

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2 Exhibit)

DATE

February 2007

BUDGET ACTIVITY

**RDT&E DEFENSE-WIDE/
BA1 - Basic Research**

PE NUMBER AND TITLE

**0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC
RESEARCH)**

COST (In Thousands)	FY 2006	FY 2007	FY 2008	FY 2009	FY 2010	FY 2011	FY 2012	FY 2013	Cost to	Total Cost
	Actual	Estimate	Complete							
Total Program Element (PE) Cost	91281	104257	72003	59191	55484	52990	56651	54348	Continuing	Continuing
CB1 CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	26823	26987	24324	24424	24350	23167	26836	25681	Continuing	Continuing
TB1 MEDICAL BIOLOGICAL DEFENSE (BASIC RESEARCH)	53873	66569	35241	22388	18131	17480	16942	15616	Continuing	Continuing
TC1 MEDICAL CHEMICAL DEFENSE (BASIC RESEARCH)	10585	10701	12438	12379	13003	12343	12873	13051	Continuing	Continuing

A. Mission Description and Budget Item Justification: This program element (PE) funds the Joint Service core research program for chemical and biological (CB) defense (medical and physical sciences). The basic research program aims to improve the operational performance of present and future Department of Defense (DoD) components by expanding knowledge in relevant fields for CB defense. Moreover, basic research supports a Joint Force concept of an integrated, supportable, highly mobile force with enhanced performance by the individual soldier, sailor, airman, or marine. Specifically, the program promotes theoretical and experimental research in the chemical, biological, medical, and related sciences.

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2 Exhibit)		DATE February 2007
BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research	PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	
<p>Research areas are aligned and prioritized to meet Joint Service needs as stated in mission area analyses and Joint operations requirements, and to take advantage of scientific opportunities. Basic research is executed by government laboratories, industry, and academia to include; Historically Black Colleges and Universities and Minority Institutions (HBCU/MIs). Funds directed to these laboratories and research organizations capitalize on scientific talent, specialized and uniquely engineered facilities, and technological breakthroughs. The work in this program element is consistent with the Chemical Biological Defense Program Research, Development, and Acquisition (RDA) Plan. Basic research efforts lead to expeditious transition of the resulting knowledge and technology to the applied research (PE 0602384BP) and advanced technology development (PE 0603384BP) activities. This project also covers the conduct of basic research efforts in the areas of real-time sensing and diagnosis and immediate biological countermeasures. The projects in this PE include basic research efforts directed toward providing fundamental knowledge for the solution of defense-related problems and new-improved military capabilities, and therefore, are correctly placed in Budget Activity 1.</p>		
Line No: 006	Page 2 of 34 Pages	Exhibit R-2 (PE 0601384BP)

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2 Exhibit)	DATE February 2007
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BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research	PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)
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B. <u>Program Change Summary:</u>	<u>FY 2006</u>	<u>FY 2007</u>	<u>FY 2008</u>	<u>FY 2009</u>
Previous President's Budget (FY 2007 PB)	94366	99182	79149	64565
FY08 President's Budget	91281	104257	72003	59191
Total Adjustments	-3085	5075	-7146	-5374
a. Congressional General Reductions	0	-15395	0	0
b. Congressional Increases	0	20470	0	0
c. Reprogrammings	-869	0	0	0
d. SBIR/STTR Transfer	-918	0	0	0
e. Other Adjustments	-1298	0	-7146	-5374

Change Summary Explanation:

Funding: N/A - Adjustments less than 10% of total program.

Schedule: N/A

Technical: N/A

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)	DATE February 2007
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BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research	PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	PROJECT CB1
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COST (In Thousands)	FY 2006	FY 2007	FY 2008	FY 2009	FY 2010	FY 2011	FY 2012	FY 2013	Cost to	Total Cost
	Actual	Estimate	Complete							
CB1 CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	26823	26987	24324	24424	24350	23167	26836	25681	Continuing	Continuing

A. Mission Description and Budget Item Justification:

Project CB1 CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH): This project funds basic research in chemistry, physics, mathematics, life sciences, and fundamental information in support of new detection concepts for chemical and biological agents; advanced concepts in individual and collective protection; new concepts in decontamination; innovative concepts in modeling and simulation; and scientific discovery on the chemistry and toxicology of threat agents and related materials.

B. Accomplishments/Planned Program

	<u>FY 2006</u>	<u>FY 2007</u>	<u>FY 2008</u>	<u>FY 2009</u>
Congressional Interest Items	12279	10865	0	0

Accomplishments/Planned Program	FY2006	FY2007	FY2008	FY2009
FY 06 - Photoscrub - Conducted basic research of an innovative technology based upon the ultraviolet light induced catalytic ionization of titanium dioxide.	990	0	0	0

Project CB1/Line No: 006

Page 4 of 34 Pages

Exhibit R-2a (PE 0601384BP)

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)	DATE February 2007
--	------------------------------

BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research	PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	PROJECT CB1
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Accomplishments/Planned Program (Cont):	FY2006	FY2007	FY2008	FY2009
<p>CBDP Basic Research Initiative -</p> <p>FY 06 - Solicited proposals from degree-granting universities, nonprofit organizations, and commercial concerns, to include small businesses, in support of the Chemical and Biological Defense Program (CBDP) for chemical and biological defense science and technology projects across a wide-range of military operations.</p> <p>FY 07 - Refine proposals from degree-granting universities, nonprofit organizations, and commercial concerns, to include small businesses, in support of the CBDP to explore new and innovative ideas to fill identified technology gaps.</p>	6931	4951	0	0
<p>Fluorescence Activated Sensing Technology (FAST) Integrated Threat Management System -</p> <p>FY 06 - Refined the multi-phased basic research program that included Deoxyribonucleic acid (DNA) amplification, using multiple displacement amplification (MDA) technology, of anthrax, staph. aureus with the Staph. Enterotoxin B (SEB) gene, tularemia, plague and a smallpox surrogate. Evaluated the detection system for the above threat agents using fluorescent probes; evaluated techniques consistent with the FAST process to identify Ribonucleic acid (RNA) viruses, protein toxins and nerve and mustard agents; developed a prototype stand-alone instrument with an integrated air sampler and sonicator and a decision and control system with external communications.</p> <p>FY 07 - Enhance and evaluate the prototype stand-alone instrument with an integrated air sampler and sonicator and a decision and control system with external communications.</p>	1981	991	0	0

UNCLASSIFIED

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)		DATE February 2007			
BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research		PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)		PROJECT CB1	
Accomplishments/Planned Program (Cont):		FY2006	FY2007	FY2008	FY2009
<p>Detection of Biological Agents in Water - FY 06 - Smart Sensors and Integrated Microsystems (SSIM) - Investigated the basic techniques required to measure the Raman signature of a wide array of bio-chemical agents, including bacteria, viruses, and biological and chemical toxins, over a full spectra of excitation wave lengths ranging from the deep UV thru the near IR regions of the electromagnetic spectra in potable water sources.</p> <p>FY 07 - Refine investigation of the basic techniques required to measure the Raman signature of a wide array of bio-chemical agents, including bacteria, viruses, and biological and chemical toxins, over a full spectra of excitation wave lengths ranging from the deep UV thru the near IR regions of the electromagnetic spectra in potable water sources.</p>		1386	1486	0	0
<p>New York Structural Biology Center - FY 06 - Continued a basic research program that leverages exceptional sensitivity and resolution of high-yield Nuclear Magnetic Resonance Spectrometers (NMRS) technology to permit atomic-level structural characterization of chemical compounds. Validated protocols that monitor the fate of chemical and biological warfare agents in battlefield and civilian environments such as concrete, asphalt, soil and water.</p> <p>FY 07 - Refine the basic research program that leverages exceptional sensitivity and resolution of high-yield NMRS technology to permit atomic-level structural characterization of chemical compounds.</p>		991	1159	0	0
FY 07 - Next Generation Protective Gear Research.		0	991	0	0
FY 07 - Organic Light Emitting Receptor Based Nanosensors.		0	1287	0	0
Total		12279	10865	0	0
<p>Project CB1/Line No: 006</p> <p align="center">Page 6 of 34 Pages</p> <p align="right">Exhibit R-2a (PE 0601384BP)</p>					

UNCLASSIFIED

UNCLASSIFIED

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)	DATE February 2007
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BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research	PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	PROJECT CB1
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	<u>FY 2006</u>	<u>FY 2007</u>	<u>FY 2008</u>	<u>FY 2009</u>
Basic Research Core	0	0	24324	24424

Accomplishments/Planned Program	FY2006	FY2007	FY2008	FY2009
FY 08/09 - Integrated Basic Research - Leveraging efforts undertaken in previous Basic Research efforts, initiate a multi-faceted, integrated, and cross-cutting program involving industry, academia, and federally funded research efforts to determine best basic research investments and integration into the core applied research program.	0	0	8324	8424
FY 08/09 - Integrated Basic Research - Initiate and continue to leverage previous Basic Research efforts in fundamental phenomena to address requirements for the Transformational Countermeasure Technologies Initiative (TCTI).	0	0	16000	16000
Total	0	0	24324	24424

	<u>FY 2006</u>	<u>FY 2007</u>	<u>FY 2008</u>	<u>FY 2009</u>
Threat Agent Science	14544	15856	0	0

Accomplishments/Planned Program	FY2006	FY2007	FY2008	FY2009
Threat Agent Science - FY 06/07 - Investigated genetic and biochemical variability as a potential new source of exploitable signatures and characterized the population dynamics of bacterial germination and migration within the body (toxicokinetics) and infection of target tissue under natural and altered physiological states (toxicodynamics). Continue investigation of toxicokinetics and toxicodynamics. In FY 08, program name changes to Basic Research Core.	1140	1165	0	0

UNCLASSIFIED

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)	DATE February 2007
--	------------------------------

BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research	PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	PROJECT CB1
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Accomplishments/Planned Program (Cont):	FY2006	FY2007	FY2008	FY2009
Integrated Basic Research - FY 06/07 - Integrated a cross-cutting program involving industry, academia, and federally funded research efforts to determine best basic research investments and integration into the core applied research program. Continue research efforts to determine best basic research investments and integration into the core applied research program. In FY 2008, program name changes to Basic Research Core.	5060	6226	0	0
Detection Science - FY 06/07 - Initiated investigation of nano-technologies as sensors and investigation of a theory-guided approach to the design of molecular sensing devices and systems. Continue investigation of nano-technologies use as sensors and design theory studies.	1155	1180	0	0
Modeling/Simulation Science - FY 06/07 - Conducted basic research to understand fundamental relationships of atmospheric phenomena, linked equations of motion for terrestrial and space environments, investigated relationships between sensor data and dispersion forecasts, and improved the basic understanding of atmospheric turbulence in the stable boundary level. Continue basic research and improve basic understanding of atmospheric turbulence in the stable boundary level.	3750	3775	0	0
Special Projects (Nano-technology Initiative) - FY 06/07 - Initiated a survey on the \$1-Billion federal government's annual investment in nano-technology, developed a knowledge base for nano-technology research relative to chemical-biological defense, and leveraged identified nano-science and nano-technologies from sources identified by the survey. Continue to leverage identified nano-science and nano-technologies from sources identified by the survey.	2470	2495	0	0
Decontamination Science -	969	1015	0	0

Project CB1/Line No: 006	Page 8 of 34 Pages	Exhibit R-2a (PE 0601384BP)
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UNCLASSIFIED

UNCLASSIFIED

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)			DATE February 2007	
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BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research		PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)		PROJECT CB1
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Bullet Text (cont)	FY2006	FY2007	FY2008	FY2009
FY 06/07 - Investigated the growth of hydrophobic polymer chains from enzymes as solvent-soluble decontaminating biocatalysts, and characterized the reactions between vaporous hydrogen peroxide and chlorine dioxide on metallic, metal-oxide and polymeric surfaces. Continue investigating the growth of hydrophobic polymer chains from enzymes as solvent-soluble decontaminating biocatalysts, and characterize the reactions between vaporous hydrogen peroxide and chlorine dioxide on metallic, metal-oxide and polymeric surfaces.	969	1015	0	0
Total	14544	15856	0	0

	<u>FY 2006</u>	<u>FY 2007</u>	<u>FY 2008</u>	<u>FY 2009</u>
SBIR/STTR	0	266	0	0

Accomplishments/Planned Program	FY2006	FY2007	FY2008	FY2009
SBIR - FY 07 - Small Business Innovative Research.	0	266	0	0
Total	0	266	0	0

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)	DATE February 2007
--	------------------------------

BUDGET ACTIVITY RDTE&E DEFENSE-WIDE/ BA1 - Basic Research	PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	PROJECT CB1
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C. <u>Other Program Funding Summary:</u>	<u>FY 2006</u>	<u>FY 2007</u>	<u>FY 2008</u>	<u>FY 2009</u>	<u>FY 2010</u>	<u>FY 2011</u>	<u>FY 2012</u>	<u>FY 2013</u>	<u>To Compl</u>	<u>Total Cost</u>
CB2 CHEMICAL BIOLOGICAL DEFENSE (APPLIED RESEARCH)	123291	128766	114744	113870	100816	91998	94854	95173	Cont	Cont
CB3 CHEMICAL BIOLOGICAL DEFENSE (ATD)	105134	113081	20662	21028	21935	14241	14310	13823	Cont	Cont
TT3 TECHBASE TECHNOLOGY TRANSITION	13661	12623	7667	8150	8463	8329	9430	9533	Cont	Cont

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)	DATE February 2007
--	------------------------------

BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research	PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	PROJECT TB1
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	COST (In Thousands)	FY 2006	FY 2007	FY 2008	FY 2009	FY 2010	FY 2011	FY 2012	FY 2013	Cost to	Total Cost
		Actual	Estimate	Complete							
TB1	MEDICAL BIOLOGICAL DEFENSE (BASIC RESEARCH)	53873	66569	35241	22388	18131	17480	16942	15616	Continuing	Continuing

A. Mission Description and Budget Item Justification:

Project TB1 MEDICAL BIOLOGICAL DEFENSE (BASIC RESEARCH): This project area funds basic research which seeks to promote the development of vaccines and therapeutic drugs to provide effective medical defense against validated biological threat agents including bacteria, toxins, and viruses. This basic research advances promising biotechnology with the potential to rapidly identify, diagnose, prevent, and treat disease due to exposure to biological threat agents. Categories for this project area include core science and technology program areas in medical biological defense capability areas (Pretreatments, Diagnostics, Therapeutics) and directed research areas such as the Transformational Medical Technologies Initiative (TMTI). The TMTI was launched in FY06 as a key Quadrennial Defense Review initiative to respond to the threat of emerging or intentionally bioengineered biological threats. It augments the core science and technology area by expanding the novel programs currently funded under the core Therapeutics program and introducing new technologies for developmental focus. TMTI is a novel experiment to develop drugs that are broad spectrum in nature by using non-traditional and high risk approaches to accelerate the development and licensure of new medicines. The basic research supported by the TMTI is focused on delineating the pathogenic mechanisms of intracellular pathogens and hemorrhagic fever viruses. Teaming the core program and TMTI provides a complementary strategy (single agent versus broad spectrum, conventional versus emerging threats and established model systems versus expanded integration of novel technology, respectively) towards the development of effective medical countermeasures against biothreat agents.

B. Accomplishments/Planned Program

	<u>FY 2006</u>	<u>FY 2007</u>	<u>FY 2008</u>	<u>FY 2009</u>
Congressional Interest Items	9709	9410	0	0

UNCLASSIFIED

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)	DATE February 2007
--	------------------------------

BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research	PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	PROJECT TB1
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Accomplishments/Planned Program	FY2006	FY2007	FY2008	FY2009
FY 06 - Vaccine Development Program - Developed a non-live virus vaccine for smallpox using a poxvirus antigen that is conjugated to antigen presenting cell (APC)-binding antibodies.	991	0	0	0
FY 06 - Monoclonal Antibody Manufacturing for the Treatment of Emerging Infections.	991	0	0	0
FY 06 - DNA Safeguard Project at Boise State University - Developed a stable, DNA-based chemical marker (DNA barcode) capable of encoding information that can be added to any DNA sample in order to label the sample and guarantee its integrity.	991	0	0	0
FY 06 - Ricin & Anthrax Countermeasures - Determined the in vivo efficacy of Phosphorodiamidate Morpholino Oligomers (PMOs) as effective countermeasures for Ricin and Anthrax.	1981	0	0	0
FY 06 - Biomarker Molecular Toxicology Initiative - Studied reactions to chemical and biological perturbations and then correlated these with the levels of organ-specific secreted proteins for the relevant organ (liver, kidney, etc).	2773	0	0	0
FY 06 - Selective Biological Countermeasures - Developed a procedure which will measure drug-protein binding between host proteins and pharmaceuticals.	991	0	0	0

<p>Project TB1/Line No: 006</p> <p align="center">Page 12 of 34 Pages</p> <p align="right">Exhibit R-2a (PE 0601384BP)</p>
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UNCLASSIFIED

UNCLASSIFIED

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)	DATE February 2007
--	------------------------------

BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research	PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	PROJECT TB1
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Accomplishments/Planned Program (Cont):	FY2006	FY2007	FY2008	FY2009
Northeast Biodefense Center - FY 06 - Increased laboratory capacity so that urgent local, national and global needs can be met without compromising ongoing research programs. Key research objectives include: establishing new technologies for producing monoclonal antibodies for passive administration; establishing new technologies for rapid active immunization employing dendritic cell, macrophage and B-cell interactions; discovering novel therapeutic preventive and immunomodulatory targets and molecules for bacterial and viral pathogens. FY07 - Increased laboratory capacity so that urgent local, national and global needs can be met without compromising ongoing research programs. Key research objectives include: establishing new technologies for producing monoclonal antibodies for passive administration; establishing new technologies for rapid active immunization employing dendritic cell, macrophage and B-cell interactions; discovering novel therapeutic preventive and immunomodulatory targets and molecules for bacterial and viral pathogens.	991	991	0	0
FY 07 - Anthrax Vaccine Research.	0	496	0	0
FY 07 - Mismatch Repair Derived Medicines to treat Clostridium, Staphylococcus and Bacillus Bioweapons.	0	1981	0	0
FY 07 - UCLA High Speed, High Volume Laboratory Network for Infectious Diseases - Initiate development of a high speed, high volume (high-throughput) laboratory capability that will be linked in a network and operated by several premier institutions.	0	5942	0	0
Total	9709	9410	0	0

	<u>FY 2006</u>	<u>FY 2007</u>	<u>FY 2008</u>	<u>FY 2009</u>
Transformational Medical Technology Initiative	27205	33008	23001	10211

UNCLASSIFIED

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)	DATE February 2007
--	------------------------------

BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research	PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	PROJECT TB1
--	--	-----------------------

Accomplishments/Planned Program	FY2006	FY2007	FY2008	FY2009
<p>Multiagent (Broad Spectrum) Medical Countermeasures -</p> <p>FY 06 - Initiated efforts to identify common biomarkers for several broad classes of Pathogenic Agents (e.g. intracellular facultative bacilli, hemorrhagic viruses). Initiated development of a systematic evaluation of pathogen biomarkers for categories of Biological Warfare (BW) Pathogenic Agents that tie to commonality in pathogenic mechanisms of action. Started a program to develop in silico and other methodologies to predict three-dimensional structure and comparative assessment of virulence moieties on important protein virulence molecules from genetic sequences. Commenced assessing the feasibility of re-engineering host cellular response patterns that have been compromised by pathogen-directed shifts in pathways (e.g., override of host apoptosis (programmed cell death) pathways, immune down-regulation, signal transduction agonists/antagonists, etc.).</p> <p>FY 07 - Continue to identify common biomarkers for several broad classes of Pathogenic Agents with specific applications to intracellular facultative bacilli and hemorrhagic viruses. Develop a problem solving approach that will focus on four major modules of broad-spectrum effort (host immune response, small molecule therapeutics, nucleotide therapeutics, protein based therapeutics) with the emphasis on developing adaptive technology to speed drug approval process and next generation break-thru technology. Accelerate a systematic evaluation of pathogen biomarkers for categories of BW Pathogenic Agents that tie to commonality in pathogenic mechanisms(s) of action. Identify primary or common host pathways/networks that respond to pathogenesis events to uncover promising intervention points for broad-spectrum therapeutic approaches. Exploit advances in genomics, proteomics and systems biology studies to identify pathogenesis pathways and networks using two classes agents (hemorrhagic fever viruses and intracellular bacterial pathogens) as model systems. Pursue collaborations and continue development of in silico and other methodologies to predict three-dimensional structure and comparative assessment of virulence moieties on important protein virulence molecules from genetic sequences. Build on knowledge of host cellular response patterns that have been compromised by pathogen-directed shifts in pathways.</p>	27205	33008	23001	10211

UNCLASSIFIED

UNCLASSIFIED

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)			DATE February 2007	
BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research		PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)		PROJECT TB1
Bullet Text (cont)			FY2006	FY2007
<p>FY 08 - Apply knowledge on common biomarkers for broad classes of Pathogenic Agents to specific species of intracellular facultative bacilli and hemorrhagic viruses. Validate problem solving approach focusing on four major modules of broad-spectrum effort (host immune response, small molecular therapeutics, nucleotide therapeutics, protein based therapeutics). Assess the systematic evaluation of pathogen biomarkers for categories of BW Pathogenic Agents that tie to commonality in pathogenic mechanisms(s) of action. Relate primary or common host pathways/networks that respond to pathogenesis events to uncover promising intervention points for broad-spectrum therapeutic approaches. Continue to mine advances in genomics, proteomics and systems biology studies. Solidify collaborations of in silico and other methodologies to predict three-dimensional structure and comparative assessment of virulence moieties on important protein virulence molecules from genetic sequences. Collate knowledge of host cellular response patterns that have been compromised by pathogen-directed shifts in pathways (e.g., override of host apoptosis (programmed cell death) pathways, immune down-regulation, signal transduction agonists/antagonists, etc.).</p> <p>FY 09 - Validate knowledge on common biomarkers for broad classes of Pathogenic Agents beyond intracellular facultative bacilli and hemorrhagic viruses. Continue to follow a systematic/problem solving approach towards the broad-spectrum development effort by mining advances in genomics, proteomics and systems biology studies and applying them to pathogen science; host response systems biology; adaptive technology to speed drug approval process; next generation break-through technology. Pursue promising intervention points for broad-spectrum therapeutic approaches. Continue to collate knowledge of host cellular response patterns that have been compromised by pathogen-directed shifts in pathways.</p>			27205	33008
Total			27205	33008
			23001	10211

UNCLASSIFIED

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)	DATE February 2007
--	------------------------------

BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research	PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	PROJECT TB1
--	--	-----------------------

	<u>FY 2006</u>	<u>FY 2007</u>	<u>FY 2008</u>	<u>FY 2009</u>
Diagnostics	5172	4458	4990	4710

Accomplishments/Planned Program	FY2006	FY2007	FY2008	FY2009
<p>Diagnostic Technologies -</p> <p>FY 06 - Improved the sensitivity and specificity of existing nucleic acid and immunodiagnostic assays. Designed new nucleic acid and immunodiagnostic assays to augment pathogen detection. Continued study to identify biomarkers of immunity in individuals vaccinated against biological warfare agents (BWA). Pursued new chemistries for the identification of BWA. Verified host response markers correlating with viral infections. Advanced study to develop analytic signatures of biothreat agents.</p> <p>FY 07 - Expand assay design for nucleic acid and immunoassays to additional agents/targets. Continue to improve sensitivity and specificity of existing assays, as new genomic data and techniques become available. Direct research towards increasing sample concentration and extending sample viability prior to nucleic acid testing. Collate/analyze microarray data on host response to immunization from biowarfare vaccine recipients and make recommendations for follow-on studies. Direct research towards development of a microfluidic card to automate sample preparation. Investigate surface amplification methods to enhance microarray sensitivity. Investigate novel method to produce improved immunodiagnostic reagents.</p>	5172	4458	4990	4710

Project TB1/Line No: 006	Page 16 of 34 Pages	Exhibit R-2a (PE 0601384BP)
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UNCLASSIFIED

UNCLASSIFIED

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)	DATE February 2007
--	------------------------------

BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research	PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	PROJECT TB1
--	--	-----------------------

Bullet Text (cont)	FY2006	FY2007	FY2008	FY2009
<p>FY 08 - Explore new avenues for assay design and application, focusing on those that enhance sensitivity and specificity. Validate microfluidic card to automate sample preparation. Optimize surface amplification methods for selected microarrays. Accelerate development of a novel method to produce improved immunodiagnostic reagents. Assess the applicability of novel technology platforms as new genomic techniques become available. Pursue identification of novel biomarkers identifying exposure to biological pathogens.</p> <p>FY 09 - Continue to seek novel avenues for assay design and application. Investigate cutting edge technologies as new genomic techniques become available. Accelerate identification of novel biomarkers of BWA infection and apply to assay development.</p>	5172	4458	4990	4710
Total	5172	4458	4990	4710

	<u>FY 2006</u>	<u>FY 2007</u>	<u>FY 2008</u>	<u>FY 2009</u>
Pretreatments	6742	9309	2292	3839

UNCLASSIFIED

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)	DATE February 2007
--	------------------------------

BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research	PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	PROJECT TB1
--	--	-----------------------

Accomplishments/Planned Program	FY2006	FY2007	FY2008	FY2009
<p>Pretreatments, Multiagent Vaccines -</p> <p>FY 06 - Investigated the possible inclusion of additional bacterial, viral, and toxin components in multivalent anthrax-plague vaccines. Evaluated specific combinations of target antigens and vaccine platforms, including DNA, recombinant viruses and virus-like particles (VLPs). Assessed genomics/proteomics-based high throughput approaches to identify potential vaccine target antigens for multiple agents. Investigated the use of novel approaches including recombinant protein and fusion protein constructs.</p> <p>FY 07 - Evaluate trivalent vaccine formulations using anthrax/plaque and ricin, as well as other possible components. Identify additional valid target antigens for different bio-threat agents. Expand the identification of potential vaccine target antigens for multiple agents using genomics/proteomics-based high throughput approaches. Continue to assess the use of novel approaches for vaccine construction and delivery including recombinant protein and/or fusion protein constructs.</p> <p>FY 08 - Conduct assessment of trivalent anthrax, plague, ricin vaccine. Evaluate additional target antigens as well as adjuvant combinations for efficacy against different bio-threat pathogens. Optimize DNA-based immunization strategies against bio-threat agents.</p> <p>FY 09 - Continue to characterize multivalent vaccine formulations using novel adjuvants and/or delivery systems. Evaluate novel target antigens for different bio-threat pathogens. Expand DNA-based immunization strategies against bio-threat agents.</p>	552	1760	504	845

Project TB1/Line No: 006	Page 18 of 34 Pages	Exhibit R-2a (PE 0601384BP)
--------------------------	---------------------	-----------------------------

UNCLASSIFIED

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)	DATE February 2007
--	------------------------------

BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research	PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	PROJECT TB1
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Accomplishments/Planned Program (Cont):	FY2006	FY2007	FY2008	FY2009
<p>Pretreatments, Vaccine Technology Development -</p> <p>FY 06 - Investigated DNA-based immunization platforms against multiple targets that stimulate protective immunity following minimal dosing. Evaluated high throughput gene expression systems for immune responses against selected bio-threat agents. Explored alternate immunization platforms for efficacy against selected biothreat agent pathogens. Identified common Bacillus-specific spore target antigens using a bioinformatics-based approach. Studied Toll-Like Receptor (TLR) agonists and other aspects of the innate immune system for vaccine construction and enhancement.</p> <p>FY 07 - Explore DNA vaccines and additional user friendly alternate immunization platforms/modalities that confer rapid protection following minimal dosing. Pursue refinement and development of approaches to identify potential vaccine target antigens. Investigate gene expression technologies for in vitro (inside a test tube) analysis of host responses to bacterial pathogens. Evaluate cell-mediated immune targeting of antigens for intracellular pathogens. Investigate the T-cell response against selected target antigens (analysis of cell-mediated immune response). Assess human immunodominant epitopes of selected bio-threat target antigens. Continue to investigate TLR agonists and other aspects of the innate immune system for vaccine construction and enhancement.</p> <p>FY 08 - Investigate DNA vaccine technologies and additional user friendly alternate immunization platforms/modalities that result in the rapid onset of an immune response. Investigate further refinement and development of approaches to identify potential vaccine target antigens. Pursue the use of immunomodulatory peptides or dendritic cell targeting peptides to enhance vaccine efficacy in animal models. Explore aspects of the innate immune response with respect to vaccine enhancement strategies. Continue the further evaluation of cell-mediated immune targeting of antigens for intracellular pathogens. Characterize the T-cell response against selected target antigens (analysis of cell-mediated immune response).</p>	2000	2000	481	806

UNCLASSIFIED

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)			DATE February 2007			
BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research		PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)		PROJECT TB1		
Bullet Text (cont)			FY2006	FY2007	FY2008	FY2009
FY 09 - Optimize additional user friendly alternate immunization platforms/modalities that confer rapid protection following minimal dosing. Continue refinement and development of approaches to identify potential vaccine target antigens. Study aspects of the innate immune response with respect to vaccine enhancement strategies. Explore the use of immunomodulatory peptides or dendritic cell targeting peptides to enhance vaccine efficacy. Evaluate cell-mediated immune targeting of antigens for intracellular pathogens. Characterize the T-cell response against selected target antigens (analysis of cell-mediated immune response).			2000	2000	481	806
<p>Vaccine Research Support - Pretreatment</p> <p>FY 06 - Identified new target antigens for intracellular pathogens. Conducted basic studies in anthrax and plague pathogenic mechanisms. Investigated alternative delivery platform strategies for immunization. Pursued the development of next generation recombinant vaccine candidates for botulinum neurotoxins. Evaluated various platforms for compatibility with the V3526 (VEE) vaccine candidate. Characterized vaccine efficacy against Bacillus anthracis strains of diverse geographic origin.</p> <p>FY 07 - Evaluate gene expression technologies for in vitro analysis of host responses to bacterial pathogens. Analyze information in the genomics/bioinformatics database to aid in the design of unique target antigens. Conduct basic pathogenicity studies of selected biothreat agents. Continue B and T cell epitope mapping of lead antigen candidates. Characterize in vitro correlates of immunity for biothreat agents.</p> <p>FY 08 - Expand evaluation of human immune response to bacterial and viral pathogens. Continue basic pathogenicity studies of selected biothreat agents. Develop and refine in vitro correlates of immunity for vaccines under development. Identify and evaluate new target antigens for intracellular pathogens. Expand B and T cell epitope mapping to additional lead antigen candidates.</p>			4190	5549	1307	2188
Project TB1/Line No: 006			Page 20 of 34 Pages	Exhibit R-2a (PE 0601384BP)		

UNCLASSIFIED

UNCLASSIFIED

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)	DATE February 2007
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BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research	PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	PROJECT TB1
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Bullet Text (cont)	FY2006	FY2007	FY2008	FY2009
FY 09 - Expand human immune responses to bacterial and viral pathogens. Continue basic pathogenicity studies of selected biothreat agents. Develop and refine in vitro correlates of immunity for new antigen in relation to vaccines under development. Pursue the identification and evaluation of novel target antigens for intracellular pathogens. Optimize epitope mapping of lead antigen candidates.	4190	5549	1307	2188
Total	6742	9309	2292	3839

	<u>FY 2006</u>	<u>FY 2007</u>	<u>FY 2008</u>	<u>FY 2009</u>
Therapeutics	5045	9741	4958	3628

UNCLASSIFIED

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)	DATE February 2007
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BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research	PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	PROJECT TB1
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Accomplishments/Planned Program	FY2006	FY2007	FY2008	FY2009
<p>Therapeutics, Viral -</p> <p>FY 06 - Enhanced aerobiology capabilities and animal model development to facilitate viral therapeutics research. Optimized drug discovery assays with application to identifying and testing antivirals against threat agents. Validated potential mediators of shock and toxemia. Determined the basis for treatment of shock or toxemia in appropriate animal models. Studied the pathogenic processes associated with viral infection. Evaluated the utility of combining approaches that target different aspects of viral replication and/or disease pathogenesis.</p> <p>FY 07 - Identify host cell and viral proteins that may be susceptible to broad spectrum therapeutics. Investigate additional technologies that may integrate established and emerging viral therapeutic modalities into suitable candidate therapies in humans.</p> <p>FY 08 - Delineate the host cell response to viral infection to enhance the current understanding of viral pathogenesis, in support of therapeutic development against orthopox, filovirus, and other category A and B viral threat agents of interest. Focus on collecting data pertinent to broad spectrum countermeasure development.</p> <p>FY 09 - Focus on delineating mechanisms of pathogenesis of emerging and genetically engineered threats as therapeutics targeting specific known viral threat agents move to advanced development. Compare host response to known threats with response to genetically engineered threats to identify new therapeutic targets.</p>	500	799	595	435

Project TB1/Line No: 006	Page 22 of 34 Pages	Exhibit R-2a (PE 0601384BP)
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UNCLASSIFIED

UNCLASSIFIED

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)	DATE February 2007
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BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research	PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	PROJECT TB1
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Accomplishments/Planned Program (Cont):	FY2006	FY2007	FY2008	FY2009
<p>Therapeutics, Toxin -</p> <p>FY 06 - Defined and validated essential indicators of therapeutic efficacy against selected toxins. Established conceptual framework for protocol screening for therapeutic candidates that demonstrate threshold efficacy. Characterized aerosol models of disease to support toxin therapeutic development. Conducted studies to further delineate the mechanism of action of, and host response to, botulinum neurotoxin (BoNT). Performed structural analysis of ricin toxin and BoNT serotypes. Maintained the BoNT database, a centrally managed source of information to include pharmacokinetic parameters of toxin-induced paralysis and kinetic data obtained from ongoing studies with candidate therapeutic substances.</p> <p>FY 07 - Refine planned therapeutic animal models, to include in vivo model instrumentation, and its interface with the developed screening protocol for lead toxin therapeutics studies. Demonstrate clinical correlates for targeted endpoints that have been developed for in vivo models. Optimize aerosol models of disease to support toxin therapeutic development. Study the pathogenesis associated with aerosol exposure to ricin toxin. Initiate development of a mouse model for inhalational exposure to Staphylococcal enterotoxin B (SEB) using microinstillation technology. Conduct advanced structural analysis of BoNT serotypes, focusing on catalytic sites and substrate binding.</p> <p>FY 08 - Continue to develop a mouse model for inhalational exposure to SEB using microinstillation technology. Initiate studies to investigate the process of intracellular targeting of BoNT, with application to development of an intracellular assay system for evaluating potential therapeutics. Investigate the restoration of synaptic activity following neuromuscular paralysis due to BoNT intoxication. Utilize in silico modeling techniques and in vitro and in vivo assays to provide structural and molecular data to facilitate the design and development of therapeutic countermeasures against BoNT, SEB, and ricin toxin.</p>	1267	6059	3471	2540

UNCLASSIFIED

UNCLASSIFIED

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)	DATE February 2007
--	------------------------------

BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research	PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	PROJECT TB1
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Bullet Text (cont)	FY2006	FY2007	FY2008	FY2009
FY 09 - Improve existing in silico, in vitro, and in vivo model systems to support studies delineating mechanisms of action and host response to toxin threat agents. Complete development of a mouse model for inhalational exposure to SEB using microinstillation technology. Characterize the process of intracellular targeting of BoNT, and initiate intracellular assay model development. Determine the structural requirements of potential restorative therapeutics for neuromuscular paralysis following BoNT intoxication.	1267	6059	3471	2540
<p>Therapeutics, Bacterial -</p> <p>FY 06 - Evaluated cellular immune response to F1-V fusion protein of plague (plague vaccine). Enhanced aerobiology capabilities and animal model development to facilitate bacterial therapeutics research. Pursued development of a mouse model to study anthrax toxin function.</p> <p>FY 07 - Complete development of a mouse model to study anthrax toxin function. Identify virulence factors and biochemical pathways as potential targets for therapeutic countermeasures.</p> <p>FY 08 - Delineate host cell response to bacterial pathogenesis to identify new therapeutic targets for broad spectrum therapeutics. Demonstrate and confirm the role for selected common pathways and factors in bacterial virulence.</p> <p>FY 09 - Characterize new potential targets for therapeutic countermeasures, focusing on those identified for emerging and genetically engineered threats.</p>	3278	2883	892	653
Total	5045	9741	4958	3628

	<u>FY 2006</u>	<u>FY 2007</u>	<u>FY 2008</u>	<u>FY 2009</u>
SBIR/STTR	0	643	0	0

UNCLASSIFIED

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)	DATE February 2007
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BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research	PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	PROJECT TB1
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Accomplishments/Planned Program	FY2006	FY2007	FY2008	FY2009
SBIR - FY 07 - Small Business Innovative Research.	0	643	0	0
Total	0	643	0	0

C. <u>Other Program Funding Summary:</u>											
	<u>FY 2006</u>	<u>FY 2007</u>	<u>FY 2008</u>	<u>FY 2009</u>	<u>FY 2010</u>	<u>FY 2011</u>	<u>FY 2012</u>	<u>FY 2013</u>	<u>To Compl</u>	<u>Total Cost</u>	
TB2 MEDICAL BIOLOGICAL DEFENSE (APPLIED RESEARCH)	89183	97730	151712	63773	51565	50672	52948	52995	Cont	Cont	
TB3 MEDICAL BIOLOGICAL DEFENSE (ATD)	87910	89678	146539	299581	229306	129419	122230	113827	Cont	Cont	

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CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)	DATE February 2007
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BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research	PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	PROJECT TC1
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	COST (In Thousands)	FY 2006	FY 2007	FY 2008	FY 2009	FY 2010	FY 2011	FY 2012	FY 2013	Cost to	Total Cost
		Actual	Estimate	Complete							
TC1	MEDICAL CHEMICAL DEFENSE (BASIC RESEARCH)	10585	10701	12438	12379	13003	12343	12873	13051	Continuing	Continuing

A. Mission Description and Budget Item Justification:

Project TC1 MEDICAL CHEMICAL DEFENSE (BASIC RESEARCH): This project emphasizes understanding of the basic action mechanisms of nerve, blister (vesicating), blood, and respiratory agents. Basic studies are performed to delineate biological mechanisms and bodily sites of action of identified and emerging chemical threats to generate required information for initial design and synthesis of medical countermeasures. In addition, these studies are further designed to maintain and extend a science base. Categories for this project include science and technology program areas in medical chemical defense capability areas (Diagnostics, Therapeutics and Emerging Threats).

B. Accomplishments/Planned Program

	<u>FY 2006</u>	<u>FY 2007</u>	<u>FY 2008</u>	<u>FY 2009</u>
Congressional Interest Items	990	0	0	0

UNCLASSIFIED

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)	DATE February 2007
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BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research	PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	PROJECT TC1
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Accomplishments/Planned Program	FY2006	FY2007	FY2008	FY2009
FY 06 - Superstructural Particle Evaluation and Characterization with Targeted Reaction Analysis (SPECTRA) - Studied antioxidants (combined with other substances) to mitigate the effects of low doses of radiation on human cells and E.coli. Investigated the effects of potential bio-protective substances and combinations on human and microflora cell-level responses to radiation stressors.	990	0	0	0
Total	990	0	0	0

	<u>FY 2006</u>	<u>FY 2007</u>	<u>FY 2008</u>	<u>FY 2009</u>
Diagnostics	269	298	0	0

Accomplishments/Planned Program	FY2006	FY2007	FY2008	FY2009
Diagnostic Technologies - FY 06 - Continued basic research experiments aimed at developing detection methods in clinical samples for metabolites, adducts and/or relevant biomarkers resulting from chemical warfare agent (CWA) exposure. Reported on the potential for detecting sulfur mustard exposure by cleavage adducts formed with blood proteins. Studied the dose response and time course for skin protein (laminin-5 and integrin) degradation resulting from sulfur mustard exposure. FY 07 - Accelerate basic research experiments aimed at developing detection methods in clinical samples for metabolites, adducts and/or relevant biomarkers resulting from CWA exposure. Evaluate the hypothesis that analysis of hair samples can be used to verify exposure to CWA.	269	298	0	0
Total	269	298	0	0

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)	DATE February 2007
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BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research	PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	PROJECT TC1
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	<u>FY 2006</u>	<u>FY 2007</u>	<u>FY 2008</u>	<u>FY 2009</u>
Emerging Threats	1785	0	0	0

Accomplishments/Planned Program	FY2006	FY2007	FY2008	FY2009
Emerging Threats, Chemical Warfare Agent Defense, Non-Traditional Agents (NTAs) - FY 06 - Studied non-traditional convulsive agents to identify their oxidative metabolism. Studied the pathophysiology of additional classes of NTAs. Transitions to Therapeutics in FY07.	1285	0	0	0
Emerging Threats, Chemical Warfare Agent Defense, Low Level Chemical Warfare Agent Exposure - FY 06 - Completed studies of medical countermeasures that minimize the effects of low level chemical exposure. Determined the effects of repeated exposure to chemical agents on central nervous system gene and protein expression in rodents. Transitions to Therapeutics in FY07.	500	0	0	0
Total	1785	0	0	0

	<u>FY 2006</u>	<u>FY 2007</u>	<u>FY 2008</u>	<u>FY 2009</u>
Therapeutics	7541	10299	12438	12379

UNCLASSIFIED

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)	DATE February 2007
--	------------------------------

BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research	PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	PROJECT TC1
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Accomplishments/Planned Program	FY2006	FY2007	FY2008	FY2009
<p>Therapeutics, Respiratory and Systemic -</p> <p>FY 06 - Established exposure/effects models from the whole sequence of in vitro to in vivo systems, to identify common injury responses which may serve as broad targets for therapeutic intervention. Investigated and developed additional technologies that may be used to integrate established and emerging toxicant therapeutic modalities into suitable candidate therapies in humans. Reviewed commercially evaluated human tissue models for applicability to medical chemical defense research, including the study of inhalation exposure to chemical warfare agents and evaluation of therapeutic countermeasures.</p> <p>FY 07 - Utilize exposure/effects models to further delineate the mechanisms of injury following chemical warfare agent exposure. Pursue additional technologies that address both the direct pulmonary injury and systemic effects of chemical warfare agents, with a focus on identifying common sites for therapy at the tissue, cellular, and sub-cellular levels of injury. Initiate research into the molecular basis of injury (pulmonary) in small (rat) and large (swine) animal models. Isolate and culture non-commercial human lung tissue to improve upon existing human tissue models.</p> <p>FY 08 - Develop additional in vitro and in vivo model systems to identify new therapeutic targets, based on findings from mechanism of injury studies and focusing on common injury pathways. Investigate long term effects of pulmonary injury in large and small animal models, collecting toxicological, physiological, and biochemical data.</p> <p>FY 09 - Expand efforts to elucidate common injury pathways due to multiple agents and routes of exposure, to maximize application to the development of broad-based therapeutics.</p>	2172	3426	4975	4952

Project TC1/Line No: 006	Page 30 of 34 Pages	Exhibit R-2a (PE 0601384BP)
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UNCLASSIFIED

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)	DATE February 2007
--	------------------------------

BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research	PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	PROJECT TC1
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Accomplishments/Planned Program (Cont):	FY2006	FY2007	FY2008	FY2009
<p>Therapeutics, Cutaneous and Ocular -</p> <p>FY 06 - Explored pharmacological strategies of vesicant therapeutics, to include percutaneous, ocular, and pulmonary exposures. Analyzed in vitro effects of sulfur mustard agent on cellular energy metabolism, and apoptotic (cell death) pathways. Studied in vitro biochemical changes induced by sulfur mustard exposure.</p> <p>FY 07 - Develop animal models for cutaneous, percutaneous and ocular exposure. Optimize in vitro tissue assays with application to identifying potential therapeutic compounds. Conduct studies to correlate gene expression and histopathology of sulfur mustard exposure. Investigate the genotoxicity of agent exposure in ocular cells. Initiate toxicogenomic studies to characterize the phases of wound healing. Identify the location of dermal and sub-dermal reservoirs of chemical agents.</p> <p>FY 08 - Optimize animal models for cutaneous, percutaneous and ocular exposure. Explore novel cellular biochemical pathways as potential targets for therapeutic intervention. Maximize strategies to extend "latency" period between exposure and certain injury. Expand the study of genotoxicity of agent exposure to cutaneous cells.</p> <p>FY 09 - Extrapolate the results of genotoxicity studies to the development of cancerous conditions using the appropriate in vivo models.</p>	3673	2919	1244	1237

Project TC1/Line No: 006	Page 31 of 34 Pages	Exhibit R-2a (PE 0601384BP)
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UNCLASSIFIED

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)		DATE February 2007			
BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research		PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)		PROJECT TC1	
Accomplishments/Planned Program (Cont):		FY2006	FY2007	FY2008	FY2009
<p>Therapeutics, Neurologic -</p> <p>FY 06 - Investigated novel targets for pharmacologic measures to protect against organophosphate injury, using animal neurobehavioral, physiological, and neuroanatomical measures. Characterized the mechanism of protection seen with successful therapeutic candidates. Utilized current and novel approaches to molecular modeling and structure activity relationship (SAR) studies of oxime reactivation of nerve agent inhibited acetylcholinesterase (AChE), with the goal of understanding how different oximes interact with human and non-human AChE inhibited by different nerve agents.</p> <p>FY 07 - Improve molecular modeling capabilities, coupled with X-ray crystallographic analysis and site directed mutagenesis, for rational drug design of new neurologic therapeutics. Optimize in vitro and in vivo laboratory techniques that may be applied to develop neuroprotectants, anticonvulsants, and broad spectrum reactivators to reduce or prevent injury from nerve agents. Study known mechanisms of cell death to identify potential therapeutic targets. Develop strategies for medical intervention to prevent seizures and minimize related neuronal injury in animal models. Evaluate therapeutic delivery systems targeting the central nervous system.</p> <p>FY 08 - Exploit data from SAR studies to delineate commonality between agents and oximes. Delineate general mechanism of action for oxime reactivation as required to support FDA submissions for improved reactivators under the Animal Rule.</p> <p>FY 09 - Research mechanisms of action of nerve agents and therapeutic interventions using whole animal models, with a focus on data required to support FDA submissions under the Animal Rule.</p>		1696	1173	1286	1291
<p>Therapeutics, Medical Toxicology - Non Traditional Agents (NTAs) and Other Agents -</p> <p>FY 07 - Conduct exploratory and comparative studies of emerging non-traditional chemical nerve agents. Focus on structure, function, and mechanism of action.</p>		0	2781	3731	3714
Project TC1/Line No: 006		Page 32 of 34 Pages		Exhibit R-2a (PE 0601384BP)	

UNCLASSIFIED

UNCLASSIFIED

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)			DATE February 2007	
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BUDGET ACTIVITY RDT&E DEFENSE-WIDE/ BA1 - Basic Research		PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)		PROJECT TC1
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Bullet Text (cont)	FY2006	FY2007	FY2008	FY2009
FY 08 - Collect mechanistic and kinetic data derived from chemical agent exposure studies. Initiate exploratory studies to determine the mode/mechanism of action of NTAs.	0	2781	3731	3714
FY 09 - Demonstrate the biological equivalency of NTA toxicity mechanisms across relevant species.				
Therapeutics, Medicinal Chemistry Core Capability - FY 08 - Synthesize new compounds, and analogs of existing compounds, designed as potential therapeutic countermeasures against a variety of chemical and biological warfare agents. Synthesis is customized to the needs of scientists working in all areas of chemical and biological defense within the DoD system. Characterize compounds using state-of-the-art analytical techniques (i.e. gas/liquid chromatography-tandem mass spectrometry, nuclear magnetic resonance spectroscopy, etc.). Test compounds for toxicity in silico and in vitro. FY 09 - Test the synthesis, characterization, and toxicity of potential therapeutic countermeasures.	0	0	1202	1185
Total	7541	10299	12438	12379

	<u>FY 2006</u>	<u>FY 2007</u>	<u>FY 2008</u>	<u>FY 2009</u>
SBIR/STTR	0	104	0	0

Accomplishments/Planned Program	FY2006	FY2007	FY2008	FY2009
SBIR - FY 07 - Small Business Innovative Research.	0	104	0	0
Total	0	104	0	0

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2a Exhibit)	DATE February 2007
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BUDGET ACTIVITY RD&E DEFENSE-WIDE/ BA1 - Basic Research	PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	PROJECT TC1
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<u>C. Other Program Funding Summary:</u>	<u>FY 2006</u>	<u>FY 2007</u>	<u>FY 2008</u>	<u>FY 2009</u>	<u>FY 2010</u>	<u>FY 2011</u>	<u>FY 2012</u>	<u>FY 2013</u>	<u>To Compl</u>	<u>Total Cost</u>
TC2 MEDICAL CHEMICAL DEFENSE (APPLIED RESEARCH)	27172	30796	36881	37072	35033	33328	38282	38614	Cont	Cont
TC3 MEDICAL CHEMICAL DEFENSE (ATD)	20499	18225	28976	28526	29218	30777	31833	32133	Cont	Cont

<p data-bbox="126 1425 415 1458">Project TC1/Line No: 006</p> <p data-bbox="940 1425 1169 1458">Page 34 of 34 Pages</p> <p data-bbox="1549 1425 1906 1458">Exhibit R-2a (PE 0601384BP)</p>
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