RDT&E BUDGET ITEM JUSTIFICATION SHEET (R-2 Exhibit)									DATE June 2001	
APPROPRIATION/BUDGET ACTIVITY RDT&E, Defense Wide/BA 2							**R-1 ITEM NOMENCLATURE** Medical Technology **PE 0602787D8Z**			
COST *(In Millions)*	FY 2000	FY 2001	FY 2002						Cost to Complete	Total Cost
Total Program Element (PE) Cost	8.829	8.600	8.971						Continuing	Continuing
Radiation Injury Assessment and Therapeutic Approach/P505	8.829	8.600	8.971						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 counter terrorism 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 four 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 the toxicity of depleted uranium (DU); (4) 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.

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(U) The Armed Forces Radiobiology Research Institute (AFRRI), because of its multidisciplinary staff and facility resources, is uniquely qualified to execute the program prescribed by its mission. AFRRI`s radiation sources allow the simulation of any radiological environment that might be encountered. 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) FY 2000 Accomplishments:

(U) Demonstrated therapeutic efficacy of keratinocyte growth factor (KGF) for treating radiation-induced gastrointestinal injury.($ 0.500 million)

(U) Established a cDNA screening assay for monitoring variable gene expression, and refined other experimental processes needed for rational discovery and development of preventive strategies based on fundamental mechanisms of cellular and molecular injury and repair of blood-forming (hematopoietic) and gastrointestinal organ systems. ($ 1.000 million)

(U) Extended gene-based drug screening protocols to assess efficacy of an aminothiol-based radioprotectant being developed to mitigate the adverse genomic consequences caused by acute or chronic radiation exposures and that lead to long-term health consequences.($ 0.500 million)

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(U) Identified and partially characterized radioprotective qualities of a class of nutritional supplements (isoflavones) that are non-toxic by oral administration. Demonstrated efficacy of radioprotectant compounds such as androstene steroids in reducing the frequency of neoplastic transformation and related long-term adverse health effects. ($ 1.819 million)

(U) Completed and published refinements of the Premature Chromosome Condensation (PCC) interphase-chromosome aberration bioassay used for radiation dose assessment across a broad dose range from biological samples such as blood. Further refined the PCC assay by developing a cytogenetic staining technique, making the assay amenable to automated image analysis and scoring of chromosomal aberrations. ($ 1.121 million)

(U) Further demonstrated predictable dose responses of selected molecular-based biological markers of radiation exposure that can be measured by rapid field-based polymerase chain reaction (PCR) techniques. Using an in vitro human peripheral blood model, identified messenger-RNA, DNA and protein species that yield measureable reproducible responses to ionizing radiation. Confirmed utility of a fluorogenic nuclease PCR procedure to effectively measure radiation-induced altered gene expression and DNA mutations.($ 0.357 million)

(U) Continued assessing the effects of combined radiation and B. anthracis exposures on status of protective immunity. Continued to collect and analyze data to quantify the biological interactions of radiation and non-lethal, incapacitating bacterial agents. Completed initial mortality studies on combined exposure to radiation and viral agents (e.g. VEE). Continued animal model studies to collect and analyze experimental data to improve and expand the predictive value of casualty prediction models and to provide information to improve clinical management of combined injuries. ($ 1.462 million)

(U) Completed animal model experimentation to assess treatment strategies for endemic shigellosis in irradiated animals. Continued assessment of the combined effects of radiation exposure and sleep deprivation on brain wave patterns and sleep-wake cycle alterations ($ 1.118 million).

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(U) Continued work on the carcinogenic potential of DU and other militarily relevant heavy metals by measuring transformat ion potential and genotoxicity in in vitro cell culture systems. Completed pilot studies on immune system effects resulting from long-term DU exposure. Completed cell culture pilot study to assess tungsten toxicity. ($ 0.952 million)

(U) FY 2001 Plans:

(U) Develop simplified drug delivery systems for new drug prototypes. Commence initial design and testing of vehicles for oral and subcutaneous administration of metabolite- and nutritional-based radioprotectants (androstendiol, vitamin E, isoflavones).($ 1.430 million)

(U) Initiate use of molecular biomarker and other functional assays to assess host immune defense response to combined radiation/virus-bacteria exposures. Complete studies on the interaction of radiation and sleep deprivation on seizure incidence, brain waves and sleep-wake cycles.($ 0.689 million)

(U) Continue to identify promising new radioprotectants and therapeutics using newly established drug screening assays. Continue to refine and test preventive teatment strategies based on fundamental mechanisms of cellular and molecular injury and repair of blood-forming (hematopoietic) and gastointestinal organ systems. ($ 1.043 million)

(U) Continue to extend and refine high-throughput, gene-based drug screening protocols to assess effi cacy of newly identified radioprotectants, therapeutics, or combinations for both early- and late-arising injuries. ($ 0.796 million)

(U) Test efficacy of second-generation, slow-release radioprotectant implants under chronic irradiation exposure.($ 0.74 6 million)

(U) Continue development of a clinical cytogenetic-based bioassay system by extending improvements in sample preparation, imaging and data analysis, and by broadening the operating range of dose measurement.($ 0.844 million)

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(U) Continue development of molecular biomarker systems for field use. Continue to assess dose-ranges and time-window characteristics for gene expression and protein radiation biomarkers. Continue building a library of gene expression, DNA mutation and protein biomarkers that can be rapidly measured in mutiplex arrays to give enhanced precision and accuracy of radiation dose assessment. Incorporate the use of automated data analysis systems to more efficiently evaluate promising candidate molecular biomarkers.($ 0.539 million)

(U) Complete the assessment of prophylactic efficacy of the anthrax vaccine to provide protection from infection following a combined radiation/B.anthracis exposure. Continue studies with other vaccines (e.g. for VEE) to assess effectiveness in combined radiation/infectious agent exposures. Continue to quantify the biological interactions of radiation and non-lethal, incapacitating bacterial agents. Extend mortality studies of radiation/BW agent interactions with viral threats. Continue to collect and analyze animal model data to improve and expand the predictive value of casualty prediction models.($ 1.020 million)

(U) Complete assessment of treatment strategies for endemic shigellosis in irradiated animals. Initiate evaluation of therapeutic age nts for B. anthracis and other potential BW agents for combined radiation-infectious agent exposures.($ 0.596 million)

(U) Initiate rodent life-span study of cancer risk of embedded DU and tungsten alloys. Continue studies in cultured cells of cancer risk of heavy metal exposure. Initiate full study of effects of DU exposure on the immune system. Initiate studies of DU neurotoxicity. Initiate studies of female reproductive effects of DU. ($ 0.897 million)

(U) FY 2002 Plans:

(U) Incorporate newly developed gene response and microsatellite-based genetic assays into analytical strategies for assessing radioprotectant and therapeutic drug efficacies.
($ 2.178 million)

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(U) Initiate studies to determine the therapeutic benefit of combining selected pretreatments (androstenediol, vitamin E, amifostine) with post-exposure cytokine treatments (IL-11, G-CSF). Initiate studies using recombinant KGF to further characterize the efficacy of natural KGF as a pretreatment for gastrointestinal injury.($ 1.506 million)

(U) Complete sample preparation, imaging, data analysis, and operating dose range system improvements for the clinical cytogenetic-based (PCC) bioassay. Conduct tests to determine laboratory testbed performance specifications (sample throughput, accuracy, precision)($ 0.906 million)

(U) Continue to refine and optimize system characteristics and operating range performance for a molecular biomarker bioassay capable of field use. Continue to explore use of automated data analysis systems to efficiently evaluate candidate biomarkers.($ 0.757 million)

(U) Complete assessment of efficacy of VEE vaccines for combined radiation/BW agent exposures. Continue to assess efficacy of other vaccines for combined exposure. Continue to collect and analyze data to quantify biological interactions of combined exposures. Complete first phase of mortality studies with combined radiation/viral agent exposures. Continue to collect and analyze animal model data to improve and expand the predictive value of casualty prediction models.($ 1.406 million)

(U) Continue efficacy assessment of therapeutic drugs for combined radiation/infectious agent exposures. Initiate studies of combining treatments of immunomodulators with antimicrobials for combined exposures. Initiate studies to determine therapeutic effectiveness of isoflavones for combined injury. Initiate studies to determine effectiveness of vaccines to manage endemic disease of the gastrointestinal system after radiation exposure.($ 0.806 million)

(U) Continue use of molecular biomarker and other functional assays to assess host immune response to combined radiation/bacteria-virus exposures.($ 0.406 million)

(U) Complete studies of female reproductive effects of DU. Continue studies in cultured cells and rodents of cancer risk of DU and the long-term effects on the immune and nervous systems.($ 1.006 million)

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(U) B. Program Change Summary	**FY 2000**	**FY 2001**	**FY 2002**	**Total Cost**
Previous President's Budget Submit	8.875	8.680	8.921	Continuing
Appropriated Value				Continuing
Adjustments to Appropriated Value				
a. Congressionally Directed Undistributed Reduction	0.000	-0.080	0.000	
b. Rescission/Below-threshold Reprogramming, Inflation Adjustment	-0.046	0.000	0.050	
c. Other	0.000	0.000	0.000	
President's Budget Submission	8.829	8.600	8.971	Continuing

Change Summary Explanation

(U) Funding: FY 2000 funding changes are due to the result of a below threshold reprogrammings. FY 2001 reductions reflect Section 8086 adjustments.

(U) Schedule: N/A

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(U) **Technical**: N/A

(U) **C.** **Other Program Funding Summary Cost**: N/A

(U) **D.** **Acquisition Strategy**: N/A

(U) **E.** **Schedule Profile**: N/A