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| <b>CBDP BUDGET ITEM JUSTIFICATION SHEET (R-2 Exhibit)</b> | DATE<br><b>February 2003</b> |
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| BUDGET ACTIVITY<br><b>RDT&amp;E DEFENSE-WIDE/<br/>         BA1 - Basic Research</b> | PE NUMBER AND TITLE<br><b>0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC<br/>         RESEARCH)</b> |
|---|---|

| COST (In Thousands)                              | FY 2002<br>Actual | FY 2003<br>Estimate | FY 2004<br>Estimate | FY 2005<br>Estimate | FY 2006<br>Estimate | FY 2007<br>Estimate | FY 2008<br>Estimate | FY 2009<br>Estimate | Cost to<br>Complete | Total Cost |
|--|-------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|------------|
| Total Program Element (PE) Cost                  | 43986             | 54829               | 35831               | 36769               | 37946               | 41001               | 43863               | 42341               | Continuing          | Continuing |
| CB1 CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH) | 10648             | 18618               | 6338                | 6413                | 7601                | 10476               | 10620               | 10818               | Continuing          | Continuing |
| TB1 MEDICAL BIOLOGICAL DEFENSE (BASIC RESEARCH)  | 23637             | 27983               | 20119               | 20728               | 19703               | 19819               | 22390               | 20467               | Continuing          | Continuing |
| TC1 MEDICAL CHEMICAL DEFENSE (BASIC RESEARCH)    | 9701              | 8228                | 9374                | 9628                | 10642               | 10706               | 10853               | 11056               | 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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BUDGET ACTIVITY  
**RDT&E DEFENSE-WIDE/  
BA1 - Basic Research**

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

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.

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| BUDGET ACTIVITY<br><b>RDT&amp;E DEFENSE-WIDE/<br/>                 BA1 - Basic Research</b> | PE NUMBER AND TITLE<br><b>0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)</b> |
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| <b>B. <u>Program Change Summary:</u></b>         | <b><u>FY 2002</u></b> | <b><u>FY 2003</u></b> | <b><u>FY 2004</u></b> | <b><u>FY 2005</u></b> |
|--|-----------------------|-----------------------|-----------------------|-----------------------|
| Previous President's Budget (FY 2003 PB)         | 45791                 | 64119                 | 36434                 | 37540                 |
| Current Biennial Budget Estimates (FY 2004/2005) | 43986                 | 54829                 | 35831                 | 36769                 |
| Total Adjustments                                | -1805                 | -9290                 | -603                  | -771                  |
| a. Congressional General Reductions              | 0                     | -25000                | 0                     | 0                     |
| b. Congressional Increases                       | 0                     | 17500                 | 0                     | 0                     |
| c. Reprogrammings                                | 1030                  | 0                     | 0                     | 0                     |
| d. SBIR/STTR Transfer                            | -775                  | 0                     | 0                     | 0                     |
| e. Other Adjustments                             | 0                     | -1790                 | -603                  | -771                  |

**Change Summary Explanation:**

**Funding:** FY03 - Transfer to the Department of Homeland Security Bioterrorism initiatives (-\$25,000K HS1) .

FY03 - Adjustment for CBD (+\$12,500K CB1; +\$5,000K TB1).

**Schedule:**

**Technical:**

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| BUDGET ACTIVITY<br><b>RDT&amp;E DEFENSE-WIDE/<br/>                 BA1 - Basic Research</b> | PE NUMBER AND TITLE<br><b>0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)</b> | PROJECT<br><b>CB1</b> |
|---|--|-----------------------|

| COST (In Thousands)                              | FY 2002 | FY 2003  | FY 2004  | FY 2005  | FY 2006  | FY 2007  | FY 2008  | FY 2009  | Cost to    | Total Cost |
|--|---------|----------|----------|----------|----------|----------|----------|----------|------------|------------|
|  | Actual  | Estimate | Complete   |            |
| CB1 CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH) | 10648   | 18618    | 6338     | 6413     | 7601     | 10476    | 10620    | 10818    | 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 compounds.

**B. Accomplishments/Planned Program**

|           | <u>FY 2002</u> | <u>FY 2003</u> | <u>FY 2004</u> | <u>FY 2005</u> |
|-----------|----------------|----------------|----------------|----------------|
| Detection | 3699           | 3550           | 3434           | 3412           |

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| BUDGET ACTIVITY<br><b>RDT&amp;E DEFENSE-WIDE/<br/>BA1 - Basic Research</b>   | PE NUMBER AND TITLE<br><b>0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)</b> | PROJECT<br><b>CB1</b>        |
| <p><b>FY 2002 Accomplishments:</b></p> <ul style="list-style-type: none"> <li>3699 Point and Standoff Detection - Completed electromagnetic scattering for particle identification. Initiated effort to use modified chemresistor for chemical warfare (CW) agent detection. Completed evaluations of imprinted polymers for molecular recognition. Completed DNA-based biorecognition studies. Initiated investigation using neurons to detect presence of toxic agents. Initiated effort to isolate and identify biological weapon (BW) agents in fluid streams using light pressure. Initiated studies to measure rotational and transitional diffusion rates by Nuclear Magnetic Resonance (NMR) spectroscopy. Initiated investigations of methodology to identify CW agents and degradation products.</li> </ul> <p><b>Total 3699</b></p> <p><b>FY 2003 Planned Program:</b></p> <ul style="list-style-type: none"> <li>3550 Point and Standoff Detection - Continue investigation using neurons to detect presence of toxic agents. Continue effort to isolate and identify BW agents in fluid streams using light pressure. Complete studies to measure rotational and transitional diffusion rates by NMR spectroscopy. Initiate effort to identify biological agents using channel-based sensors. Initiate effort to identify biological agents using linear magnetic trappings. Initiate effort to investigate advanced spectroscopies and signal processing for CW agent identification. Initiate effort to assess utility of micro channel mixing for BW agent processing and detection. Initiate effort to determine enhancement of cavitands couple with liquid crystals for CW agent detection. Initiate efforts to assess utility of advanced (2-D) NMR for macromolecular structure determination and analysis of difficult samples. Initiate effort to determine if dioxiranes are suitable for gas and liquid phase decontamination applications.</li> </ul> <p><b>Total 3550</b></p> |  |                              |
| Project CB1/Line No: 008   | Page 5 of 33 Pages   | Exhibit R-2a (PE 0601384BP)  |

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| BUDGET ACTIVITY<br><b>RDT&amp;E DEFENSE-WIDE/<br/>                 BA1 - Basic Research</b> | PE NUMBER AND TITLE<br><b>0601384BP CHEMICAL/BIOLOGICAL DEFENSE (BASIC RESEARCH)</b> | PROJECT<br><b>CB1</b> |
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**FY 2004 Planned Program:**

- 3434 Point and Standoff Detection - Complete investigation using neurons to detect presence of toxic agents. Complete effort to isolate and identify BW agents in fluid streams using light pressure. Continue effort to identify biological agents using channel-based sensors. Continue effort to identify biological agents using linear magnetic trapping. Continue effort to investigate advanced spectroscopies and signal processing for CW agent identification. Continue effort to assess utility of micro channel mixing for BW agent processing and detection. Continue effort to determine enhancement of cavitands couple with liquid crystals for CW agent detection. Continue efforts to assess utility of advanced (2-D) NMR for macromolecular structure determination and analysis of difficult samples. Initiate novel research efforts with potential for CB advanced agent detection capability. Initiate novel research efforts with potential for advanced agent individual or collective protection capability.

**Total** 3434

**FY 2005 Planned Program:**

- 3412 Point and Standoff Detection - Complete effort to identify biological agents using channel-based sensors. Complete effort to identify biological agents using linear magnetic trapping. Complete effort to investigate advanced spectroscopies and signal processing for CW agent identification. Complete effort to assess utility of micro channel mixing for BW agent processing and detection. Complete effort to determine enhancement of cavitands couple with liquid crystals for CW agent detection. Complete efforts to assess utility of advanced (2-D) NMR for macromolecular structure determination and analysis of difficult samples. Complete effort to evaluate efficacy of artificial nucleases for decontamination of BW and mid-spectrum agents. Continue novel research efforts with potential for CB advanced agent detection capability.

**Total** 3412

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|            | <u>FY 2002</u> | <u>FY 2003</u> | <u>FY 2004</u> | <u>FY 2005</u> |
|------------|----------------|----------------|----------------|----------------|
| Protection | 772            | 600            | 611            | 630            |

**FY 2002 Accomplishments:**

- 772 Collective and Individual Protection - Initiated effort to investigate use of self-assembled monolayer materials for protective barriers. Completed fundamental study of filtration performance and modeling.

**Total** 772

**FY 2003 Planned Program:**

- 600 Collective and Individual Protection - Continue effort to investigate use of self-assembled monolayer materials for protective barriers. Initiate effort to assess protection enhancement of fabrics using patterned electrospray. Initiate effort to determine fate of CW agents adsorbed onto reactive media.

**Total** 600

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**FY 2004 Planned Program:**

- 611 Collective and Individual Protection - Conduct effort to investigate use of self-assembled monolayer materials for protective barriers. Complete investigations of methodology to identify CW agents and degradation products. Continue effort to assess protection enhancement of fabrics using patterned electrospray. Continue effort to determine fate of CW agents adsorbed onto reactive media.

**Total**      611

**FY 2005 Planned Program:**

- 630 Collective and Individual Protection - Complete effort to assess protection enhancement of fabrics using patterned electrospray. Conduct novel research efforts with potential for advanced agent individual or collective protection capability. Complete effort to determine fate of CW agents adsorbed onto reactive media. Initiate novel research efforts with potential for advanced agent individual or collective protection capability.

**Total**      630

|                 | <u>FY 2002</u> | <u>FY 2003</u> | <u>FY 2004</u> | <u>FY 2005</u> |
|-----------------|----------------|----------------|----------------|----------------|
| Decontamination | 842            | 1351           | 1522           | 1567           |

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| <p><b>FY 2002 Accomplishments:</b></p> <ul style="list-style-type: none"> <li>842 Decontamination - Completed investigations of peroxide activation to develop more effective and environmentally benign CB agent decontamination materials. Continued investigations of solvent effects for sub-surface decontamination of CW agents.</li> </ul> <p><b>Total 842</b></p> <p><b>FY 2003 Planned Program:</b></p> <ul style="list-style-type: none"> <li>1351 Decontamination - Initiate effort to determine if dioxiranes are suitable for gas and liquid phase decontamination applications. Complete studies of solvent effects on decon efficacy.</li> </ul> <p><b>Total 1351</b></p> <p><b>FY 2004 Planned Program:</b></p> <ul style="list-style-type: none"> <li>1522 Decontamination - Continue effort to determine if dioxiranes are suitable for gas and liquid phase decontamination applications. Continue effort to evaluate efficacy of artificial nucleases for decontamination of BW and mid-spectrum agents. Initiate novel research efforts with potential for advanced agent decontamination capability.</li> </ul> <p><b>Total 1522</b></p> |  |                              |
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**FY 2005 Planned Program:**

- 1567 Decontamination - Complete effort to determine if dioxiranes are suitable for gas and liquid phase decontamination applications. Complete effort to evaluate efficacy of artificial nucleases for decontamination of BW and mid-spectrum agents. Continue novel research efforts with potential for advanced agent decontamination capability.

**Total** 1567

|                                   | <u>FY 2002</u> | <u>FY 2003</u> | <u>FY 2004</u> | <u>FY 2005</u> |
|-----------------------------------|----------------|----------------|----------------|----------------|
| Supporting Science and Technology | 0              | 350            | 341            | 352            |

**FY 2003 Planned Program:**

- 350 Supporting Science and Technology - Measure the volatility of CW agents in humid environments. Initiate effort to measure volatility of thickened CW agents.

**Total** 350

**FY 2004 Planned Program:**

- 341 Supporting Science and Technology - Complete effort to measure the volatility of volatility of thickened CW agents.

**Total** 341

**FY 2005 Planned Program:**

- 352 Supporting Science and Technology - Initiate project to assess physical properties of prospective CW Agents.

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**FY 2005 Planned Program (Cont):**

**Total**     352

|                                | <u>FY 2002</u> | <u>FY 2003</u> | <u>FY 2004</u> | <u>FY 2005</u> |
|--------------------------------|----------------|----------------|----------------|----------------|
| Information Systems Technology | 489            | 0              | 430            | 452            |

**FY 2002 Accomplishments:**

- 489 CB Planning, Training and Analysis - Initiated simulation hazard modeling for systems and forces via distributed simulations systems. Initiated examination of sensitivity of hazard evolution/prediction models for agent toxicity.

**Total**     489

**FY 2004 Planned Program:**

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

**Total**     430

**FY 2005 Planned Program:**

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

**Total**     452

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|                | <u>FY 2002</u> | <u>FY 2003</u> | <u>FY 2004</u> | <u>FY 2005</u> |
|----------------|----------------|----------------|----------------|----------------|
| Basic Research | 4846           | 12500          | 0              | 0              |

**FY 2002 Accomplishments:**

- 2423 Magnetic Resonance Spectrometer - Purchased a 900 MHz magnetic resonance spectrometer for the New York Structural Biology Center.
- 2423 Lightweight Chemical and Biological Sensors - Completed the final phase of prototype testing of a sensor platform using Surface Acoustic Wave (SAW) and Semi-conducting Metal Oxides (SMO) devices for the detection of CW agents. Initiated a feasibility study to provide biological agent detection capability that may be combined with the chemical sensor. The technology is based on molecular imprinted polymers for biological materials.

**Total** 4846

**FY 2003 Planned Program:**

- 3500 Nanoemulsions for Decontamination - Develop, and validate the efficacy of nanoemulsions for the purpose of decontaminating chemical and biological threat agents.
- 3500 Detection of Chemical and Biological Pollutant Agents in Water - Investigate and develop novel technologies for the detection of chemical and biological threat agents in potable water sources.
- 1000 Chemical Agent Exposure Research - Develop novel approaches to interpreting the consequences of human exposures to chemical threat agents.

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**FY 2003 Planned Program (Cont):**

- 3500 Biological Process Development Facility - Design and develop a facility to evaluate cutting-edge technologies for processing and producing biotechnology reagents applicable to chemical and biological threat agent defense.
- 1000 Agroterrorist Attack Response - Develop novel and innovative response/implementation technologies to enhance multi-agency response to agroterrorist attack.

**Total 12500**

|           | <u>FY 2002</u> | <u>FY 2003</u> | <u>FY 2004</u> | <u>FY 2005</u> |
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| SBIR/STTR | 0              | 267            | 0              | 0              |

**FY 2003 Planned Program:**

- 267 SBIR

**Total 267**

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| <b>C. <u>Other Program Funding Summary:</u></b>       | <u>FY 2002</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<br/>Compl</u> | <u>Total<br/>Cost</u> |
|---|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|---------------------|-----------------------|
| CB2 CHEMICAL BIOLOGICAL DEFENSE<br>(APPLIED RESEARCH) | 93534          | 113169         | 65872          | 63494          | 66507          | 52915          | 49249          | 50169          | Cont                | Cont                  |
| CB3 CHEMICAL BIOLOGICAL DEFENSE<br>(ATD)              | 18531          | 47349          | 33414          | 33027          | 25908          | 30903          | 31328          | 31914          | Cont                | Cont                  |
| CP3 COUNTERPROLIFERATION<br>SUPPORT (ATD)             | 11791          | 11075          | 4714           | 5257           | 4575           | 4122           | 3196           | 3255           | Cont                | Cont                  |

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|     | COST (In Thousands)                         | FY 2002 | FY 2003  | FY 2004  | FY 2005  | FY 2006  | FY 2007  | FY 2008  | FY 2009  | Cost to    | Total Cost |
|-----|---|---------|----------|----------|----------|----------|----------|----------|----------|------------|------------|
|     |   | Actual  | Estimate | Complete   |            |
| TB1 | MEDICAL BIOLOGICAL DEFENSE (BASIC RESEARCH) | 23637   | 27983    | 20119    | 20728    | 19703    | 19819    | 22390    | 20467    | 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 technologies, bacterial therapeutics, toxin therapeutics, viral therapeutics, bacterial vaccines, toxin vaccines, and viral vaccines) and directed research efforts (Anthrax Studies and Engineered Pathogen Identification and Countermeasures Program [formerly Bug to Drug Identification and Countermeasures Program]).

**B. Accomplishments/Planned Program**

|              | <u>FY 2002</u> | <u>FY 2003</u> | <u>FY 2004</u> | <u>FY 2005</u> |
|--------------|----------------|----------------|----------------|----------------|
| Therapeutics | 12553          | 12842          | 9134           | 9411           |

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**FY 2002 Accomplishments:**

- 1033 Therapeutics, Bacterial - Evaluated therapeutic indices for new (investigational) antibiotic agents identified by in vitro assays in mouse models. Studied the effect of immunomodulators on the host response to Burkholderia mallei (glanders) and Yersinia pestis (plague) candidate vaccines and identified modulators effective in enhancing candidate vaccines. Conducted studies on the effects of established therapeutic compounds on Brucella in vitro.
- 4455 Therapeutics, Toxin - Developed high-throughput, cell-free screening assays for assessment of putative therapeutic inhibitors of several botulinum neurotoxin serotypes. Acquired and evaluated extramural combinatorial libraries of compounds and natural extracts, as well as custom therapeutics as potential botulinum neurotoxin inhibitors. Obtained high-resolution crystal structures of selected inhibitors bound to botulinum neurotoxins. Continued development of cell-free screening models for assessment of staphylococcal enterotoxin (SE) therapeutics. Initiated high-throughput screening technology to investigate potential ricin therapeutics.
- 2065 Therapeutics, Viral - Determined the therapeutic potential of candidate drugs for treatment of disease caused by filovirus or orthopox infections. Characterized filovirus polymerase as a potential antiviral drug target and initiated the development of in vitro assays incorporating filovirus polymerase to assess antiviral activity.
- 5000 Therapeutics, Anthrax Studies - Initiated development and testing of new approaches for the treatment of inhalational anthrax. Focused on two classes of compounds that inhibit the activity of the lethal toxin produced during anthrax infection and on an enzyme target, nicotinamide adenine dinucleotide (NAD) synthetase, which is critical for the germination and vegetative life cycle of B. anthracis.

**Total** 12553

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**FY 2003 Planned Program:**

- 982 Therapeutics, Bacterial - Correlate metabolic measurements as a rapid and sensitive means to detect antibiotic activity with conventional susceptibility determinations and appropriate animal models of infection. Establish collaborative research and development agreements with pharmaceutical companies to test new and investigational antibiotics. Initiate evaluation of selected therapeutic compounds against Brucella.
- 4800 Therapeutics, Toxin - Identify novel human and chimeric monoclonal antibodies by phage display methodology to aid in determining potential as botulinum neurotoxin therapeutics. Perform custom synthesis of lead compounds identified by high-throughput screening assays for botulinum neurotoxin and SE toxins. Co-crystallize toxin and lead therapeutics and collect x-ray diffraction datasets. Support development of combinatorial libraries and diversity sets for potential toxin therapeutics.
- 2060 Therapeutics, Viral - Initiate development of intervention strategies for filovirus-induced shock and therapeutic approaches that combine antiviral and anti-shock drug therapy. Continue research for development of in vitro assays utilizing filovirus polymerase as a potential antiviral drug target.
- 5000 Therapeutics, Anthrax Studies - Continue extramural research efforts toward the development and testing of new approaches for the treatment of inhalational anthrax. Focus will continue on two classes of compounds that inhibit the activity of the lethal toxin produced during anthrax infection and on the enzyme target NAD, which is critical for the germination and vegetative life cycle of B. anthracis.

**Total** 12842

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**FY 2004 Planned Program:**

- 1249 Therapeutics, Bacterial - Evaluate novel lead antimicrobial compounds in small animal models for anthrax and plague. Initiate in vitro studies on the efficacy of established and investigational antibiotics against Francisella tularensis (tularemia).
- 5387 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.
- 2498 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.

**Total** 9134

**FY 2005 Planned Program:**

- 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.

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**FY 2005 Planned Program (Cont):**

- 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. Utilize in vitro assays based on filovirus polymerase to screen potential antiviral drugs.

**Total** 9411

|          | <u>FY 2002</u> | <u>FY 2003</u> | <u>FY 2004</u> | <u>FY 2005</u> |
|----------|----------------|----------------|----------------|----------------|
| Vaccines | 5833           | 5670           | 7054           | 7267           |

**FY 2002 Accomplishments:**

- 2925 Vaccines, Bacterial - Obtained genetic sequencing data and established a database for *Y. pestis*, *B. mallei*, *B. anthracis* (anthrax), and *Brucella* spp.; evaluated data for potential for genetic engineering and genetic modification and determined genetic identifiers of various isolates of the organisms. Evaluated genetically modified strains of these pathogens for virulence in animals and identified genes that encode for novel virulence factors that may be new vaccine targets. Expanded and characterized strain collections of bacterial threat agents to identify strains that may be resistant to existing vaccines and/or those under development. Characterized in vitro host cell gene expression during infection with plague, glanders, anthrax, and brucella and identified novel bacterial genes expressed. Tested multiagent vaccine constructs in avirulent anthrax and brucella platforms for immunogenicity in mice.

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| <p><b>FY 2002 Accomplishments (Cont):</b></p> <ul style="list-style-type: none"> <li>• 1454 Vaccines, Toxin - Completed experiments involving the crystallization of toxins and toxin vaccine candidates for structural studies and biophysical characterization. Assessed novel adjuvants and delivery vehicles for aerosol-administered vaccines. Investigated potential neutralizing epitopes in the translocation domains of botulinum neurotoxin serotypes.</li> <li>• 1454 Vaccines, Viral - Continued investigating poxvirus immunity to determine the feasibility of replacing vaccinia immune globulin (VIG) with monoclonal antibodies and of constructing a safe and effective vaccine to replace the vaccinia virus vaccine for variola (smallpox).</li> </ul> <p><b>Total 5833</b></p> <p><b>FY 2003 Planned Program:</b></p> <ul style="list-style-type: none"> <li>• 2778 Vaccines, Bacterial - Develop mutations in various biological agents for in vivo expressed genes to examine role in virulence. Characterize the mechanism(s) of vaccine resistance in selected strains of various biological agents. Determine mechanisms and correlates of protection with efficacious B. mallei vaccines. Evaluate differences in the course of brucella infection in different mouse strains. Test multiagent vaccine constructs for immunogenicity in animal models.</li> <li>• 927 Vaccines, Toxin - Compare the efficacy of constructs with neutralizing epitopes in other domains of botulinum neurotoxin serotypes with the current heavy chain (Hc) subunit toxin vaccine candidates.</li> <li>• 1965 Vaccines, Viral - Complete investigating poxvirus immunity to determine the feasibility of replacing VIG with monoclonal antibodies and constructing a new vaccine to replace the vaccinia virus vaccine. Investigate the role of cytotoxic T cells in the Ebola virus-mouse model.</li> </ul> <p><b>Total 5670</b></p> |  |                              |
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**FY 2004 Planned Program:**

- 3538 Vaccines, Bacterial - Continue studies on the molecular mechanisms of pathogenesis of plague, glanders, and anthrax. Identify additional virulence determinants of Brucella spp. Initiate a study to identify and characterize novel virulence proteins of F. tularensis.
- 1758 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.
- 1758 Vaccines, Viral - Complete investigating the role of cytotoxic T cells in the Ebola virus-mouse model. Initiate research to investigate the role of cytotoxic T cells in the filovirus model in higher animal species.

**Total** 7054

**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.

**Total** 7267

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|  | <u>FY 2002</u> | <u>FY 2003</u> | <u>FY 2004</u> | <u>FY 2005</u> |
|--|----------------|----------------|----------------|----------------|
| Engineered Pathogen Identification and Countermeasures Program | 2000           | 5000           | 0              | 0              |

**FY 2002 Accomplishments:**

- 2000 Engineered Pathogen Identification and Countermeasures Program (formerly Bug to Drug Identification and Countermeasures Program) - Conducted research directed toward decreasing the time required to identify and counter biological threats. Focused on rapidly identifying host proteins altered by infection with biological threat pathogens and rapidly developing countermeasures based on how the countermeasures affect the host, outside of their desired effect against the pathogen. This research utilized structure-based small molecule design, microfluidics-based bioassays, and computational molecular biology and pathway modeling.

**Total** 2000

**FY 2003 Planned Program:**

- 5000 Engineered Pathogen Identification and Countermeasures Program (formerly Bug to Drug Identification and Countermeasures Program) - Identify the impact of bio warfare pathogens on the human body using computer models and direct protein analysis. 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** 5000

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|             | <u>FY 2002</u> | <u>FY 2003</u> | <u>FY 2004</u> | <u>FY 2005</u> |
|-------------|----------------|----------------|----------------|----------------|
| Diagnostics | 3251           | 4062           | 3931           | 4050           |

**FY 2002 Accomplishments:**

- 3251 Diagnostic Technologies - Continued investigating new diagnostic technologies based upon state-of-the-art biotechnological approaches for the enhanced recognition of infections by biological threats of military interest including new gene analysis chemistries and immunodiagnostics. Continued research to identify new biological markers and host responses for early recognition of infection including primer and probe sets against new gene targets. Continued to identify unique host immune markers using in vitro and in vivo models and developed primer and probe sets for these markers.

**Total** 3251

**FY 2003 Planned Program:**

- 4062 Diagnostic Technologies - Conduct basic research on new diagnostic approaches to the early recognition of infection; develop reagents and associated assays to aid in identifying new host and agent-specific biological markers that can be used for early recognition of infection. Continue 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.

**Total** 4062

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**FY 2004 Planned Program:**

- 3931 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.

**Total** 3931

**FY 2005 Planned Program:**

- 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.

**Total** 4050

|           | <u>FY 2002</u> | <u>FY 2003</u> | <u>FY 2004</u> | <u>FY 2005</u> |
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| SBIR/STTR | 0              | 409            | 0              | 0              |

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**FY 2003 Planned Program:**

- 409 SBIR

**Total 409**

| <b>C. <u>Other Program Funding Summary:</u></b>      | <b><u>FY 2002</u></b> | <b><u>FY 2003</u></b> | <b><u>FY 2004</u></b> | <b><u>FY 2005</u></b> | <b><u>FY 2006</u></b> | <b><u>FY 2007</u></b> | <b><u>FY 2008</u></b> | <b><u>FY 2009</u></b> | <b><u>To<br/>Compl</u></b> | <b><u>Total<br/>Cost</u></b> |
|--|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|----------------------------|------------------------------|
| TB2 MEDICAL BIOLOGICAL DEFENSE<br>(APPLIED RESEARCH) | 34195                 | 40977                 | 22699                 | 22622                 | 15415                 | 15692                 | 16442                 | 13095                 | Cont                       | Cont                         |
| TB3 MEDICAL BIOLOGICAL DEFENSE<br>(ATD)              | 34554                 | 35515                 | 49939                 | 44621                 | 39530                 | 39527                 | 42528                 | 38573                 | Cont                       | Cont                         |

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Exhibit R-2a (PE 0601384BP)

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| COST (In Thousands)                           | FY 2002<br>Actual | FY 2003<br>Estimate | FY 2004<br>Estimate | FY 2005<br>Estimate | FY 2006<br>Estimate | FY 2007<br>Estimate | FY 2008<br>Estimate | FY 2009<br>Estimate | Cost to<br>Complete | Total Cost |
|---|-------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|------------|
| TC1 MEDICAL CHEMICAL DEFENSE (BASIC RESEARCH) | 9701              | 8228                | 9374                | 9628                | 10642               | 10706               | 10853               | 11056               | 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 (Pretreatments, Therapeutics, and Diagnostics) and directed research efforts (Low Level Chemical Warfare Agent Exposure and Non-Traditional Agents).

**B. Accomplishments/Planned Program**

|   | <u>FY 2002</u> | <u>FY 2003</u> | <u>FY 2004</u> | <u>FY 2005</u> |
|---|----------------|----------------|----------------|----------------|
| Low Level Chemical Warfare Agent Exposure | 4500           | 4000           | 2000           | 1000           |

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| <p><b>FY 2002 Accomplishments:</b></p> <ul style="list-style-type: none"> <li>4500 Low Level Chemical Warfare Agent Exposure - Continued studies on identification of chronic pathological and behavioral effects of low level chemical warfare agent (CWA) exposures. Investigated putative mechanisms of low level toxicity. Developed 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 higher animal species. Examined alterations in muscle physiology produced by repetitive low-dose nerve agent exposures. Measured in vitro membrane electrical alterations caused by low concentrations of nerve agent. Investigated effects of acute and chronic exposure to low dose CWA on blood and brain cell apoptosis.</li> </ul> <p><b>Total 4500</b></p> <p><b>FY 2003 Planned Program:</b></p> <ul style="list-style-type: none"> <li>4000 Low Level Chemical Warfare Agent Exposure - Continue studies on neurotoxic effects of low dose CWA exposure. Continue investigation of alterations in muscle physiology due to repetitive low dose CWA exposure. Characterize ultrastructural morphology, immunochemistry, and gene expression following low level chemical exposure. Study the effects of low level chemical exposure on extracellular neurotransmitter levels. Evaluate organophosphate anhydrolase enzyme for potential use as a biomarker to confirm low level chemical exposure.</li> </ul> <p><b>Total 4000</b></p> <p><b>FY 2004 Planned Program:</b></p> <ul style="list-style-type: none"> <li>2000 Low Level Chemical Warfare Agent Exposure - Identify biomarker(s) to confirm low level chemical exposure and develop behavior assessment model. Identify potential medical countermeasures for low level chemical exposure.</li> </ul> |  |                              |
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**FY 2004 Planned Program (Cont):**

**Total** 2000

**FY 2005 Planned Program:**

- 1000 Low Level Chemical Warfare Agent Exposure - Continue to identify biomarker(s) to confirm low level chemical exposure. Validate neurobehavioral deficits following low level chemical exposure.

**Total** 1000

|                        | <u>FY 2002</u> | <u>FY 2003</u> | <u>FY 2004</u> | <u>FY 2005</u> |
|------------------------|----------------|----------------|----------------|----------------|
| Non-Traditional Agents | 1000           | 0              | 0              | 0              |

**FY 2002 Accomplishments:**

- 1000 Non-Traditional Agents - Developed strategies to improve efficacy of current medical countermeasures against non-traditional agents (NTAs). Studied the effects of NTAs on energy metabolism in cardiac muscle cells.

**Total** 1000

|               | <u>FY 2002</u> | <u>FY 2003</u> | <u>FY 2004</u> | <u>FY 2005</u> |
|---------------|----------------|----------------|----------------|----------------|
| Pretreatments | 2108           | 1883           | 3700           | 4330           |

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| <p><b>FY 2002 Accomplishments:</b></p> <ul style="list-style-type: none"> <li>2108 Pretreatments - Identified peptide for potential use as pretreatment for vesicant exposure. Exploited new technology to develop recombinant biological scavengers. Initiated studies to investigate gene encoding serum carboxylesterase (CaE).</li> </ul> <p><b>Total 2108</b></p> <p><b>FY 2003 Planned Program:</b></p> <ul style="list-style-type: none"> <li>1883 Pretreatments - Target mechanism of vesicant injury and explore intervention of pro-inflammatory mediators and calcium modulators. Investigate efficacy of sulfur donors as anti-cyanide pretreatments. Develop animal model to test cyanide pretreatment compounds. Express and purify a recombinant human CaE for crystallization. Evaluate circulatory stability of recombinant bioscavengers.</li> </ul> <p><b>Total 1883</b></p> <p><b>FY 2004 Planned Program:</b></p> <ul style="list-style-type: none"> <li>3700 Pretreatments - Continue pretreatment intervention studies of vectors to deliver bioscavenger genes. Identify mechanism of action of vesicant pretreatment compounds. Evaluate cyanide toxicity using an inhalation model. Determine x-ray crystallographic structure of catalytic scavengers. Investigate efficacy of sulfur donors and methemoglobin formers as cyanide pretreatments.</li> </ul> <p><b>Total 3700</b></p> |  |                              |
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**FY 2005 Planned Program:**

- 4330 Pretreatments - Explore purification and delivery strategies of vesicant pretreatments. Screen anti-cyanide compounds for efficacy.

**Total** 4330

|              | <u>FY 2002</u> | <u>FY 2003</u> | <u>FY 2004</u> | <u>FY 2005</u> |
|--------------|----------------|----------------|----------------|----------------|
| Therapeutics | 1495           | 1458           | 2624           | 3070           |

**FY 2002 Accomplishments:**

- 1495 Therapeutics - Identified through gene sampling target sites for neuroprotection. Identified vesicant therapeutic targets for candidate compound combination therapies. Initiated efforts to determine the optimal hypochlorite concentration for use in decontaminating chemical agent-exposed skin and agent-contaminated wounds. Determined the role of pro-inflammatory mediators derived from the release of arachidonic acid following sulfur mustard (HD) exposure. Studied biochemical mechanisms of HD toxicity and protection.

**Total** 1495

**FY 2003 Planned Program:**

- 1458 Therapeutics - Incorporate biomarker panels into screening modules. Evaluate combination therapies for neuroprotection efficacy. Evaluate antidotes representing new strategies to address medical countermeasure requirements against conventional and emerging agents.

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**FY 2003 Planned Program (Cont):**

**Total** 1458

**FY 2004 Planned Program:**

- 2624 Therapeutics - Characterize animal models to test efficacy of nerve agent bioscavengers. Test physiologic pharmacokinetic model of CWAs. Determine effects of 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. Investigate enzymatic targets of HD. Evaluate drug treatment strategies and combinations of therapies for nerve agent-induced seizures.

**Total** 2624

**FY 2005 Planned Program:**

- 3070 Therapeutics - Identify intervention targets to acute lung injury caused by HD.

**Total** 3070

|             | <u>FY 2002</u> | <u>FY 2003</u> | <u>FY 2004</u> | <u>FY 2005</u> |
|-------------|----------------|----------------|----------------|----------------|
| Diagnostics | 598            | 766            | 1050           | 1228           |

**FY 2002 Accomplishments:**

- 598 Diagnostics - Investigated in vitro validation of sulfur mustard (HD)-induced proteases as biomarkers for exposure.

**Total** 598

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**FY 2003 Planned Program:**

- 766 Diagnostics - Conduct electrophysiological analysis of CWAs in cultured cells. Analyze central nervous system (CNS) and peripheral protein production following soman exposure. Develop new assays for HD adducts in plasma and for diagnosing cyanide exposure.

**Total** 766

**FY 2004 Planned Program:**

- 1050 Diagnostics - Identify molecular intracellular proteomic changes following HD exposure.

**Total** 1050

**FY 2005 Planned Program:**

- 1228 Diagnostics - Pursue development of a nanodevice for diagnosing CWA exposure using synthetic modeling and molecular imprinting.

**Total** 1228

|           | <u>FY 2002</u> | <u>FY 2003</u> | <u>FY 2004</u> | <u>FY 2005</u> |
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| SBIR/STTR | 0              | 121            | 0              | 0              |

**FY 2003 Planned Program:**

- 121 SBIR

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**FY 2003 Planned Program (Cont):**  
**Total 121**

| <b>C. <u>Other Program Funding Summary:</u></b>    | <u>FY 2002</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<br/>Compl</u> | <u>Total<br/>Cost</u> |
|--|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|---------------------|-----------------------|
| TC2 MEDICAL CHEMICAL DEFENSE<br>(APPLIED RESEARCH) | 17977          | 19216          | 17880          | 18269          | 19994          | 20104          | 20368          | 21750          | Cont                | Cont                  |
| TC3 MEDICAL CHEMICAL DEFENSE<br>(ATD)              | 10672          | 11470          | 13199          | 13489          | 12571          | 12644          | 12818          | 13058          | Cont                | Cont                  |

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