathogens from third-world environments.			

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2011	FY 2012	FY 2013

A current emphasis is on the discovery and development of technologies that will allow a rapid response (within weeks) to unanticipated threats, whether they are naturally encountered emerging diseases or agents from intentional attack. This thrust has a goal of radically transforming the protein design process by researching and developing new mathematical and biochemical approaches to the in silico design of proteins with specific functions. This significantly decreases the time needed and increases the probability of success for biological warfare vaccine development. An additional focus is the development of entirely new technologies that will allow the rapid, cost-effective manufacture of complex therapeutic proteins such as monoclonal antibodies and vaccine antigens; these technologies will reduce the time for biologics manufacture from years (or even decades) to only weeks. Select efforts funded under Unconventional Therapeutics transfer to the Medical Program Element 0602115E, in FY 2012.

FY 2011 Accomplishments:

- Ascertained minimal dose of vaccine necessary for antibody protection.
- Completed a first-in-human FDA-approved Phase I human clinical trial to evaluate the safety (primary endpoint) and immunogenicity (secondary endpoint) of a plant-derived recombinant H1N1 vaccine candidate protein.
- Demonstrated in clinical trial that two 90 Microgram (µg) doses of a plant-made H1N1 vaccine candidate is as safe and as immunogenic as one 15 µg dose of a licensed egg-based vaccine.
- Demonstrated the feasibility of using the Modular Immune In Vitro Constructs (MiMIC) technology to conduct a "clinical trial in a test tube" in which the immunogenicity of a plant-derived recombinant H1N1 vaccine candidate protein was evaluated in parallel in MIMIC with the Phase I human clinical trial.
- Completed one of three proof-of-concept demonstrations to produce 1kg or 10 million doses of a recombinant H1N1 vaccine candidate protein using large-scale plant-based manufacturing capabilities.
- Demonstrated in pre-clinical animal studies that a plant-made H1N1 vaccine candidate formulated with standard aluminum salts adjuvant is capable of fully protecting immunized mice from a lethal H1N1 viral infection.
- Developed approaches to counter pathogenic processes of any known, unknown, naturally occurring or unnaturally-evolved (engineered) pathogen.
- Demonstrated various technologies that increase the median infectious dose (ID50) of a given pathogen by 10-fold compared to the untreated control ID50 in an animal model.
- Demonstrated a 2-fold increase in survival time in an animal model after a high dose challenge of a given pathogen.
- Demonstrated 95% survival against a first medium dose challenge of a given pathogen in an animal model using a therapy developed within 14 days of receipt of an unknown pathogen.
- Demonstrated 95% three week survival after three medium dose challenges of a given pathogen in an animal model spaced 1 week apart.

FY 2012 Plans:

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2011	FY 2012	FY 2013
- Complete remaining two proof-of-concept demonstrations to produce 1kg or 10 million doses of a recombinant H1N1 vaccine candidate protein using large-scale plant-based manufacturing capabilities. - Evaluate the immunogenicity and efficacy in pre-clinical animal studies of recombinant H1N1 vaccine candidate proteins produced in the large-scale proof-of-concept demonstration runs using large-scale plant-based manufacturing capabilities. - Demonstrate the flexibility and versatility of the plant-expressed protein platform to express human butyrylcholinesterase with pharmacokinetics and enzyme activity levels comparable to human plasma derived butyrylcholinesterase. - Conduct a first-in-human FDA-approved Phase I human clinical trial to evaluate the safety (primary endpoint) and immunogenicity (secondary endpoint) of a plant-derived recombinant H1N1 vaccine candidate protein combined with a novel oil in water emulsion as an adjuvant. - Continue the development of vaccine candidates that have enhanced immunogenicity. - Continue the development of platform technologies that shorten the time to optimal vaccine immunogenicity.			
Title: Chemical Reconnaissance	18.692	10.502	-
Description: The Chemical Reconnaissance program will enable exhaustive, accurate, and economical collection of atmospheric trace constituents to support chemical mapping of urban and military environments. The system will demonstrate materials, packaging, and extraction technologies that sample atmospheric impurities with concentrations ranging from 10 parts per trillion to 50 parts per million by volume, from 100 liter-atmospheres of gas, in less than five minutes. The analysis system will integrate high-resolution separation and spectroscopic techniques with automated analysis software to enable identification and ranking (by concentration) of all components present in complex gas mixtures. Reproducible analysis of atmospheric samples using sophisticated analytical technology will yield data for baseline conditions, natural variability, and permit detections of nefarious anomalies associated with production, movement, and storage of weapons, even under shifting backgrounds driven by meteorological and seasonal events. ***FY 2011 Accomplishments:*** - Engineered portable prototype systems for autonomous collection on mobile and stationary platforms. - Integrated sample labeling with meteorological data, time, and geographic coordinates. - Extended accuracy and fidelity of sampling coupons. - Delivered and field tested functional sampling technology prototypes for autonomous vehicle-borne operation. - Demonstrated adsorbent manufacturing technology and economical collection. ***FY 2012 Plans:*** - Demonstrate prototype of automated analysis system with high fidelity and accuracy. - Design and validate a system to analyze a large number of samples at low cost that fits into a standard shipping container. - Integrate sample coupon processing with automated laboratory analysis system.			

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C. Accomplishments/Planned Programs ($ in Millions)	FY 2011	FY 2012	FY 2013
- Deliver and expand field testing of ruggedized sampling technology prototypes with transition partners.			
Accomplishments/Planned Programs Subtotals	35.318	30.421	19.236

D. Other Program Funding Summary ($ in Millions)

N/A

E. Acquisition Strategy

N/A

F. Performance Metrics

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