RDT&E BUDGET ITEM JUSTIFICATION SHEET (R-2 Exhibit)	DATE February 2002
APPROPRIATION/BUDGET ACTIVITY RDT&E, Defense Wide/BA 2	**R-1 ITEM NOMENCLATURE** Medical Technology **PE 0602787D8Z**

COST *(In Millions)*		FY 2001	FY 2002	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	Cost to Complete	Total Cost
Total Program Element (PE) Cost		8.600	8.971	0	0	0	0	0	Continuing	Continuing
Radiation Injury Assessment and Therapeutic Approach/P505		8.600	8.971	0	0	0	0	0	Continuing	Continuing

(U) A. Mission Description and Budget Item Justification

(U) BRIEF DESCRIPTION OF ELEMENT

(U) This program supports developmental 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. Program objectives focus on mitigating the health consequences from exposures to ionizing radiation that represent the highest probable threat to US forces under current tactical, humanitarian and counter terrorism mission environments. New protective and therapeutic strategies will broaden the operations for military operates in nuclear or radiological environments, while minimizing both short- and long-term risks of adverse health consequences. Advancements in field-based biological dose assessment systems to measure radiation exposures will enhance triage, treatment decisions and risk assessment. Accurate models to predict casualties will promote effective command decisions and force structure planning to ensure mission success. [NOTE: Funds for this program will transfer to NIH beginning in FY 03.]

(U) The program has three primary goals: (1) rational development of prophylactic and therapeutic strategies based on fundamental knowledge of radiation-induced pathophysiology and on leveraging advances in medicine and biotechnology from industry and academia; (2) development of novel biological markers and delivery platforms for rapid, field-based individual dose assessment; (3) understanding toxic consequences from chronic exposure to tissue-embedded depleted uranium (DU).

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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 2001 Accomplishments:

(U) In FY 2001, this program supported essential military missions through the following accomplishments: Determined that natural-killer (NK) lymphocytes are the principal immune cell type acted upon by the radioprotectant 5-androstenediol (5-AED). Demonstrated that 5-AED functions in part by activating the antimicrobial and anti-neoplastic activities of NK-cells. ($ 1.033 million)

(U) Characterized pharmacokinetic profiles of injected alpha tocopherol (vitamin E) in irradiated and non-irradiated animals. Identified an early-occurring, radiation-elicited depletion of circulating blood levels of alpha tocopherol. Characterized relationship between alpha tocopherol prophylaxis and reduced rates of programmed cell death (apotosis) within vital tissues of the body ($ 0.790 million)

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(U) Developed simplified drug delivery strategies for new radioprotective drugs and therapies. Completed initial design and testing phases of vehicles for oral and subcutaneous administration of synthetic chemical-, metabolite-, and nutritional-based radioprotectants (aminothiol, androstendiol, alpha tocopherol, and isoflavone radioprotectants). Completed initial efficacy testing of modified delivery regimens for therapeutic cytokines. ($ 1.549 million)

(U) Continued systematic survey of potential radioprotectant and therapeutic compounds under a drug screening protocol. Continued studies on the fundamental mechanisms of cellular and molecular injury, and the repair of blood-forming (hematopoietic) and gastointestinal systems to provide rational basis for improving preventive treatment strategies. ($ 1.315 million)

(U) Filed U.S. provisional patent application (60/271743) on novel cytogenetic bioassay system that does rapid analysis of radiation exposure across broad dose range. Improved sample preparation, incorporated differential chromosome staining technique, applied automated image analysis, and broadened operational dose range to enhance clinical cytogenetic bioassay system. ($ 0.845 million)

(U) Continued development of novel molecular biomarker systems that run on rugged, rapid field-based operating platforms. Continued establishing operational parameters of rapid polymerase chain reaction (PCR) technique for quantifying radiation-induced altered gene expression as dose dependent marker of exposure. Completed initial characterization of the gene expression response to neutron radiation. ($ 0.548 million)

(U) Completed assessment of anthrax vaccine in incases of combined radiation/*B.anthracis* exposure, showing that a sub-lethal dose of radiation causes 20% reduction in protective efficacy. Collected and analyzed animal model data to improve and expand the predictive value of casualty prediction models. ($ 1.019 million)

(U) Completed assessment of treatment strategies for endemic shigellosis in irradiated animals. Completed initial evaluation of therapeutic agents for combined exposure to radiation of *B. anthracis*. ($ 0.598 million)

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(U) Initiated rodent life-span study of cancer risk of embedded DU and tungsten alloys. Continued studies in cultured cells of cancer risk of heavy metal exposure. Initiated full study of effects of DU exposure on the immune system. Initiated studies of female reproductive effects of DU. ($ 0.903 million)

(U) FY 2002 Plans:

(U) In FY 2002, this program will continue to support essential military missions through the following activities: Develop and test surrogate indicators (cellular, sub-cellular, and molecular) of 5-AED drug prophylactic efficacy in preparation for IND application. Assess structural analogs of 5-AED radioprotectants for efficacy and toxicity. ($ 1.098 million)

(U) Assess, optimize, and simplify vehicles and routes of administration for candidate chemical- and nutritional-based radioprotectant drugs (amifostine, vitamin E and genistein). ($ 1.001 million)

(U) Initiate studies to determine therapeutic benefit of combining selected pretreatments (androstenediol, vitamin E, genistein, 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. ($ 0.388 million)

(U) Incorporate new gene response and microsatellite genetic assays into analytical strategy for assessing efficacy of radioprotectant and therapeutic compounds under development for late-arising radiation injuries. Assess efficacy of metabolite- and nutritional-based radioprotectants in blocking radiation-induced leukemogenesis in a small animal model. ($ 0.743 million)

(U) Develop PCR-based bioassay to quantify persistent DNA mutations for diagnostic biodosimetry application. Establish performance parameters of candidate gene expression and protein biomarkers for radiation exposure in an *in vitro* model system of human lymphocytes. Continue studies to characterize radiation quality and inter-individual variation effects on candidate molecular biomarkers. ($ 0.784 million)

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(U) Improve sample preparation for premature chromosome condensation assay to allow development of automated image analysis software. Continue optimizing and extending operating range of novel molecular biomarkers for incorporation into rapid field-deployable platform. Establish reagent sets needed to test and validate molecular biomarker system. Establish analytical system for assessment of antigen-based protein biomarker. ($ 0.920 million)

(U) Initiate and complete validation of a lethal-radiation rodent model involving pathogenic translocation of gut microflora, and ascertain the genus/species spectrum of microorganisms that establish systemic infections in the model. ($ 1.550 million)

(U) Initiate efficacy studies on combined immunomodulator and antimicrobial treatments for cases of exposure to sublethal doses of radiation complicated by endemic disease threats. Initiate studies to determine effectiveness of vaccines to manage endemic disease of the gastrointestinal system after radiation exposure. ($ 0.872 million)

(U) Complete studies of female reproductive effects of DU. Continue studies of carcinogenicity and immunotoxicity of DU and tungsten alloys in cultured cells and rodents. Initiate investigation to determine if males implanted with DU or tungsten alloys transmit genetic damage to offspring. ($ 1.615 million)

(U) FY 2003 Plans: Transferred to National Institutes of Health (NIH).

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(U) B. Program Change Summary	FY 2001	FY 2002	FY 2003	Total Cost
Previous President's Budget Submit	8.680	8.921	9.190	Continuing
Delta	-0.080	0.050	0.000	
FY 2002 Amended President's Budget Submission	8.600	8.971	9.190	Continuing
Appropriated Value	8.680	8.971	0.000	Continuing
Adjustments to Appropriated Value				
a. Congressionally Directed Undistributed Reduction	0.000	0.000	0.000	
b. Rescission/Below-threshold Reprogramming, Inflation Adjustment	-0.080	0.000	0.000	
c. Other	0.000	0.000	-9.190	
Current FY 2003 Budget Submission	8.600	8.971	0.000	Continuing

Change Summary Explanation:

(U) **Funding**: FY 2001 reductions reflect Section 8086 adjustments.

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

(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