

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2 Exhibit)	DATE February 2004
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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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COST (In Thousands)	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008	FY 2009	Cost to	Total Cost
	Actual	Estimate	Estimate	Estimate	Estimate	Estimate	Estimate	Complete	
Total Program Element (PE) Cost	53162	51380	36769	37839	40913	43835	42399	Continuing	Continuing
CB1 CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	14421	12797	6413	7580	10454	10614	10833	Continuing	Continuing
TB1 MEDICAL BIOLOGICAL DEFENSE (BASIC RESEARCH)	30705	29309	20728	19647	19776	22375	20495	Continuing	Continuing
TC1 MEDICAL CHEMICAL DEFENSE (BASIC RESEARCH)	8036	9274	9628	10612	10683	10846	11071	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 non-medical). 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 a lethal, 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.

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<p>Research areas are determined 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 academia, including Historically Black Colleges and Universities and Minority Institutions (HBCU/MIs), and government research laboratories. 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 Joint Service Nuclear, Biological, and Chemical (NBC) Defense 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>		
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B. <u>Program Change Summary:</u>		<u>FY 2003</u>	<u>FY 2004</u>	<u>FY 2005</u>
Previous President's Budget (FY 2004 PB)		54829	35831	36769
Current Biennial Budget Estimates (FY 2005)		53162	51380	36769
Total Adjustments		-1667	15549	0
a. Congressional General Reductions		0	-551	0
b. Congressional Increases		0	16100	0
c. Reprogrammings		-886	0	0
d. SBIR/STTR Transfer		-797	0	0
e. Other Adjustments		-89	0	0

Change Summary Explanation:

Funding: FY04 - Congressional adjustment for CBD (+\$6,600K CB1; +\$9,500K TB1).

Schedule:

Technical:

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COST (In Thousands)	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008	FY 2009	Cost to Complete	Total Cost
	Actual	Estimate	Estimate	Estimate	Estimate	Estimate	Estimate		
CB1 CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	14421	12797	6413	7580	10454	10614	10833	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 and improved detection technologies for biological agents and toxins; new and improved detection technologies for chemical threat agents; advanced concepts in individual and collective protection; new concepts in decontamination; and information on the chemistry and toxicology of threat agents and related materials.

B. Accomplishments/Planned Program

	<u>FY 2003</u>	<u>FY 2004</u>	<u>FY 2005</u>
Detection	6912	3991	3412

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FY 2003 Accomplishments:

- 1870 Biological Agent Identification Detection - Initiated experimental apparatus to evaluate a novel optical signature called Polarization Opposition Effect (POE) for use as a bacterial spore particle (aerosol) discriminator. Initiated synthesis of candidate stochastic sensor elements based on biotinylated oligosaccharides; initiated screening testing. Completed validation of experimental apparatus. Demonstrated optical separation of similar bacterial species. Initiated investigations of micro-channel mixing via configurable heating and surfaces.
- 666 Chemical Stand-off Detection - Initiated investigations of the applicability of new techniques to the analysis of hyperspectral Fourier transform infrared data. Initiated investigations of a novel two-photon fluorescence spectroscopy method and potential applicability to stand-off CB detection.
- 1006 Integrated CB Detection - Initiated proof of principle investigations of novel materials for selective interactions with CW agent simulants in conjunction with optical (liquid crystal) amplification to enhance detection. Continued investigations of surface modified gold nanoclusters for detection of CW agents.
- 3370 Detection of Chemical and Biological Pollutant Agents in Water - Initiated development of advanced wide bandgap piezoelectric semiconductors and micro machined sensing structures. Initiated development of and immobilized phages/antibodies as specific sensing elements. Initiated evaluation of test bed sensors for real time detection.

Total 6912

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FY 2004 Planned Program:

- 2449 Biological Agent Identification Detection - Complete proof of principle experimentation; complete theoretical correlations to experimental data for POE. Continue synthesis of candidate stochastic sensor elements; continue screening testing. Demonstrate proof of principle for separation of BW agent surrogates. Complete initial investigations of the relationships between physical-chemical properties and optical separation of biological agent simulants. Continue investigations of micro-channel mixing via configurable heating and surfaces by comparison of data and model prediction. Initiate investigations of antimicrobial peptides for applicability as bio-detection elements; initiate testing program. Initiate effort to characterize polymorphic regions of B. mallei genome using ribotyping, repetitive sequence polymerase chain reaction, and Randomly Amplified Polymorphic DNAs.
- 320 Chemical Stand-off Detection - Complete investigations of the applicability of new techniques to the analysis and processing hyperspectral Fourier Transform Infrared data. Complete investigations of novel two-photon fluorescence spectroscopy method and potential applicability to stand-off CB detection. Transition to BA2 as appropriate.
- 1222 Integrated CB Detection - Complete proof of principle investigations of novel materials for selective interactions with CW agent simulants in conjunction with optical amplification to enhance detection. Complete investigations of surface modified gold nanoclusters for detection of CW agents. Initiate investigations of modified nanofilaments for detection of CB warfare agents.

Total 3991

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FY 2005 Planned Program:

- 2344 Biological Agent Identification Detection - Complete testing of candidate ion channel stochastic sensor elements. Complete investigations of micro-channel mixing via configurable heating and surfaces. Complete development of test articles and procedures. Continue testing of antimicrobial peptides. Continue effort to characterize polymorphic regions of B. mallei genome using ribotyping, repetitive sequence polymerase chain reaction, and randomly amplified polymorphic DNAs.
- 1068 Integrated CB Detection - Complete investigation of modified nanoelectrodes for the detection of CB agents. Initiate novel approaches for improved CB detection as appropriate.

Total 3412

	<u>FY 2003</u>	<u>FY 2004</u>	<u>FY 2005</u>
Protection	1499	663	630

FY 2003 Accomplishments:

- 300 Respiratory Protection - Initiated theoretical and empirical studies related to the physical and chemical interactions of vapors with surfaces.
- 235 Individual Protection (Clothing) - Initiated use of patterned electrospray of nanofibers to enhance particulate protection. Continued investigations of surface-modified membranes and measurement of differential permeation rates for chemical vapors and water vapor.

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FY 2003 Accomplishments (Cont):

- 964 Chemical Warfare Protection Research Project - Purchased a state-of-the-art mass spectrometer. The sensitive instrument was used to accurately identify minute quantities of biomarkers from exposures to nerve agents, as well as biomarkers of other organophosphates that inhibit nerve signal transmission. Until recently, the only biomarkers indicating exposure to nerve agents are enzymes known as cholinesterases. However, recent research indicates certain proteins also react with nerve agents. Research on the proteins and their respective mechanisms could lead to an improved prophylaxis for nerve agents.

Total 1499

FY 2004 Planned Program:

- 269 Individual Protection (Clothing) - Evaluate effectiveness of nanofiber-coated fabrics for protection against particulate materials. Complete investigations of surface modified membranes.
- 172 Respiratory Protection - Complete theoretical and empirical investigations of the mechanisms of interactions of vapors with active surfaces.
- 222 Shelter Protection - Initiate investigations of the interrelationships between the chemical, physical, and transport properties of novel butyl rubber membranes prepared by electrospinning.

Total 663

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FY 2005 Planned Program:

- 330 Shelter Protection - Continue investigations of the interrelationships between the chemical, physical, and transport properties of novel butyl rubber membranes prepared by electrospinning.
- 300 Respiratory Protection - Initiate research into understanding physical adsorption processes for toxic industrial chemicals and CW agents on novel adsorbent materials.

Total 630

	<u>FY 2003</u>	<u>FY 2004</u>	<u>FY 2005</u>
Decontamination	4699	1125	1567

FY 2003 Accomplishments:

- 1150 Solution Decontamination - Initiated investigations of and developed methodology for determination of the chemical structure semi-solid materials with absorbed CB agents. Initiated studies of the decontamination mechanism of secondary catalytic oxidants generated by the addition of monovalent salts to a peracid-dioxirane. Initiated investigations of the efficacy of artificial nucleases for anti-bacterial and anti-viral activity. Initiated investigations of the utility of high-field Nuclear Magnetic Resonance (NMR) methodology in conjunction with tandem mass spectrometry to determine structures of biologically derived toxins. Continued investigations of chemical strategies designed for fast dissolution and deactivation/destruction of CW agents rapidly in organic nanoemulsions.

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<p>FY 2003 Accomplishments (Cont):</p> <ul style="list-style-type: none"> • 180 Sensitive Equipment Decontamination - Initiated investigation of efficacy of vaporous dimethyl dioxirane for decontamination of BW agents. • 3369 Nanoemulsions for Decontamination - Developed and validated the efficacy of nanoemulsions for the purpose of decontaminating biological threat agents. The nanoemulsion can be formulated into a cream, liquid, or spray. <p>Total 4699</p> <p>FY 2004 Planned Program:</p> <ul style="list-style-type: none"> • 900 Solution Decontamination - Complete feasibility studies for determination of semi-solid materials chemical composition with absorbed CB agents. Complete studies of the decontamination mechanism of secondary catalytic oxidants generated by the addition of monovalent salts to a peracid-dioxirane. Complete investigations of the efficacy of artificial nucleases for anti-bacterial and anti-viral activity. Complete investigations of the utility of high-field NMR methodology in conjunction with tandem mass spectrometry to determine structures of biologically derived toxins. Complete investigations of chemical strategies designed for dissolution and deactivation/destruction of CW agents rapidly in organic nanoemulsions. • 225 Sensitive Equipment Decontamination - Complete investigation of efficacy of vaporous dimethyl dioxirane for decontamination of BW agents. <p>Total 1125</p>		
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FY 2005 Planned Program:

- 1567 Decontamination - Initiate novel research efforts with potential for advanced agent decontamination capability.

Total 1567

	<u>FY 2003</u>	<u>FY 2004</u>	<u>FY 2005</u>
Supporting Science and Technology	350	275	352

FY 2003 Accomplishments:

- 350 Chemical Threat Agents - Investigated simulant volatility in humidified air.

Total 350

FY 2004 Planned Program:

- 275 Chemical Threat Agents - Investigate CW agents volatility in humidified air.

Total 275

FY 2005 Planned Program:

- 352 Chemical Threat Agents - Continue investigations of thickened CW agent volatility in humidified air.

Total 352

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	<u>FY 2003</u>	<u>FY 2004</u>	<u>FY 2005</u>
Information Systems Technology	961	0	452

FY 2003 Accomplishments:

- 961 Agroterrorist Attack Response - Studied simulated response to a virus introduced into livestock.

Total 961

FY 2005 Planned Program:

- 452 Information Systems Technology - Initiate basic research effort(s) in support of information systems technology.

Total 452

	<u>FY 2003</u>	<u>FY 2004</u>	<u>FY 2005</u>
Basic Research	0	6527	0

FY 2004 Planned Program:

- 1976 Brooks City Base Biotechnology - Investigate technologies for Brooks City Base Biotechnology.
- 989 Fluorescence Activated Sensing Technology (FAST) - Investigate technologies for Fluorescence Activated Sensing Technology.

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FY 2004 Planned Program (Cont):

- 1089 Advanced Sensor Design and Threat Detection Facility - Develop sensors and sensory materials that can identify and remediate threats to national security as well as public health.
- 1484 Detection of Biological Agents in Water - Investigate technologies for the detection of biological agents in potable water sources.
- 989 Biodetection Research - Investigate technologies for biodetection.

Total 6527

	<u>FY 2003</u>	<u>FY 2004</u>	<u>FY 2005</u>
SBIR/STTR	0	216	0

FY 2004 Planned Program:

- 216 SBIR - Small Business Innovative Research

Total 216

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C. <u>Other Program Funding Summary:</u>	<u>FY 2003</u>	<u>FY 2004</u>	<u>FY 2005</u>	<u>FY 2006</u>	<u>FY 2007</u>	<u>FY 2008</u>	<u>FY 2009</u>	<u>To Compl</u>	<u>Total Cost</u>
CB2 CHEMICAL BIOLOGICAL DEFENSE (APPLIED RESEARCH)	104232	81482	63494	66321	52802	49219	50237	Cont	Cont
CB3 CHEMICAL BIOLOGICAL DEFENSE (ATD)	46712	93505	40527	25836	30838	31309	31957	Cont	Cont
CP3 COUNTERPROLIFERATION SUPPORT (ATD)	10815	4208	5257	4563	4114	3194	3259	Cont	Cont

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COST (In Thousands)	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008	FY 2009	Cost to	Total Cost
	Actual	Estimate	Estimate	Estimate	Estimate	Estimate	Estimate	Complete	
TB1 MEDICAL BIOLOGICAL DEFENSE (BASIC RESEARCH)	30705	29309	20728	19647	19776	22375	20495	Continuing	Continuing

A. Mission Description and Budget Item Justification:

Project TB1 MEDICAL BIOLOGICAL DEFENSE (BASIC RESEARCH): This project funds basic research on the development of vaccines and therapeutic drugs to provide effective medical defense against validated biological threat agents including bacteria, toxins, and viruses. This project also funds basic research employing biotechnology to rapidly identify, diagnose, prevent, and treat disease due to exposure to biological threat agents. Categories for this project include current science and technology program areas in medical biological defense (diagnostic technology, bacterial therapeutics, toxin therapeutics, viral therapeutics, bacterial vaccines, toxin vaccines, and viral vaccines) and directed research efforts.

B. Accomplishments/Planned Program

	<u>FY 2003</u>	<u>FY 2004</u>	<u>FY 2005</u>
Therapeutics	16187	8835	9411

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FY 2003 Accomplishments:

- 979 Therapeutics, Bacterial - Correlated metabolic measurements as a rapid and sensitive means to detect antibiotic activity with conventional susceptibility determinations and appropriate animal models of infection. Established collaborative research and development agreements with pharmaceutical companies to test new and investigational antibiotics. Initiated evaluation of selected therapeutic compounds against Brucella.
- 4786 Therapeutics, Toxin - Identified novel human and chimeric monoclonal antibodies by phage display methodology to aid in determining potential as botulinum neurotoxin therapeutics. Performed custom synthesis of lead compounds identified by high-throughput screening assays for botulinum neurotoxin and staphylococcal enterotoxins (SE). Co-crystallized toxin and lead therapeutics and collected x-ray diffraction datasets. Supported development of combinatorial libraries and diversity sets for potential toxin therapeutics.
- 2055 Therapeutics, Viral - Initiated development of intervention strategies for filovirus-induced shock and therapeutic approaches that combine antiviral and anti-shock drug therapy. Further characterized the innate immune response in mice, which indicated that a subset of cytokines can protect mice from lethal Ebola virus challenge. Continued research for development of in vitro assays utilizing filovirus polymerase as a potential antiviral drug target. Developed an assay for high-throughput interaction between Ebola virus proteins (VP40 and TSG101). Completed sequencing of Marburg and Ebola virus strains and isolates.

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<p>FY 2003 Accomplishments (Cont):</p> <ul style="list-style-type: none"> • 5000 Therapeutics, Anthrax Studies - Continued extramural research efforts toward the development and testing of new approaches for the treatment of inhalational anthrax. Focus continued on two classes of compounds that inhibit the activity of the lethal toxin produced during anthrax infection and on the enzyme target nicotinamide adenine dinucleotide (NAD), which is critical for the germination and vegetative life cycle of Bacillus anthracis, the etiologic agent for anthrax. • 3367 Therapeutics, Toxin, Bioprocessing Facility - Developed a detailed design for the construction of a current Good Manufacturing Practice (cGMP) compliant facility capable of producing human monoclonal antibodies (MAbs) to botulinum neurotoxins (BoNT) for use in phase I clinical trials. <p>Total 16187</p> <p>FY 2004 Planned Program:</p> <ul style="list-style-type: none"> • 1208 Therapeutics, Bacterial - Evaluate novel lead antimicrobial compounds in small animal models for anthrax and plague. • 5211 Therapeutics, Toxin - Continue custom synthesis of structural analogs of lead compounds identified by high-throughput screening assays for botulinum and SE toxins. Refine x-ray data for toxin-inhibitor co-crystal structures of most promising botulinum neurotoxin and SE inhibitors. Perform computational chemistry studies to refine lead compound co-crystal structures. 		
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<p>FY 2004 Planned Program (Cont):</p> <ul style="list-style-type: none"> 2416 Therapeutics, Viral - Continue research for development of intervention strategies for filovirus-induced shock and therapeutic approaches that combine antiviral and anti-shock drug therapy. Complete research for development of in vitro assays utilizing filovirus polymerase as a potential antiviral drug target. Generate baculovirus-expressed Ebola virus proteins for use in research studies. Identify sequences within Ebola virus genes that are highly susceptible to short interfering RNA-mediated degradation. <p>Total 8835</p> <p>FY 2005 Planned Program:</p> <ul style="list-style-type: none"> 1287 Therapeutics, Bacterial - Perform expanded in vivo studies on novel antimicrobial compounds against validated biological warfare threat agents. 5551 Therapeutics, Toxin - Evaluate experimental neuronal drug delivery systems for lead botulinum neurotoxin treatment modalities in vitro and ex vivo. Explore theoretical feasibility of a single therapeutic to target multiple botulinum neurotoxin serotypes. 2573 Therapeutics, Viral - Continue research for development of intervention strategies for filovirus-induced shock and therapeutic approaches that combine antiviral and anti-shock drug therapy. Test antiviral compounds in rodent models. Utilize in vitro assays based on filovirus polymerase to screen potential antiviral drugs. Screen functional knockout libraries with virus-like particles and live virus to identify pathogenicity determining factors. Engineer heterologous viruses to express Ebola virus-specific short interfering RNAs and assess their ability to inhibit Ebola virus replication in tissue culture. <p>Total 9411</p>		
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	<u>FY 2003</u>	<u>FY 2004</u>	<u>FY 2005</u>
Vaccines	5655	11323	7267

FY 2003 Accomplishments:

- 2771 Vaccines, Bacterial - Developed mutations in various biological agents for in vivo expressed genes to examine role in virulence. Characterized the mechanism(s) of vaccine resistance in selected strains of various biological agents. Determined mechanisms and correlates of protection with efficacious Burkholderia mallei vaccines. Evaluated differences in the course of Brucella infection in different mouse strains. Tested multiagent vaccine constructs for immunogenicity in animal models.
- 924 Vaccines, Toxin - Compared the efficacy of constructs with neutralizing epitopes in other domains of botulinum neurotoxin serotypes with the current heavy chain (Hc) subunit toxin vaccine candidates.
- 1960 Vaccines, Viral - Completed investigating poxvirus immunity to determine the feasibility of replacing vaccinia immune globulin (VIG) with monoclonal antibodies and for constructing a new vaccine to replace the vaccinia virus vaccine for smallpox. Investigated the role of cytotoxic T cells in the Ebola virus-mouse model.

Total 5655

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FY 2004 Planned Program:

- 3554 Vaccines, Bacterial - Continue studies on the molecular mechanisms of pathogenesis of selected BW threat agents. Identify additional virulence determinants of Brucella species. Initiate a study to identify and characterize novel virulence proteins of F. tularensis.
- 1701 Vaccines, Toxin - Conduct computational chemistry studies to develop next generation botulinum neurotoxin and recombinant ricin toxin A-chain (rRTA) vaccines. Evaluate theoretical feasibility of multivalent vaccines by protein engineering. Evaluate the role of glycosylation or other structural modifications in reducing efficacy of botulinum neurotoxin vaccines.
- 1701 Vaccines, Viral - Complete investigating the role of cytotoxic T cells in the Ebola virus-mouse model. Examine the use of virus-like particles (VLP) as antigen for vaccines for filoviruses. Initiate research to investigate the role of cytotoxic T cells in the filovirus model in non-human primates.
- 3396 Vaccines, Plant Vaccine Development - Develop plant-based subunit vaccines as countermeasures against biological warfare agents.
- 971 Vaccines, Plant Derived Vaccine Against Anthrax and Smallpox - Develop plant-based subunit vaccines against anthrax and smallpox as countermeasures against agents of biological warfare. Express both proposed vaccines in edible plants using a constitutive expression system based on transgenic plants. Express in spinach functionally important epitopes of the anthrax recombinant Protective Antigen (rPA) and the B5R protein of the smallpox virus, using a transient expression system based on plant virus vectors. Evaluate immunogenicity of plant-based vaccines in animal models.

Total 11323

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FY 2005 Planned Program:

- 3645 Vaccines, Bacterial - Continue to characterize novel virulence genes and gene products of selected bacterial threat agents to support discovery of new medical countermeasures.
- 1811 Vaccines, Toxin - Clone and express chimeric constructs to evaluate practical feasibility of multivalent toxin vaccines by protein engineering.
- 1811 Vaccines, Viral - Continue investigating the role of cytotoxic T cells in the higher animal model of filovirus infection. Continue development of animal models of aerosol infection with filoviruses. Continue evaluation of the use of virus-like particles (VLP) as antigens for vaccines for filoviruses.

Total 7267

	<u>FY 2003</u>	<u>FY 2004</u>	<u>FY 2005</u>
Diagnostics	4051	3803	4050

FY 2003 Accomplishments:

- 4051 Diagnostic Technologies - Conducted basic research on new diagnostic approaches to the early recognition of infection; developed reagents and associated assays to aid in identifying new host and agent-specific biological markers that can be used for early recognition of infection. Continued research to develop, evaluate, and explore new technological approaches for diagnosis of potential biological warfare threat agents and for concentrating and processing clinical samples to support rapid identification and diagnostics.

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<p>FY 2003 Accomplishments (Cont): Total 4051</p> <p>FY 2004 Planned Program:</p> <ul style="list-style-type: none"> 3803 Diagnostic Technologies - Continue basic research on new diagnostic approaches to the early recognition of infection focusing on technologies compatible with future comprehensive integrated diagnostic systems. Continue to develop reagents and assays for appropriate biological markers for early recognition of infection and identify new host and agent-specific biological markers. Continue research directed toward new technological approaches for diagnosis of biological threat agents and new sample processing technologies. <p>Total 3803</p> <p>FY 2005 Planned Program:</p> <ul style="list-style-type: none"> 4050 Diagnostic Technologies - Continue research on diagnostic approaches for early recognition of infections compatible with future comprehensive integrated diagnostic systems; continue to develop and identify new host and agent-specific biological markers that can be used for early recognition of infection. Continue research directed toward new technological approaches for diagnosis of biological threat agents and toward concentrating and processing clinical samples to support rapid diagnostics. <p>Total 4050</p>		
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	<u>FY 2003</u>	<u>FY 2004</u>	<u>FY 2005</u>
Medical Biological Warfare Defense	4812	4851	0

FY 2003 Accomplishments:

- 4812 Medical Biological Warfare Defense, Engineered Pathogen Identification and Countermeasures Program - Identified the impact of biowarfare pathogens on the human body using computer models and direct protein analysis. Developed counteracting drugs based on a comprehensive understanding of how the potential drug candidates impact the human body, outside of their desired effect against the pathogen.

Total 4812

FY 2004 Planned Program:

- 4851 Medical Biological Warfare Defense, Engineered Pathogen Identification and Countermeasures Program (Bug to Drug) - Identify the impact of biowarfare pathogens on the human body using computer models and direct protein analysis. Continue to develop counteracting drugs based on a comprehensive understanding of how the potential drug candidates impact the human body, outside of their desired effect against the pathogen.

Total 4851

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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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	<u>FY 2003</u>	<u>FY 2004</u>	<u>FY 2005</u>
SBIR/STTR	0	497	0

FY 2004 Planned Program:

- 497 SBIR - Small Business Innovative Research

Total 497

C. Other Program Funding Summary:

	<u>FY 2003</u>	<u>FY 2004</u>	<u>FY 2005</u>	<u>FY 2006</u>	<u>FY 2007</u>	<u>FY 2008</u>	<u>FY 2009</u>	<u>To Compl</u>	<u>Total Cost</u>
TB2 MEDICAL BIOLOGICAL DEFENSE (APPLIED RESEARCH)	47183	47747	22622	15371	15658	16431	13113	Cont	Cont
TB3 MEDICAL BIOLOGICAL DEFENSE (ATD)	34677	45944	55621	39416	39440	42499	38625	Cont	Cont

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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 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008	FY 2009	Cost to	Total Cost
	Actual	Estimate	Estimate	Estimate	Estimate	Estimate	Estimate	Complete	
TC1 MEDICAL CHEMICAL DEFENSE (BASIC RESEARCH)	8036	9274	9628	10612	10683	10846	11071	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 mechanisms and 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 (Nerve Agent Defense, Vesicant Agent Defense and Chemical Warfare Agent (CWA) Defense) and directed research efforts (Low Level CWA Exposure and Non-Traditional Agents).

B. Accomplishments/Planned Program

	<u>FY 2003</u>	<u>FY 2004</u>	<u>FY 2005</u>
Nerve Agent Defense	1311	410	850

FY 2003 Accomplishments:

- 295 Nerve Agent Defense, Nerve Agent Anticonvulsants - Evaluated antidotes representing new strategies to address medical countermeasure requirements against conventional and emerging agents.

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FY 2003 Accomplishments (Cont):

- 623 Nerve Agent Defense, Biological Scavengers - Expressed and purified a recombinant human carboxylesterase for crystallization. Evaluated circulatory stability of recombinant bioscavengers.
- 393 Nerve Agent Defense, Neuroprotection - Evaluated combination therapies for neuroprotection efficacy. Developed neurobehavioral assessment necessary to evaluate efficacy of neuroprotective therapies.

Total 1311

FY 2004 Planned Program:

- 410 Nerve Agent Defense, Neuroprotection - Evaluate drug treatment strategies and combinations of therapies for nerve agent-induced seizures.

Total 410

FY 2005 Planned Program:

- 850 Nerve Agent Defense, Neuroprotection - Continue to evaluate drug treatment strategies and combinations of therapies for nerve agent-induced seizures.

Total 850

	<u>FY 2003</u>	<u>FY 2004</u>	<u>FY 2005</u>
Vesicant Agent Defense	1959	3542	4078

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FY 2003 Accomplishments:

- 1959 Vesicant Agent Defense, Vesicant Medical Countermeasures - Targeted mechanism of vesicant injury and explored intervention of pro-inflammatory mediators and calcium modulators. Conducted proteomic analysis of sulfur mustard toxicity.

Total 1959

FY 2004 Planned Program:

- 3542 Vesicant Agent Defense, Vesicant Medical Countermeasures - Identify mechanism of action of vesicant pretreatment compounds. Determine effects of sulfur mustard (HD) on cell structure using multiphoton laser scanning microscopy. Analyze in vitro effects of HD on cellular energy metabolism. Study in vitro biochemical changes induced by HD.

Total 3542

FY 2005 Planned Program:

- 4078 Vesicant Agent Defense, Vesicant Medical Countermeasures - Explore purification and delivery strategies of vesicant pretreatments. Continue to analyze in vitro effects of HD on cellular energy metabolism. Continue to study in vitro biochemical changes induced by HD.

Total 4078

	<u>FY 2003</u>	<u>FY 2004</u>	<u>FY 2005</u>
Chemical Warfare Agent Defense	4766	5165	4700

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FY 2003 Accomplishments:

- 274 Chemical Warfare Agent Defense, Cyanide Medical Countermeasures - Investigated efficacy of sulfur donors as anti-cyanide pretreatments. Developed animal model to test cyanide pretreatment compounds.
- 197 Chemical Warfare Agent Defense, Inhalation Therapeutics - Assessed respiratory dynamics and lung biochemical function in male and female guinea pigs following exposure to chemical warfare agents.
- 295 Chemical Warfare Agent Defense, Medical Diagnostics - Incorporated biomarker panels into screening modules. Conducted electrophysiological analysis of chemical warfare agents (CWAs) in cultured cells. Analyzed central nervous system (CNS) and peripheral protein production following soman exposure. Developed new assays for HD adducts in plasma and for diagnosing cyanide exposure.
- 4000 Chemical Warfare Agent Defense, Low Level Chemical Warfare Agent Exposure - Investigated alterations in muscle physiology due to repetitive low dose CWA exposure. Characterized ultrastructural morphology, immunochemistry, and gene expression following low level chemical exposure. Studied the effects of low level chemical exposure on extracellular neurotransmitter levels. Evaluated organophosphate anhydrolase enzyme for potential use as a biomarker to confirm low level chemical exposure.

Total 4766

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FY 2004 Planned Program:

- 1800 Chemical Warfare Agent Defense, Inhalation Therapeutics - Investigate enzymatic targets of HD. Conduct a dose-response assessment of early acute lung injury in rodents administered intravascular HD. Determine the biochemical effects in male and female guinea pigs following exposure to chemical warfare agents.
- 265 Chemical Warfare Agent Defense, Medical Diagnostics - Identify molecular intracellular proteomic changes following HD exposure.
- 2000 Chemical Warfare Agent Defense, Low Level Chemical Warfare Agent Exposure - Identify biomarker(s) to indicate low level chemical exposure. Continue studies of neurotoxic effects of low dose chemical agent exposure. Examine potential for immunological deficits following nerve agent exposures. Identify potential medical countermeasures for low level chemical warfare nerve agent and HD exposure.
- 1100 Chemical Warfare Agent Defense, Non-Traditional Agents (NTAs) - Investigate changes to pulmonary airway resistance and permeability of pulmonary microvessels induced by exposure to various concentrations of platelet activating factor (PAF). Identify changes in the global gene expression profile of cultured human epidermal keratinocytes (HEK) in response to NTA exposure using DNA microarrays and genomics techniques to aid in considering strategies leading to medical countermeasures.

Total 5165

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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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FY 2005 Planned Program:

- 2000 Chemical Warfare Agent Defense, Inhalation Therapeutics - Identify intervention targets to acute lung injury caused by CWAs. Continue dose-response assessment of any acute lung injury in rodents administered intravascular CWAs. Conduct histopathology studies in male and female guinea pigs following exposure to CWAs.
- 1000 Chemical Warfare Agent Defense, Low Level Chemical Warfare Agent Exposure - Examine multiple biomarkers as confirmatory for low level chemical exposure. Continue studies of possible immunological deficit following low level chemical nerve agent exposure. Examine physiological parameters that may alter sensitivity to low level CWAs. Continue to identify potential medical countermeasures for low level CWA exposures.
- 200 Chemical Warfare Agent Defense, Medical Diagnostics - Pursue development of a nanodevice for diagnosing CWA exposure using synthetic modeling and molecular imprinting.
- 1500 Chemical Warfare Agent Defense, Non-Traditional Agents (NTAs) - Compare the direct effects of PAF on smooth muscle, hematic constituents, and lung to determine role in toxicity. Continue to identify changes in the global gene expression profile of cultured HEK exposed to NTAs using DNA microarrays and genomic techniques to aid in considering strategies leading to medical countermeasures.

Total 4700

	<u>FY 2003</u>	<u>FY 2004</u>	<u>FY 2005</u>
SBIR/STTR	0	157	0

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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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FY 2004 Planned Program:

- 157 SBIR - Small Business Innovative Research

Total 157

C. <u>Other Program Funding Summary:</u>	<u>FY 2003</u>	<u>FY 2004</u>	<u>FY 2005</u>	<u>FY 2006</u>	<u>FY 2007</u>	<u>FY 2008</u>	<u>FY 2009</u>	<u>To Compl</u>	<u>Total Cost</u>
TC2 MEDICAL CHEMICAL DEFENSE (APPLIED RESEARCH)	18768	22143	18269	19936	20059	20354	21779	Cont	Cont
TC3 MEDICAL CHEMICAL DEFENSE (ATD)	11197	11045	13489	12534	12615	12808	13075	Cont	Cont

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