CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2 Exhibit)

DATE: **June 2001**

BUDGET ACTIVITY: **RDT&E DEFENSE-WIDE/ BA1 - Basic Research**

PE NUMBER AND TITLE: **0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)**

COST (In Thousands)		FY 2000 Actual	FY 2001 Estimate	FY 2002 Estimate							
	Total Program Element (PE) Cost	42827	39532	39066							
CB1	CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	8377	9068	5990							
TB1	MEDICAL BIOLOGICAL DEFENSE (BASIC RESEARCH)	26689	20563	23200							
TC1	MEDICAL CHEMICAL DEFENSE (BASIC RESEARCH)	7761	9901	9876							

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. 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 military problems and therefore are correctly placed in Budget Activity 1.

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DATE: June 2001

BUDGET ACTIVITY: **RDT&E DEFENSE-WIDE/ BA1 - Basic Research**

PE NUMBER AND TITLE: **0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)**

B. Program Change Summary:	FY 2000	FY 2001	FY 2002	
FY 2001 President's Budget	44040	33197	30990	
Appropriated Value	44886	39897	0	
Adjustment to Appropriated Value	0	0	0	
a. Congressional General Reductions	0	0	0	
b. SBIR/STTR	-638	-279	0	
c. Omnibus or Other Above Threshold Reductions	-89	0	0	
d. Below Threshold Reprogramming	-862	0	0	
e. Rescissions	-470	-86	0	
Adjustments to Budget Years Since FY 2001 PB	0	0	8076	
FY2002/2003 President's Budget	42827	39532	39066	

Change Summary Explanation:

Funding: FY02 - Increases to the technology base to accelerate the investigation and development of CBD technologies, support response to emerging threat requirements, and protect critical technology base infrastructure (CB1 $2,500K; TB1 $650K; TC1 $352K). Increase to provide additional research on compounds that inhibit the activity of lethal toxins produced during anthrax infection ($5,000K). General reduction to fund higher priority efforts (-$624K) and increase for inflation assumptions ($198K).

Schedule:

Technical:

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2A Exhibit)

DATE: June 2001

BUDGET ACTIVITY: **RDT&E DEFENSE-WIDE/ BA1 - Basic Research**

PE NUMBER AND TITLE: **0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)**

PROJECT: **CB1**

COST (In Thousands)		FY 2000 Actual	FY 2001 Estimate	FY 2002 Estimate							
CB1	CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	8377	9068	5990							

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 compounds.

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2A Exhibit)

DATE: June 2001

BUDGET ACTIVITY	PE NUMBER AND TITLE	PROJECT
RDT&E DEFENSE-WIDE/ BA1 - Basic Research	0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	CB1

FY 2000 Accomplishments:

- 800 Biosensors - Synthesized purified aptamer (deoxyribonucleic acid/DNA oligomer) recognition elements for the detection of Bacillus anthracis (anthrax) and Yersinia pestis (plague). Completed conjugate synthesis and integration of specific fluorescent polymer/binding agent complexes for these agents. Completed synthesis of antibody/dendrimer tag complexes and began work on the demonstration of separation/identification of dendrimer bound antibody/antigen couples via capillary electrophoresis.
- 320 Aerosol Science - Initiated laboratory experiments to validate new backscattering theorem projections. Made adjustments to the computer code.
- 1123 Chemistry and Toxicology of Bioactive Compounds - Demonstrated methodology for cytotoxicity screening for toxicological evaluations and transitioned to the toxicology program. Made a selection of the coating technology to be used in the molecular imprinting technique. Expanded rate studies on the percarbonate (candidate peroxide) based decontaminant formulation to include work with surety materials. Investigated other methods of peroxide activation with promise for greater percent hydrogen ion (pH) range efficacy. Began project to create a filtration performance model based upon an understanding of adsorption equilibria and rate processes. Began development of data base of adsorption equilibrium measurements. Began project to study pharmacokinetics and pharmacodynamics of novel threat materials.
- 3307 Thin Film Technology Development - Continued development and refinement of semiconductor metal-oxide (SMO) thin film technology with controlled architecture to detect chemical agents (e.g. nerve, blister, blood) and interferent species (e.g. volatile hydrocarbons, water, and other battlefield interferents) as dictated by Joint Service requirements. Developed and optimized films for both point and cumulative exposure detection applications. Conducted laboratory testing tc optimize the sensitivity, selectivity, and stability of SMO sensor elements and arrays as a function of gas environments.

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2A Exhibit)

DATE: June 2001

BUDGET ACTIVITY	PE NUMBER AND TITLE	PROJECT
RDT&E DEFENSE-WIDE/ BA1 - Basic Research	0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	CB1

FY 2000 Accomplishments (Cont):

- 1911 Integrated Detection of Energetic and Hazardous Materials - Conducted a multidisciplinary project which developed integrated detection methodologies for sensing the presence of chemical and biological warfare agents. This effort consisted of the following sub-tasks: ion trap mass spectrometry analytical techniques, micro-sensors for chemical and biological warfare agents, and bioanalytical detection.
- 916 Optical Recognition Technologies - Investigated improved and more cost-effective techniques for the recognition of chemical agents in the atmosphere. Chemometrics were used to design sophisticated multi-layered optical filters which have been tested against simulants and interferents.

Total 8377

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2A Exhibit)

DATE: June 2001

BUDGET ACTIVITY	PE NUMBER AND TITLE	PROJECT
RDT&E DEFENSE-WIDE/ BA1 - Basic Research	0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	CB1

FY 2001 Planned Program:

- 807 Biosensors - Sequence and synthesize DNA aptamer recognition elements to Staphylococcal enterotoxin B. Complete conjugate synthesis and integration of specific DNA/fluorescent polymer conjugates. Demonstrate separation and identification of dendrimer bound antibody/antigen couples via capillary electrophoresis.
- 437 Aerosol Science - Complete validation of the scattering model theorem by demonstrating imaging of biological cluster particles.
- 1120 Chemistry and Toxicology of Bioactive Compounds - Continue materials selection for molecular imprinting technique in preparation for integration into a passive thin film chemical detection badge. Continue studies of the percarbonate based decontaminant formulations by determining reaction product distributions and correlate equilibrium concentrations with solvent properties. Complete measurement of requisite adsorption rate data and begin development of a continuous adsorption model for filter performance. Continue project to understand the toxicological mechanisms of one or two members of a class of potential new threat agents.
- 1658 Thin Film Technology Development - Continue development of semiconducting metal oxide (SMO) thin film technology to detect chemical agents. Seek to minimize power requirements, weight, and volume with an overall intent to reduce burden to the individual user. Focus on approaches to maximize selectivity/elimination of false alarms including mixed metal oxide films and nanocluster structures. Examine prefiltration/preconcentration through chemical vapor deposition (CVD) methods. Continue improvements in signal processing and control.

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2A Exhibit)

DATE: June 2001

BUDGET ACTIVITY	PE NUMBER AND TITLE	PROJECT
RDT&E DEFENSE-WIDE/ BA1 - Basic Research	0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	CB1

FY 2001 Planned Program (Cont):

- 4892 Chemical/Biological Agent Detection - Conduct a multidisciplinary project to establish the proof of principle for detection methodologies and to develop detection systems for sensing the presence of chemical and biological warfare (CBW) agents. Investigate development of a small-scale experimental detector for point detection of chemical warfare (CW) agents. Produce a design for a point detector to achieve highly specific and rapid detection of the CW agents in air using Ion Trap Mass Spectrometry (ITMS). This extremely sensitive type of mass spectrometer is particularly promising for in situ applications because of its small size and weight. Research using ITMS methodologies for the point detection of biological warfare (BW) agents will be conducted. Investigate neutron based CW detection.
- 154 SBIR

Total 9068

FY 2002 Planned Program:

- 2000 Biosensors - Sequence Venezuelan Equine Encephalitis (VEE) aptamers and incorporate all available aptamers into Multiplex Electronic/Photonic Sensor (MEPS). Conduct optimization and assess miniaturization potential of the capillary electrophoresis detection system and validate concept.
- 1550 Chemistry and Toxicology of Bioactive Compounds - Construct "film badge" package to be used in the molecular imprinting technique for Individual Passive Chemical Agent Technologies and complete validation of concept for potential transition into 6.2 development. Conduct determination of rate laws for other organic oxidations using the new peroxide-based decontamination formulations. Complete development and validate filter model incorporating adsorption equilibria and dynamic behavior. Initiate a project to model filter performance concepts for individual protection systems. Expand pharmacokinetic and pharmacodynamic investigation to include additional new threat materials.

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2A Exhibit)

DATE: June 2001

BUDGET ACTIVITY	PE NUMBER AND TITLE	PROJECT
RDT&E DEFENSE-WIDE/ BA1 - Basic Research	0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	CB1

FY 2002 Planned Program (Cont):

▪	2440	New Detection Technologies - Initiate research on methods of combining chemical and biological agent detection on surfaces into one device. Include a variety of spectroscopic techniques focusing on portions of the electromagnetic spectrum not previously utilized for Chemical and Biological (CB) agent detection.
Total	5990	

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2A Exhibit)

DATE: June 2001

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

COST (In Thousands)		FY 2000 Actual	FY 2001 Estimate	FY 2002 Estimate							
TB1	MEDICAL BIOLOGICAL DEFENSE (BASIC RESEARCH)	26689	20563	23200							

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 Plans (STEP) in medical biological defense (diagnostic technology, bacterial therapeutics, toxin therapeutics, viral therapeutics, bacterial vaccines, toxin vaccines, and viral vaccines) and directed research efforts (laboratory-based and analytical threat assessment research and anthrax studies).

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2A Exhibit)

DATE: June 2001

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

FY 2000 Accomplishments:

- 4855 Diagnostic Technologies - Identified alternative immunological targets and gene sequences for Bacillus anthracis (B. anthracis), Yersinia pestis (Y. pestis), Francisella tularensis (F. tularensis), Brucella spp., alphaviruses, filoviruses, and botulinum toxins that will enhance the depth and diversity of the current capability. Identified rapid medical specimen processing approaches compatible with portable nucleic acid identification of biological threat agents that will improve post-exposure treatment and force protection. Assessed biotechnical innovations such as the development of molecular probes and recombinant antibodies and antigens to provide rapid diagnostic capabilities that support enhanced warfighter medical care and force protection.
- 1531 Therapeutics, Bacterial - Established and validated a method for determining antibiotic susceptibilities for biological warfare (BW) agents to accepted international standards; evaluated 28 antibiotics on 11 strains of Burkholderia mallei (B. mallei) (causative agent of glanders), and one strain of B. anthracis to identify the most effective compounds; established agreements to test 15 additional novel (investigational) antibiotics developed by outside drug companies.
- 3282 Therapeutics, Toxin - Identified molecular biology and target mechanisms of action of botulinum toxin and staphylococcal enterotoxin (SE) for exploitation in investigating therapeutic approaches to toxin exposure. Performed structural studies for toxins and critical enzymes using x-ray crystallography and other cutting-edge analytical methodologies. Developed and refined computational chemistry techniques for use in screening massive chemical databases for compounds as potential inhibitors of toxin activity. Developed biosensor-based method to measure SE-receptor interactions for screening inhibitory molecules. Developed recombinant, enzymatically active light chain for botulinum toxin serotype A as a reagent for efforts focused on therapeutic countermeasures to botulinum neurotoxins. Demonstrated host chaperone protein, SNAP-25, could be replaced with a botulinum-resistant version in vitro, using DNA technologies. Initiated efforts to evaluate the anaerobic bacterial origins of saxitoxin.
- 2564 Therapeutics, Viral - Investigated mechanisms of Ebola and Marburg virus pathogenesis in nonhuman primate models for potential targets for therapeutic intervention; defined apoptosis as the mechanism for lymphocyte death.

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2A Exhibit)	DATE June 2001
BUDGET ACTIVITY **RDT&E DEFENSE-WIDE/** **BA1 - Basic Research**	PE NUMBER AND TITLE **0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)**
	PROJECT **TB1**

FY 2000 Accomplishments (Cont):

- 3487 Vaccines, Bacterial - Identified an expression system for multivalent Brucella vaccine; continued studying pathogenesis, host immune responses, virulence factors, strain diversity, molecular pathogenesis, and correlates of immunity for organisms responsible for plague Y. pestis, glanders (B. mallei), and anthrax (B. anthracis). Refined and optimized aerosol exposure animal models for glanders required to address Food and Drug Administration (FDA) regulatory requirements.
- 2608 Vaccines, Toxin - Completed in vitro experiments establishing delivery of recombinant vaccines using mouse mesenchymal stem cells that differentiate into antigen presenting cells in vivo. Established mouse/human CD4 and human leukocyte antigen (HLA)-DR1, DR3, DQ6, and DQ8 transgenic colonies in class II-deficient mice. Showed that the lymphocytes obtained from the humanized mice and humans reacted similarly to various BW agents. Initiated mucosal immunization studies using Streptococcus gordonii, cholera toxin, and hepatitis virus-like particles as delivery platforms.
- 1609 Vaccines, Viral - Demonstrated and defined the protective contribution of antibody specific for Ebola virus glycoproteins in the mouse model. Defined immunogens (glycoprotein and nucleocapsid protein) that induce protection against Musoke isolate of Marburg virus in animal models and that can serve as vaccine antigens.

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2A Exhibit)

DATE: June 2001

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

FY 2000 Accomplishments (Cont):

▪	6753	Laboratory-based and Analytical Threat Assessment Research - Expanded earlier investment between DoD, Department of Energy (DOE) and academia in development of a genetic information database for threat agents to greater than 100,000 agent records. Merged database with DOE efforts, and created tools and access for secure website use by key customers. Initiated development of a proteomics-based system for identifying novel threats based on structural motif. Initiated pathophysiology studies to determine the molecular basis for virus transmission of mosquito-borne agent Venezuelan equine encephalitis (VEE) and evaluated real-time imaging of other biological threat agents in hosts. Assessed aerosol threat posed by selected components of snake toxin. Developed new assays to detect brevetoxins and genetically modified (engineered) superantigen toxins. Demonstrated concept of using serum peptide patterns as a marker of host infection with specific threat agents and performed molecular fingerprint analyses of Brucella and Yersinia strains. Initiated basic studies of the common structural motifs of staphylococcal and streptococcal superantigens. Identified common mechanisms of macrophage infection by bacterial pathogens and host lymphocyte gene response patterns to VEE viruses. Evaluated host cellular gene response profiles following infection with Yersinia and administration of streptococcal pyrogenic exotoxins.
Total	26689	

CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2A Exhibit)

DATE: June 2001

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

FY 2001 Planned Program:

- 3014 Diagnostic Technologies - Investigate new medical diagnostic technologies based upon state-of-the-art biotechnological approaches for the enhanced recognition of infections by validated biological threats (bacteria, viruses, and toxins) of military interest.
- 316 Therapeutics, Bacterial - Study host cellular and subcellular responses to BW threat agents (B. anthracis, B. mallei, Y. pestis) exposure to identify likely molecular targets for intervention by "next generation" (i.e., beyond present day) novel therapeutic strategies; evaluate possible generic intervention points in agent-induced pathophysiology. Assess broad-spectrum therapeutic strategies for exposures to multiple BW threat agents. These strategies will focus on intervention in disease pathogenesis at the molecular level and identify common host cellular targets for the pathogenic response. Develop methodologies utilizing biochemical (metabolic) processes for assaying in vivo antibiotic activity. Develop infection models in rodent species to evaluate antibiotic therapeutic indices.
- 5522 Therapeutics, Toxin - Identify sites of molecular action and mechanisms of intervention for therapies for botulinum toxin and SE threats; develop models for therapeutic intervention. Define endpoints for in vivo assessment of efficacy of therapeutic intervention for botulinum toxin and SE and surrogate endpoints of human clinical efficacy. Initiate high-output generation of candidate therapeutic moieties for botulinum and SE toxins using combinatorial chemistry.
- 2757 Therapeutics, Viral - Humanize mouse monoclonal antibodies specific for Ebola virus to test as an immunotherapeutic. Investigate mechanisms of filovirus transcription and replication focusing on polymerase as potential target for antiviral therapy.
- 4712 Vaccines, Bacterial - Investigate pathogenesis (cellular and molecular) and host immune responses; characterize additional virulence factors; define strain diversities; establish correlates of immunity for plague (Y. pestis), glanders (B. mallei), and anthrax (B. anthracis).

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DATE: June 2001

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

FY 2001 Planned Program (Cont):

- 995 Vaccines, Toxin - Initiate studies to identify potential neutralizing epitopes in the translocation domains of the botulinum neurotoxins. Investigate the variability of clostridium botulinum strains in terms of their neurotoxic isoforms and the presence of other toxins produced by various strains. Initiate structural and biophysical characterization studies of recombinant protein vaccines antigens. Construct enzymatically inactivated mutant of ricin A-chain for evaluation as a potential vaccine candidate. Initiate evaluation of adjuvants that may enhance the host immune response to aerosol-administered vaccines and assess delivery vehicles that may enhance the uptake of aerosol-administered vaccines.
- 2899 Vaccines, Viral - Determine the role of cytotoxic T cells in conferring protection against Ebola virus in the mouse model. Investigate poxvirus immunity to determine if it is feasible to replace vaccinia immune globulin (VIG) with monoclonal antibodies and to construct a safe and effective vaccine to replace the vaccinia virus vaccine for variola.
- 348 SBIR

Total 20563

FY 2002 Planned Program:

- 3557 Diagnostic Technologies - Continue investigating new medical diagnostic technologies based upon state-of-the-art biotechnological approaches for the enhanced recognition of infections by potential biological threats (bacteria, viruses, and toxins) of military interest.
- 1130 Therapeutics, Bacterial - Evaluate therapeutic indices for new (investigational) antibiotic agents identified by in vitro assays in suitable animal models. Study the effect of immunomodulators on the host response to B. mallei and Y. pestis candidate vaccines; identify those modulators that are effective in enhancing candidate vaccines.

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

FY 2002 Planned Program (Cont):

- 4874 Therapeutics, Toxin - Refine and standardize in vivo screening models for assessment of efficacy of therapeutic intervention in botulinum toxin and SE intoxication and standardize in vitro assays for neutralizing activity of lead inhibitors. Conduct high-output generation of candidate therapeutic moieties for botulinum and SE toxins using combinatorial chemistry. Evaluate inhibitor delivery strategies and demonstrate in vitro proof-of-concept. Begin high-throughput screening technology to investigate therapeutic candidates for exposure to ricin toxin.
- 2259 Therapeutics, Viral - Determine the therapeutic potential of candidate drugs for treatment of disease for filovirus or orthopox infections. Characterize filovirus polymerases as potential antiviral drug targets and incorporate into in vitro assays.
- 3200 Vaccines, Bacterial - Obtain genetic sequencing data from a panel of validated threat agents; establish genetic sequences into a database; evaluate sequence data for the potential for genetic engineering and genetic modification of the pathogens; determine genetic fingerprints (genetic identifiers) of various isolates of the organism responsible for plague (Y. pestis), glanders (B. mallei), and anthrax (B. anthracis). Evaluate genetically modified strains of Y. pestis, B. mallei, and B. anthracis for their level of virulence in animals. Identify genes from Y. pestis, B. mallei, and B. anthracis that encode for novel virulence factors. Expand and characterize strain collections of bacterial threat agents; identify strains of various agents that may be resistant to existing vaccines and/or those under advanced development.
- 1590 Vaccines, Toxin - Complete experiments involving the crystallization of vaccine candidates for structural studies and biophysical characterization of vaccines and toxins. Complete assessment of novel adjuvants and delivery vehicles for aerosol-administered vaccines.
- 1590 Vaccines, Viral - Continue investigating poxvirus immunity to determine if it is feasible to replace VIG with monoclonal antibodies and to construct a safe and effective vaccine to replace the vaccinia virus vaccine for variola.

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DATE: June 2001

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

FY 2002 Planned Program (Cont):

▪	5000	Anthrax studies - Initiate development and testing of new approaches for the treatment of inhalational anthrax. Focus will be placed on two classes of compounds that inhibit the activity of the lethal toxin produced during anthrax infection and on a novel enzyme target, NAD synthetase, which is critical for the germination and vegetative life cycle of Bacillus anthracis.

Total 23200

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DATE: June 2001

BUDGET ACTIVITY	PE NUMBER AND TITLE	PROJECT
RDT&E DEFENSE-WIDE/ BA1 - Basic Research	0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	TC1

COST (In Thousands)		FY 2000 Actual	FY 2001 Estimate	FY 2002 Estimate							
TC1	MEDICAL CHEMICAL DEFENSE (BASIC RESEARCH)	7761	9901	9876							

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 site 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 Plans (Pretreatments, Therapeutics, and Diagnostics) and directed research efforts (Low Level Chemical Warfare Agent Exposure).

FY 2000 Accomplishments:

- 3673 Pretreatments - Developed necessary knowledge for molecular modeling and site-directed mutagenesis to optimize next generation pretreatments to nerve agent poisoning. Began efforts to establish source for BuChE. Investigated intervention points for potential for pretreatment of vesicant exposures.
- 1698 Therapeutics - Explored potential for new technologies to intervene or serve as biomarkers in the mustard injury cascade. Identified 12 oximes that are superior to 2-PAM for efficacy against Fourth Generation Agents.
- 2390 Low Level Chemical Warfare Agent Exposure - Initiated mechanistic studies of nerve agent toxicity at low doses. Continued building a scientific database relevant to the underlying pathological effects of low level exposures to nerve agents. Identified information gaps in nerve agent exposures.

Total 7761

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RDT&E DEFENSE-WIDE/ BA1 - Basic Research	0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	TC1

FY 2001 Planned Program:

▪	2619	Pretreatment - Evaluate catalytic scavengers designed by site-directed mutagenesis. Develop candidate next generation pretreatments using knowledge gained from studies in molecular modeling and site-directed mutagenesis. Identify new candidate compounds with potential as pretreatment for vesicant injury based on current research strategies.
▪	1443	Therapeutics - Develop science base to identify specific factors leading to and/or preventing neuronal death in status epilepticus caused by nerve agents. Identify potential synergistic interactions of midazolam with anticholinergic drugs in rodent species. Define the optimal hypochlorite concentration for use in decontaminating chemical agent-exposed skin and agent-contaminated wounds.
▪	4164	Low Level Chemical Warfare Agent Exposure - Begin filling identified data gaps on the pathological and behavioral effects of low level chemical warfare nerve agent exposures. Investigate possible cellular mechanisms of low level chemical warfare agent injury. Develop highly sensitive, forward deployable diagnostic techniques to determine exposure to low levels of CW agents and subsequent physiological and toxicological effects.
▪	1507	Fourth Generation Agents - Determine mechanism by which Fourth Generation Agents produce toxicity that is not responsive to current nerve agent countermeasure pretreatments using knowledge gained from studies in molecular modeling and site-directed mutagenesis.
▪	168	SBIR
Total	9901	

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BUDGET ACTIVITY	PE NUMBER AND TITLE	PROJECT
RDT&E DEFENSE-WIDE/ BA1 - Basic Research	0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	TC1

FY 2002 Planned Program:

▪	2819	Pretreatments - Evaluate organophosphate anhydrolase for potential use as catalytic scavenger. Continue efforts tc identify compounds for potential use as pretreatments for vesicant exposure.
▪	1557	Therapeutics - Identify target sites for neuroprotection. Identify therapeutic targets for candidate compound combination therapies.
▪	4500	Low Level Chemical Warfare Agent Exposure - Continue studies on identification of chronic pathological and behavioral effects of low level chemical warfare agent exposures. Investigate putative mechanisms of low level toxicity. Develop consensus for a coherent methodology for studies across endpoints and model species to permit integration of disparate endpoints, post-hoc analysis of research results, and extrapolation to nonhuman primate models.
▪	1000	Fourth Generation Agents - Develop strategies to improve efficacy of current medical countermeasures against Fourth Generation Agents. Transition program to applied research.
Total	9876	