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<b>RDT&amp;E BUDGET ITEM JUSTIFICATION SHEET (R-2 Exhibit)</b>								<b>DATE</b> February 1999		
<b>APPROPRIATION/BUDGET ACTIVITY</b> RDT&E, Defense Wide/BA 2							<b>R-1 ITEM NOMENCLATURE</b> Medical Technology PE 0602787D8Z			
<i>COST(In Millions)</i>	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY 2003	FY 2004	FY 2005	Cost to Complete	Total Cost
Total Program Element (PE) Cost	8.559	9.212	8.903	8.742	8.990	9.210	9.380	9.526	Continuing	Continuing
Radiation Injury Assessment and Therapeutic Approa/P505	8.559	9.212	8.903	8.742	8.990	9.210	9.380	9.526	Continuing	Continuing

(U) **A. Mission Description and Budget Item Justification**

(U) **BRIEF DESCRIPTION OF ELEMENT**

(U) This program supports applied research to investigate new approaches that will lead to advancements in biomedical strategies for preventing, treating, assessing and predicting the health effects of ionizing radiation, either alone or in combination with other biological warfare (BW)/chemical warfare (CW) toxicants. The premise is that DoD must be ready to conduct tactical, humanitarian or counterterrorism missions within radiation environments. Development of protective and therapeutic strategies will enable military forces to operate, when required, in nuclear or radioactive combat environments, while minimizing both short- and long-term risks of adverse health consequences. Advancements in tools to measure radiation exposure to military personnel will be used in triage, treatment decisions and risk assessment. Accurate models to predict casualties, particularly in combined nuclear-biological-chemical NBC environments, will promote effective command decisions and force structure planning to ensure mission success.

(U) The program has three primary goals: (1) to understand the pathological consequences of radiation injury and radiological hazards in order to provide a rational basis for prophylactic and therapeutic drug development; (2) to develop novel biological markers and delivery platforms for rapid, field-based individual dose assessment; (3) to define any interactions between radiation and BW or CW agents that cause more severe injury and the drugs used to protect against them -- with the goal of developing new models to predict casualties.

(U) This program is executed by the Armed Forces Radiobiology Research Institute (AFRRI) which, because of its multidisciplinary staff and facility resources, is uniquely qualified to carry out this mission. AFRRI's radiation sources allow the simulation of any radiological environment that might be encountered. Because national laboratories operated by the Department of Energy no longer support research efforts relevant to military medical radiobiology, the AFRRI is currently the sole laboratory with the combined capabilities needed to conduct this research.

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(U) **Project Number and Title: P505 Radiation Injury Assessment and Therapeutic Approach**

(U) **PROGRAM ACCOMPLISHMENTS AND PLANS**

(U) **FY1998 Accomplishments:**

(U) Developed new strategies for preventive treatments of both acute and chronic radiation injuries based on (a) fundamental mechanisms of cellular and molecular injury, (b) selecting less toxic drug alternatives, (c) pharmacologic quenching to reduce drug toxicity, and (d) new drug delivery alternatives. (\$ 2.114 Million)

(U) Developed enhanced treatments for radiation-associated infections using immune system stimulators. (\$ 2.045 Million)

(U) Evaluated newly developed delivery platform for cytogenetic-based radiation dose assessments in individuals. The system will provide standardized operational simplicity needed to carry out dose assessments in clinical and reference laboratories, enabling better medical management of large numbers of casualties. (\$ 0.664 Million)

(U) Identified and initiated development of two classes of novel molecular markers potentially useful as diagnostic determinants of radiation doses received by individuals. Observed that ionizing radiation induces a specific deletion in the genomes of mitochondrial DNA and alterations in oncogene expression, both of which are quantifiable in a dose-dependent fashion. Both classes of markers can be easily and quickly measured using newly developed polymerase chain reaction (PCR) methods for nucleic acid sequence analysis. (\$ 0.658 Million)

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(U) Quantified the increased mortality rates seen in irradiated mice infected via the pulmonary route with *Bacillus anthracis* (Sterne) spores. Initiated studies to assess effects of radiation on the immune status of individuals vaccinated with the anthrax vaccine. Established *in vitro* model systems to assess radiation/viral interactions. Data will be used to build casualty prediction models and develop treatment protocols for combined injuries. (\$ 1.054 Million)

(U) Identified a synergistic consequence that causes redistribution of blood flow within the body resulting from the interaction of sub-lethal radiation and therapeutic levels of the nerve agent prophylactic pyridostigmine. These data will be used to assess treatment of combined injuries. (\$ 0.961 Million)

(U) Initiated studies to assess the cancer-causing potential of depleted uranium (DU) in laboratory animals. Initiated a pilot study to assess the effects on the immune system of tissue-embedded DU fragments. Initiated development of a potentially fieldable method to measure uranium in the urine of military personnel. (\$ 0.792 Million)

(U) Planned study and initiated pilot experiments to determine the toxicity associated with tungsten, which is a proposed replacement metal for DU in munitions manufacturing. (\$ 0.271 Million)

(U) **FY1999 Plans:**

(U) Initiate studies to assess efficacy of conventional or slow-released radioprotectants to prevent or reduce late-arising health consequences of radiation, including cancer and chronic immune system suppression. (\$ 2.222 Million)

(U) Develop and test second-generation radioprotective modalities that improve efficacy through sustained effectiveness. Assess newly available drug prototypes for protective efficacy against acute radiation injury. (\$ 2.009 Million)

(U) Continue development of clinical bioassays that provide a rapid dose assessment capability for radiation exposures involving a broad spectrum of radiation qualities (gamma, neutron, etc.). Develop an automated analytical capability that allows high sample-number throughput and operability by generalist laboratory technicians. (\$ 0.748 Million)

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- (U) Continue identification and development of new biological markers and compact, portable instrumentation for radiation dose assessments that provide a simple and easy-to-use forward-fielded screening system. Measure effects of incremental doses and time-course of exposures to evaluate the practical utility of candidate assays. (\$ 0.779 Million)
- (U) Extend radiation/BW agent interaction studies to assess incapacitation resulting from combined exposures to a variety of doses, and add this endpoint to casualty prediction models. Continue studies to determine the effect of radiation on the immune status of individuals vaccinated against anthrax. Extend *in vitro* models for viral/radiation interactions to *in vivo* model systems. (\$ 1.222 Million)
- (U) Initiate studies to determine how radiation and nerve agents interact to adversely affect military personnel upon combined exposure. Continue assessments of the physiologic consequences of combined exposure to radiation and the nerve agent prophylactic pyridostigmine. (\$ 1.219 Million)
- (U) Continue laboratory animal studies on the cancer risk of DU to refine recommendations for treatment of military personnel wounded by DU. Initiate full study on the toxicity of tungsten. Initiate pilot studies to determine the long-term effects on the immune, nervous, and male reproductive systems from exposure to DU. (\$ 1.013 Million)
- (U) **FY2000 Plans:**
- (U) Continue to develop and test second generation of radioprotective treatments with sustained effectiveness. Assess efficacy of newly synthesized drug prototypes for protection from acute radiation injury. (\$ 2.043 Million)
- (U) Design, synthesize, and provide initial testing of drug prototypes to treat immune system deficiencies after radiation exposure. (\$ 2.043 Million)
- (U) Continue development of clinical bioassays for assessment of radiation exposures. Optimize protocol to permit assessment of prior radiation exposure. Develop a rapid sample processing procedure involving the use of a portable incubator to minimize cell culture delays for the analysis of samples using the clinical bioassays. (\$ 0.721 Million)

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- (U) Continue evaluation of new assays to detect radiation exposure to provide simple and easy-to-use forward-field screening exposure-assessment tools. Develop automated analysis systems to efficiently evaluate promising candidate bioassays. (\$ 0.757 Million)
- (U) Continue assessment of immunization strategies for B. anthracis in combination with radiation. Quantify the interactions of radiation with incapacitating bacterial agents for non-lethal endpoints to provide prediction models of casualties from combined injuries. Extend radiation/BW agent interaction studies to the viral threat agent Venezuelan Equine Encephalitis (VEE) virus, assessing increased mortality of the combined exposure in order to expand the capability of casualty prediction models and to provide appropriate care for casualties. (\$ 1.441 Million)
- (U) Assess the changes in sensitivity to nerve agent induced seizures with prior exposure to ionizing radiation. Initiate studies on effectiveness of therapeutic regimens to mitigate these seizures. Quantify the interactions of nerve agent and radiation in order to expand the capability of casualty prediction models. (\$ 0.918 Million)
- (U) Continue studies on the cancer risk of DU in laboratory animals, tungsten toxicity, and the long-term effects of exposure to DU on immune, nervous, and male reproductive systems. (\$ 0.980 Million)
- (U) **FY2001 Plans:**
- (U) Continue development of simple, self-administered drug delivery systems for radiation protection and treatment. Evaluate transdermal skin patches, oral administration, and autoinjector systems. (\$ 4.012 Million)
- (U) Continue development of clinical bioassays to provide rapid assessment of radiation exposure from a low dose and low dose-rate exposures. Establish protocols to process high number of samples simulating a mass-casualty incident. (\$ 0.708 Million)
- (U) Continue identification and development of new assays to detect radiation exposure. Complete in vitro evaluation studies to permit identification of suitable cytological and molecular biomarker to transition to in vivo validation studies. (\$ 0.743 Million)

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- (U) Complete assessment of effectiveness of the vaccine for anthrax to provide protection from infection with a combined radiation/B. anthracis exposure. Continue studies with other vaccines (e.g. for VEE). Assess therapeutic strategies for combined exposures to radiation and B. anthracis in order to evaluate current therapeutic strategies and to recommend the best treatments for combined injuries. (\$ 1.424 Million)
  
- (U) Continue assessment of interactions of radiation with nerve agent and nerve agent therapeutics in order to provide recommendations for appropriate treatment protocols for combined injuries. Interactions will be determined for various nerve agents, various time intervals between radiation /agent exposures and various doses of radiation and of nerve agent to fully characterize the interactions for both therapeutic strategies and casualty prediction models. (\$ 0.893 Million)
  
- (U) Continue studies on the cancer risk of DU in laboratory animals. Complete tungsten toxicity study. Complete pilot studies on long-term effects of exposure to DU on immune and nervous systems. Continue male reproductive study. (\$ 0.962 Million)

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<b>(U) B. <u>Program Change Summary</u></b>	<b><u>FY1998</u></b>	<b><u>FY1999</u></b>	<b><u>FY2000</u></b>	<b><u>FY2001</u></b>	<b><u>Total Cost</u></b>
Previous Presidents Budget	8.669	9.239	9.056	8.900	Continuing
Appropriated Value	8.407	9.239	0	0	Continuing
Adjustments to Appropriated Value					
a. Congressionally Directed Undistributed Reduction	0	-0.027			
b. Rescission/Below-threshold Reprogramming, Inflation Adjustment	0	0			
c. Other	0.152	0	-0.153	-0.158	
Current Presidents Budget	8.559	9.212	8.903	8.742	Continuing

**Change Summary Explanation:**      Funding changes are due to congressional undistributed reductions and inflation adjustments.

(U)    **Funding:**      Changes in FY99 are a result of undistributed reductions. FY2000 and FY 2001 are a result of budget adjustments.

(U)    **Schedule:**      N/A

(U)    **Technical:**

(U)    **C.    OTHER PROGRAM FUNDING SUMMARY COST:**      N/A

(U)    **D.    ACQUISITION STRATEGY:** N/A

(U)    **E.    SCHEDULE PROFILE:**      N/A