

RDT&E BUDGET ITEM JUSTIFICATION SHEET (R-2 Exhibit)

DATE

February 1999

BUDGET ACTIVITY

PE NUMBER AND TITLE

1 - Basic Research

0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)

COST (In Thousands)	FY 1998 Actual	FY 1999 Estimate	FY 2000 Estimate	FY 2001 Estimate	FY 2002 Estimate	FY 2003 Estimate	FY 2004 Estimate	FY 2005 Estimate	Cost to Complete	Total Cost
Total Program Element (PE) Cost	25263	29500	31386	31332	29705	30245	31256	32286	Continuing	Continuing
CB1 CHEMICAL/BIOLOGICAL DEFENSE (NON-MEDICAL)	2138	5865	2405	2467	3591	3305	3500	3621	Continuing	Continuing
TB1 MEDICAL BIOLOGICAL DEFENSE	13710	15625	20984	20881	17906	18576	18934	19574	Continuing	Continuing
TC1 MEDICAL CHEMICAL DEFENSE	9415	8010	7997	7984	8208	8364	8822	9091	Continuing	Continuing

A. Mission Description and Budget Item Justification: This program element funds the Joint Service core research program for chemical and biological (CB) defense. The basic research program aims to improve the operational performance of present and future DoD components by expanding knowledge in militarily 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 and medical 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), industry, and government research laboratories. Other programs include interdisciplinary research performed under the University Research Initiative (URI) program, and the In-House Laboratory Independent Research program. Funds directed to these laboratories and research organizations capitalize on scientific talent, specialized facilities and technological breakthroughs.

The work in this program element is consistent with the Joint Service Research, Development and Acquisition (RDA) Plan. Management of funding resources leads 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 immediate biological countermeasures. The projects in this PE include basic research efforts directed toward providing fundamental knowledge for the solution of military problems.

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B. Program Change Summary:	FY 1998	FY 1999	FY 2000	FY 2001
Previous President's Budget (FY1999 PB)	25190	25282	26054	26531
Appropriated Value	26336	28697		
Adjustments to Appropriated Value				
a. Congressional General Reductions				
b. SBIR/STTR	-440			
c. Omnibus or Other Above Threshold Reductions				
d. Below Threshold Reprogramming	-633	803		
e. Rescissions				
Adjustments to Budget Years Since FY 1999 PB			5332	4801
Current Budget Submit (FY2000/FY2001 PB)	25263	29500	31386	31332

Change Summary Explanation:

Funding: FY99 - TB1 (803) PDM I plus up for increased USARIID Bio RDTE efforts. FY00 - CB1 (-40) moved for higher priority efforts; TB1 (1784) PDM I plus up for increased USAMRIID RDTE efforts, TB1 (4500) PDM I plus up for increased bio vaccine RDTE, TB1 (-250) moved for higher priority efforts, TC1 (-135) moved for higher priority efforts, (-527) revised economic assumptions. FY01 - CB1 (-82) moved for higher priority efforts; TB1 (2357) PDM I plus up for increased USAMRIID RDTE efforts, TB1 (3850) PDM I plus up for increased bio vaccine RDTE, TB1 (-496) moved for higher priority efforts, TC1 (-268) moved for higher priority efforts, (-560) revised economic assumptions.

Schedule:

Technical:

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BUDGET ACTIVITY 1 - Basic Research				PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)						PROJECT CB1	
COST (In Thousands)		FY 1998 Actual	FY 1999 Estimate	FY 2000 Estimate	FY 2001 Estimate	FY 2002 Estimate	FY 2003 Estimate	FY 2004 Estimate	FY 2005 Estimate	Cost to Complete	Total Cost
CB1	CHEMICAL/BIOLOGICAL DEFENSE (NON-MEDICAL)	2138	5865	2405	2467	3591	3305	3500	3621	Continuing	Continuing
<p>A. Mission Description and Budget Item Justification:</p> <p>Project CB1 CHEMICAL/BIOLOGICAL DEFENSE (NON-MEDICAL): This project funds basic research in chemistry, physics, mathematics and life sciences, fundamental information in support of: new and improved detection systems for biological agents and toxins; new and improved detection systems 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.</p> <p>FY 1998 Accomplishments:</p> <ul style="list-style-type: none"> 640 Biosensors: Initiated work on generation of high affinity oligonucleotides to Bacillus anthracis from a large random oligonucleotide library. Began project to create a microsensor chip on which is immobilized a polymer demonstrating thermally induced delayed fluorescence. Synthesized and purified antibody-dendrimer-tag conjugates to surrogate bio warfare agents. Designed step-wise experiments for targeting multiple regulatory genes for microdetection. 480 Aerosol Science: Measured S34/S11 in UV region for Bacillus species. Designed and tested components of the improved scattering apparatus. Continued design and computer code development for a bio-aerosol 3-D imaging system based upon the inversion theory theorem completed last year. 1018 Chemistry and Tox of Bioactive Compounds: Determined basal cytotoxicity of the test compounds as indicated by irreversible inhibition of cell metabolic rates. Prepared chemical agent simulant polymer imprints and target monomers; prepared imprinted silica and initiated binding studies. Continued screen for a strain exhibiting the catalytic mustard degrading activity. Investigated the reaction mechanism, rates and products of the hydrolysis of pure T and HT at controlled pH; investigated the kinetics and mechanisms of VX hydrolysis at near neutral pH. <p>Total 2138</p>											
Project CB1		Page 3 of 11 Pages					Exhibit R-2 (PE 0601384BP)				

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CB1

FY 1999 Planned Program:

- 970 Biosensors: Begin sequencing of high affinity oligonucleotides identified last year and expand target bioagents. Synthesize diazoluminomelanin/oligomer complexes and begin integration with epoxy chips. Design capillary electrophoretic detection system based on dendrimer tags synthesized last year. Design deoxyribonucleic acid (DNA) probes to regulatory genes identified last year.
- 660 Aerosol Science: Assemble and test the improved scattering apparatus and begin rapid measurement of polarized light scattering from vegetative bacteria. Complete construction and demonstration of the bio-aerosol 3-D imaging system; transition the work to the core exploratory program.
- 661 Chemistry and Tox of Bioactive Compounds: Test specific or hypatocyte-dependent cytotoxicity on liver cells to determine if biotransformation of the test cell results in a product capable of inducing a cytotoxic effect in a particular target organ cell line. Begin to establish the system binding selectivity of the molecular imprinting system started last year; initiate studies of potential protective overcoatings for the system. Begin study of a percarbonate based reactive decontaminant formulation.
- 3476 Man-Portable Detectors: Initiate studies in the control of variability in film quality and stability through the use of silane linkages onto piezoelectric materials. Explore the use of "shape" selective surfaces attachment of biomolecules and the mechanisms for interaction on semiconductor metal oxide sensing elements.
- 98 SBIR/STTR

Total 5865

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PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)		PROJECT CB1
FY 2000 Planned Program:		
<ul style="list-style-type: none"> • 975 Biosensors: Deliver purified oligonucleotides for the detection of B. anthracis and Y. pestis. Continue conjugate synthesis and chip integration of specific DNA/Diazoluminomelanin conjugates. Complete synthesis of threat agent antibody/dendrimer tag complexes and begin demonstration of separation/identification via capillary electrophoresis. Send regulatory gene probes and protocols for their use to University College Galway for initial incorporation in detector design. • 420 Aerosol Science: Begin polarized light scattering measurements of several bacterial species in visible and UV light. Test computer model with internal structure of bacteria and/or spores against experimental data. Initiate new research project on understanding how to create a bioaerosol sampler which is better suited to the field environment than current systems; begin with a survey of ongoing aerosol physics projects in academia. • 1010 Chemistry and Tox of Bioactive Compounds: Complete project on cytotoxicity screening methods and transition the work to routine use throughout the toxicology program. Complete the initial prototype Individual Passive Chemical Agent Detector project and transition the further development to the core exploratory program. Continue rate studies on the percarbonate based decontaminant formulation to include work with surety materials. Begin evaluation of efficacy with toxic industrial materials of military concern. Begin a study of the pharmacodynamics and pharmacokinetics of the mechanisms by which novel organophosphorous agents produced delayed effects. 		
Total	2405	
FY 2001 Planned Program:		
<ul style="list-style-type: none"> • 980 Biosensors: Deliver purified oligonucleotides for the detection of three more potential threat agents. Complete conjugate synthesis and chip integration of specific DNA/Diazoluminomelanin conjugates. Demonstrate bioagent detection/identification in prototype field format via recognition of regulatory genes. Initiate a project to develop and test a universal approach for environmental sample processing prior to DNA-array-based analysis. • 560 Aerosol Science: Complete polarized light scattering measurements on bacterial species in visible and UV light. Continue project to understand novel bioaerosol sampling mechanisms; transition one or more approaches identified in the survey last year into the laboratory for fundamental studies. • 927 Chemistry and Tox of Bioactive Compounds: Complete studies of the percarbonate based decontaminant by finishing the reaction products distribution and toxicity studies. Complete the initial phases of the pharmacokinetic and pharmacodynamic study of novel nerve agents begun last year; if further work is required, transition the project to the exploratory program. Begin new projects on the design of CW agent sensors via computational chemistry approaches and on predicting the permeation of threat materials through thin films using a molecular dynamic approach. 		
Total	2467	
Project CB1		

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BUDGET ACTIVITY 1 - Basic Research	PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)	PROJECT TB1
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COST (In Thousands)	FY 1998 Actual	FY 1999 Estimate	FY 2000 Estimate	FY 2001 Estimate	FY 2002 Estimate	FY 2003 Estimate	FY 2004 Estimate	FY 2005 Estimate	Cost to Complete	Total Cost
TB1 MEDICAL BIOLOGICAL DEFENSE	13710	15625	20984	20881	17906	18576	18934	19574	Continuing	Continuing

A. Mission Description and Budget Item Justification:

Project TB1 MEDICAL BIOLOGICAL DEFENSE: This project funds basic research on the development of vaccines and drugs to provide an effective medical defense against validated biological threat agents including bacteria, toxins, viruses and other agents of biological origin. Also, by employing biotechnology, this project funds basic research to rapidly identify, diagnose, prevent, and treat disease due to exposure to biological threat agents.

FY 1998 Accomplishments:

- 1166 Identified and characterized plague virulence factors.
- 1249 Identified, cloned and sequenced virulence genes/plasmids for Brucella diagnostics and vaccines.
- 1802 Identified, cloned and sequenced virulence genes/plasmids for diagnostics for glanders and typhus.
- 1214 Evaluated pharmacologic agents for treatment of orthopox and filovirus infections.
- 2273 Performed computer simulation of structure/activity relationships for toxins of Clostridium botulinum and other toxins.
- 1523 Initiated entire genome sequencing of selected high priority bacterial and viral agents for screening of genetically engineered microbes.
- 2070 Constructed genetic libraries of staphylococcal enterotoxin producing genes and developed synthetic peptides, monoclonal antibodies and diagnostic probes.
- 999 Designed computer and in vitro model systems for design of post-exposure therapeutics for ricin.
- 1414 Continued sequence evaluation of enzootic strains of equine encephalitis viruses for multivalent vaccine and performed epitope mapping of filovirus antigens.

Total 13710

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PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)		PROJECT TB1
FY 1999 Planned Program:		
<ul style="list-style-type: none"> • 2720 Evaluate expression systems for newly cloned glanders and typhus virulence factors. • 3708 Identify modes of protection from filoviruses and orthopox viruses provided by pharmacological compounds. • 2030 Continue full genome sequencing of biological threat agents and begin gene bank search for general virulence factor sequence information. • 2338 Determine mechanism of action of staphylococcal enterotoxin induced shock and evaluate inhibitors of these mechanisms. • 1118 Complete screening of potential drugs for post-exposure therapies against ricin using in vitro model system. • 1254 Begin evaluation of potential antiviral compounds for filoviruses using in vitro models. • 1423 Test adjuvants to enhance mucosal immunity to brucellae and evaluate expression system for multivalent Brucella vaccine. • 788 Initiate basic research studies on generic countermeasures, such as broad-spectrum antitoxin and antiviral drugs, immune enhancers, and other therapeutics that are not agent-specific. Expand basic research efforts to understand agent pathogenesis and the immunology of protection against threat agents. Investigate surrogate markers of efficacy for current and future vaccines and therapies. Conduct basic research studies to exploit technologies for development of novel vaccines for genetically engineered threats. Utilize genome sequencing of threat agents and their virulence factors to identify biochemical or molecular targets for intervention with vaccines or therapeutics and targets for diagnostic tests. • 246 SBIR/STTR 		
Total	15625	
Project TB1		
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TB1

FY 2000 Planned Program:

- 1153 Investigate emerging diagnostic platform technologies providing rapid diagnostic capabilities.
- 576 Define animal models for aerosol exposure to glanders, botulinum toxin, ricin, and SEB.
- 5548 Establish database of genetic sequences of pathogenic agents for evaluation of genetic engineering. Determine genetic fingerprints of various isolates of *Yersinia pestis*.
- 1237 Continue studies of modes of protection by pharmacological compounds to filoviruses.
- 576 Continue evaluation of expression system for multivalent *Brucella* vaccine.
- 602 Investigate potential models/systems for replacement of animal models.
- 5111 Initiate studies of next generation therapeutic strategies for exposures to biological warfare agents.
- 4426 Prepare Research / Business Plan for therapies for botulinum toxin and staphylococcal enterotoxin (SE) threats; identify target mechanisms of action of botulinum toxin and SE for exploitation in investigation of therapy technologies.
- 1755 Continue basic research studies on generic countermeasures, such as broad-spectrum antitoxin and antiviral drugs, immune enhancers, and other therapeutics that are not agent-specific. Incorporate latest scientific advances in immunology into the basic research efforts to understand agent pathogenesis and the immunology of protection against threat agents. Continue investigation of surrogate markers of efficacy for current and future vaccines and therapies. Continue basic research studies to exploit technologies for development of novel vaccines for genetically engineered threats. Utilize genome sequencing of threat agents and their virulence factors to identify biochemical or molecular targets for intervention with vaccines or therapeutics and targets for diagnostic tests.

Total 20984

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TB1

FY 2001 Planned Program:

- 899 Identify new compounds that protect against filoviruses.
- 600 Continue identification of potential models/systems for replacement of animal models.
- 7561 Initiate studies of potential next generation vaccines.
- 5723 Continue studies of next generation therapeutic strategies for exposures to biological warfare agents.
- 3782 Identify sites/mechanisms of intervention for therapies for botulinum toxin and staphylococcal enterotoxin (SE) threats; develop models for therapeutic intervention for therapies for botulinum toxin and SE threats.
- 2316 Identify the most promising generic medical countermeasures against threat agents for exploratory development studies in suitable model systems. Define the most likely targets in agent pathogenesis and host immune response for further exploratory development research. Characterize the most promising surrogate markers of efficacy for selected vaccines and therapies for further exploratory development research. Identify at least one novel vaccine candidate or technology for medical countermeasures to genetically engineered threats. Select an array of biochemical and molecular targets of intervention for integration into exploratory research on specific threat agents.

Total 20881

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BUDGET ACTIVITY 1 - Basic Research				PE NUMBER AND TITLE 0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)					PROJECT TC1		
COST (In Thousands)		FY 1998 Actual	FY 1999 Estimate	FY 2000 Estimate	FY 2001 Estimate	FY 2002 Estimate	FY 2003 Estimate	FY 2004 Estimate	FY 2005 Estimate	Cost to Complete	Total Cost
TC1	MEDICAL CHEMICAL DEFENSE	9415	8010	7997	7984	8208	8364	8822	9091	Continuing	Continuing
<p>A. Mission Description and Budget Item Justification:</p> <p>Project TC1 MEDICAL CHEMICAL DEFENSE: This project emphasizes understanding of the basic mechanisms of action 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.</p> <p>FY 1998 Accomplishments:</p> <ul style="list-style-type: none"> • 4382 Elucidated immunological response to vesicants and screened analytic procedures useful for quantitating vesicant-induced inflammation. • 407 Synthesized and screened butyrylcholinesterase altered by site directed mutations guided by computer assisted design. • 1633 Explored mechanisms of action of aqueous wound decontaminant materials effective at neutralizing chemical warfare agents in wounds. • 1633 Designed and created protective active moieties for a reactive topical skin protectant (TSP). • 1360 Developed sensitive biomarkers of low dose exposure to CW agents. <p>Total 9415</p> <p>FY 1999 Planned Program:</p> <ul style="list-style-type: none"> • 3651 Screen drugs from principal classes of interest for viable post-exposure therapy of blister agents. • 528 Use crystal structure of human enzymes along with site directed mutagenesis to develop recombinant enzyme with catalytic function for nerve agent and resistance to aging by nerve agents, and evaluate novel drugs as anticonvulsants against nerve agents. • 951 Evaluate novel temporary wound dressing or skin; approaches as accelerators of healing for mustard induced wounds. • 845 Synthesize catalytic reactive moieties for topical skin protectant. • 1902 Generate a science base to understand the underlying efforts of chronic low-level exposure to CW agents. • 133 SBIR/STTR <p>Total 8010</p>											
Project TC1				Page 10 of 11 Pages				Exhibit R-2 (PE 0601384BP)			

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TC1

FY 2000 Planned Program:

- 4161 Continue generation of science base to understand the underlying efforts of chronic low-level exposure to CW agents.
- 940 Screen compounds for efficacy against novel threat agents.
- 1873 Investigate new interventions for injury from exposure to vesicating agents.
- 1023 Develop strategies leading to potential immunity to nerve agents.

Total 7997

FY 2001 Planned Program:

- 4574 Develop assays with sensitivity adequate for use in studies of chronic exposure to low doses of CW agents.
- 659 Identify candidates for use as countermeasures for exposure to novel threat agents.
- 2205 Identify new candidate compounds for use as pretreatments/treatments to vesicant injury.
- 546 Continue to develop strategies leading to potential immunity to nerve agents.

Total 7984