RDT&E BUDGET ITEM JUSTIFICATION SHEET (R-2 Exhibit)	DATE February 2002
APPROPRIATION/BUDGET ACTIVITY RDT&E, Defense Wide/BA 3	**R-1 ITEM NOMENCLATURE** Medical Advanced Technology Program **PE 0603002D8Z**

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		2.025	2.066	0	0	0	0	0	Continuing	Continuing
Risk Assessment and Biamedical Applications/P506		2.025	2.066	0	0	0	0	0	Continuing	Continuing

(U) A. Mission Description and Budget Item Justification

(U) BRIEF DESCRIPTION OF ELEMENT

(U) This program supports applied research for advanced development of biomedical strategies to prevent, treat and assess health consequences from exposure to ionizing radiation. It capitalizes on findings under PE 0602787D, Medical Technology, and from industry and academia to advance novel medical countermeasures into and through pre-clinical studies toward newly licensed products. 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. Findings from basic and developmental research are integrated into highly focused advanced technology development studies to produce: (1) protective and therapeutic strategies; (2) novel biological markers and delivery platforms for rapid, field-based individual dose assessment; and (3) experimental data needed to build accurate models for predicting casualties from complex injuries involving radiation and other battlefield insults. The Armed Forces Radiobiology Research Institute (AFRRI), because of its multidisciplinary staff and exceptional laboratory and radiation facilities, is uniquely positioned to execute the program as prescribed by its mission. Because national laboratories operated by the Department of Energy no longer support advanced research relevant to military medical radiobiology, AFRRI is currently the only national resource carrying out this mission. [NOTE: Funds for this program will transfer to NIH beginning in FY 03.]

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(U) Project Number and Title: P506 Risk Assessment and Biomedical Applications

(U) PROGRAM ACCOMPLISHMENTS AND PLANS

(U) FY 2001 Accomplishments:

(U) In FY 2001, this program supported essential military missions through the following accomplishments: Demonstrated in a large animal (canine) model that the radioprotectant, 5-androstenediol, is well tolerated when administered subcutaneously in single injected doses at concentrations at or below 20 mg/kg of body weight. Completed preliminary pharmacokinetic and hematological profiles in canines that suggest a broad time window (~24 hrs) of radioprotection can be achieved by subcutaneous administration of 5-androstenediol. ($ 0.248 million)

(U) Completed study in a large animal (canine) model designed to reduce the toxicity (nausea) of aminothiol prophylaxis by supplemental anti-emetic treatment. ($ 0.080 million)

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(U) Completed pilot study in a large animal (canine) model demonstrating that enhanced production and mobilization of blood granulocytes and platelets following a combined treatment regimen with two recombinant growth factors, interleukin 11 (IL-11) and granulocyte colony stimulating factor (G-CSF), correlates with the synergistic survival response to lethal doses of radiation seen in earlier studies of combined cytokine therapy. ($ 0.401 million)

(U) Continued *in vivo* validation of the newly patented premature chromosome condensation assay in radiation therapy patients to quantify dose-dependent chromosome aberration responses in cases of partial body exposures. Added to validation database by participating in an international scientific collaboration to study patient samples from a serious Feb 2000 radiation accident in Thailand. ($ 0.288 million)

(U) Continued optimizating single analytical platform for a field-based biodosimetry system, including development of sample preparation protocols and protocols to allow measurement of multiple gene-expression biomarkers. Using an *in vivo* mouse model, began characterizing dose-dependent elevations of gene expression at the mRNA and protein levels that had earlier been demonstrated *in vitro*. ($ 0.058 million)

(U) Distributed pre-beta version of the Biodosimetry Assessment Tool (BAT) software program for radiation casualty management to selected laboratories and clinical centers for review and comment. Field-tested two small-footprint blood cell counters for use by deployed military laboratories to quantify radiation exposure based on measuring changing lymphocyte counts in serial blood samples. ($ 0.039 million)

(U) Completed assessment of aberrations in *B. anthracis* vaccine efficacy as a consequence of exposure to ionizing radiation. Initiated efforts to incorporate performance-degrading consequences from combined radiation/BW agent exposures into the CATS casualty prediction models. ($ 0.547 million) Initiated study to increase sensitivity of mass spectrometric detection of DU in biological samples.

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(U) Initiated *in vivo* cancer and immunotoxicity studies with embedded DU and tungsten alloys. Submitted patent for a rapid, simple DU fragment identification method and generated protocol for application centers to assess the analytical procedure as a potentially fieldable methodology. Initiated study to increase sensitivity of mass spectrometric detection of DU in biological samples. DU research results used to reassess exposure guidelines. ($ 0.364 million)

(U) FY 2002 Plans:

(U) In FY 2002, this program will continue to support essential military missions through the following activities: Complete pharmacokinetic, toxicity, and efficacy assessment of 5-androstenediol as an injectable radioprotectant using a canine animal model. ($ 0.323 million)

(U) Initiate toxicity and pharmacokinetic assessments of trans-oral-mucosal rout of delivery of 5-androstenediol in both small and large animal models. ($ 0.203 million)

(U) Initiate efficacy studies of the therapeutic cytokine combination, IL-11 plus G-CSF, in the canine animal model. ($ 0.225 million)

(U) Continue validation testing of the premature chromosome condensation assay using samples from radiotherapy patients, and initiate complementary study in a murine model to develop complete data set for whole-body and partial-body exposures to full spectrum of radiation qualities, doses and dose rates. Determine marker persistency for this assay relative to time post-irradiation. Determine specificity of candidate gene expression and protein biomarkers for radiation-induced alterations relative to other battlefield toxicants of military relevance known or expected to have genotoxic effects. Develop internal reference and external calibration standards for relative and absolute quantification of gene expression and protein biomarkers. Update BAT software application to include new data (onset of vomiting, lymphocyte depletion) based on criticality accidents and distribute beta test version of software to customers. ($ 0.220 million)

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(U) Continue validation of multi-biomarker field biodosimetry system for radiation dose assessment. Initiate murine studies to begin assessing *in vivo* performance of molecular biomarker sets satisfactory *in vitro* performance. ($ 0.052 million)

(U) Begin studies to automate sample processing and to enhance chromosome separation on metaphase spreads, in order to facilitate development of a fully automated lymphocyte metaphase dicentric assay system with high sample throughput capability for managing mass casualty situations through biological dose assessment of the radiation injured. Incorporate functional parameters into the assay system that will meet or exceed International Standards Organization (ISO) guidelines. ($0.125 million)

(U) Initiate study to develop new medical countermeasures against endogenous pathogens that lead to death by sepsis. Initiate studies to evaluate genistein as a biological response modifier to enhance recovery from infection following low-dose radiation. ($ 0.543 million)

(U) Continue *in vivo* cancer and immunotoxicity studies with embedded DU and tungsten alloys. Initiate investigation to determine if males implanted with DU or tungsten alloys transmit genetic damage to offspring. Initiate tests of new analytical separation techniques to improve sensitivity of methodologies for the rapid detection of DU in urine. Finalize protocols to increase sensitivity of mass spectrometric detection of DU in biological samples. Continue data input for reassessment of DU exposure guidelines. ($ 0.375 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	2.043	2.075	2.129	Continuing
Delta	-0.018	0.011	0.000	
FY 2002 Amended President's Budget Submission	2.025	2.086	2.129	Continuing
Appropriated Value	2.043	2.086	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	-0.018	0.000	0.000	
c. Other	0.000	0.000	-2.129	
Current FY 2003 Budget Submission	2.025	2.086	0.000	Continuing

Change Summary Explanation:

(U) **Funding**: FY 2001 reductions reflect Section 8086 adjustments. FY 2003 increases support the product transition and clinical trials that are required for eventual approval by the FDA.

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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