Exhibit R-2a, RDT&E Project Justification							Date: February 2003	
Appropriation/Budget Activity RDT&E, D BA 2			Project Name and Number Medical Technology, PE 0602787D8Z					
Cost ($ in millions)	2002	2003	2004	2005	2006	2007	2008	2009
Medical Technology/ P505	8.971	0.000	9.213	10.111	10.297	10.506	10.711	10.917

A. Mission Description and Budget Item Justification:

(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 military commander's options for operating within nuclear or radiological environments by 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.

(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).

B. Accomplishments/Planned Program

	2002	2003	2004	2005
Assessment of 5-AED	0.998	0	1.033	1.135

2002: Determined that the radioprotective agent, 5-androstenediol (5-AED), has a high therapeutic index (~400), evidenced by a high maximum tolerated dose of ~4000 mg/kg and a low-dose (~10 mg/kg) requirement to effect an optimum prophylactic response. Demonstrated that 5-AED prophylaxis enhances therapeutic action of recombinant blood cell growth factors (cytokines) delivered during the post-exposure period. Developed tests for and performed initial analyses on surrogate biological indicators of efficacy at the cellular, sub-cellular, and molecular levels for 5-AED prophylactic efficacy in preparation for IND application. Assessed structural analogs of 5-AED for efficacy and toxicity.
2003: Develop, analyze and evaluate appropriate surrogate indicators of 5-androstenediol drug radioprotective efficacy based on the drug's mode-of-action at the cellular and molecular level.
2004: Use surrogate indicators to evaluate 5-AED's radioprotective efficacy across preclinical test species.
2005: Exploit surrogate indicators for bridging studies essential for the demonstration of clinically relevant radioprotective drug action.

	2002	2003	2004	2005
Non-toxic Nutraceuticals	1.001	0	0	0

2002: Demonstrated significant radioprotective effects of two non-toxic nutraceuticals [alpha tocopherol (vitamin E) analog and the plant isoflavone genistein] delivered either by injection or by oral administration. Patent application was submitted and is pending for genistein as a radioprotective agent.

	2002	2003	2004	2005
Dual-action Drug Delivery Strategy	0.316	0	0	0

2002: Developed new, simplified, dual-action drug delivery strategy for radioprotective agents. Completed initial design, construction and efficacy testing of a sustained-release, lipid-encapsulated aminothiol-based radioprotectant that can potentially enhance efficacy and reduce toxicity.

	2002	2003	2004	2005
Combined Cytokine Therapy	0.200	0	0.368	0.404

2002: Completed pathological assessments of radiation-induced gastrointestinal injury and injury alleviation using recombinant growth factor/cytokine treatments (G-CSF, IL-11, G-CSF, and KGF).
2003: Initiate studies in small rodents on the therapeutic effect of combining the two hematopoietic growth factors, IL-11 and G-CSF, with a recombinant keratinocyte growth factor (KGF) for the treatment of acute, high-dose radiation injury.
2004: Confirm therapeutic advantage of administering combined cytokine treatments (IL-11, G-CSF, KGF), demonstrating enhanced repair of acute injury with hematopoietic and gastrointestinal tissues.
2005: Optimize treatment parameters (schedule, dose, and timing) for use of combined cytokine regimen.

	2002	2003	2004	2005
Radioprotectants/Therapeutics Survey	0.443	0	1.253	1.376

2002: 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 gastrointestinal systems to enhance the rational basis for developing more effective preventive and treatment strategies.
2003: Continue to identify promising new radioprotectants and therapeutics using newly established drug-screening assays. Continue to refine, test, and analyze preventive treatment strategies based on fundamental mechanisms of cellular and molecular injury and repair of blood-forming (hematopoietic) and gastointestinal organ systems.
2004: Develop and implement alternative, high throughput *in vitro* screening assays for the initial identification of potentially useful radioprotectants.
2005: Confirm and validate utility of *in vitro* screening to identify new safe and effective radioprotectants from extended family of candidate drugs.

	2002	2003	2004	2005
New Genetic Assays & Late Effects	0.272	0	0	0

2002: Extended 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. Assessed efficacy of non-toxic metabolite- and nutritional-based radioprotectants in blocking radiation-induced neoplastic transformation/carcinogenesis in cell culture and small animal models.

	2002	2003	2004	2005
PCC Cytogenetic Assay	0.566	0	0.396	0.435

2002: Completed studies needed to file international patent application (02/28/2002) associated with US provisional patent application (#60/271,743; 02/28/2001) for the novel premature chromosome condensation (PCC) assay that permits rapid analysis of radiation exposure across a broad dose range from interphase lymphocytes of peripheral blood.
2003: Continue studies to improve sample preparation, incorporate differential chromosome staining technique, and broaden operational dose range to enhance functional utility of clinical cytogenetic bioassay system.
2004: Characterize dose-effect relationship for different radiation types for PCC cytogenetic assay.
2005: Demonstrate applicability of the assay for equivalent whole- and partial-body dose assessments.

	2002	2003	2004	2005
Early-Response Gene Expression Markers	0.683	0	0.746	0.819

2002: Continued to identify gene expression alterations as potential biomarkers of radiation exposure that can be measured quickly and with high precision using PCR-based analytical platforms that are rugged and field-deployable. Completed initial studies to define inter-individual variations in radiation-induced altered gene expression. Established a reagent set and reaction conditions to test a PCR-based single-tube assay strategy for measuring multiple genetic markers of radiation exposure.
2003: Demonstrate 24-hr and 48-hr dose response profiles of altered expression for several genes that are predictive of radiation dose. Establish reagent set and reaction conditions to test PCR-based single-tube strategy for measuring multiple genetic markers of radiation exposure.
2004: Continue gene expression studies using multiple radiation responsive biomarkers (GADD45, DDB2, and WAF-1). Complete evaluation of inter-individual effects using cohort studies following exposure to acute photon radiation.
2005: Initiate *in vitro* studies to investigate the effects of exposure to different radiation quality, dose rates, and partial-body exposure on gene expression changes.

	2002	2003	2004	2005
Blood-Based Cell and Protein Markers	0.455	0	0.608	0.667
2002: Initiated studies to develop assay procedures for blood-based protein markers of radiation exposure using a novel microsphere flow cytometry system designed to measure up to 100 analytes in a single sample by differential fluorescence spectroscopy. Continued hematological studies to develop radiation biodosimetry applications for a portable blood cell counter that employs a highly stable dry reagent system to facilitate field use. **2003:** Continue studies to develop microsphere flow cytometry system for measurement of multiple radiation responsive protein biomarkers. Complete evaluation of monocyte depletion protocol to enable utility of portable centrifuge-based blood cell counter. Establish reagent and equipment set for manual blood cell counting system to support field-based deployable hematology capability. **2004:** Complete initial phase *in vitro* studies evaluating radiation responsive protein biomarkers measured by microsphere flow cytometry system. Initiate protein biomarker studies to evaluate inter-individuals effects. Further evaluate the utility of portable centrifuge-based blood cell counter in field exercises with magnet bead depletion of monocytes. Determine blood-counter lymphocyte-count dynamic range after monocyte depletion using magnetic beads. **2005:** Complete protein biomarker interindividual variation study. Initiate *in vivo* validation of centrifuge-based blood cell counter with ex vivo irradiated blood samples using magnetic bead monocyte depletion and human blood samples from radiation therapy patients.				
	2002	2003	2004	2005
Gut-translocating Microorganisms	1.412	0	0	0
2002: Assessed the microbiology of gut-translocating microorganisms that cause polymicrobial sepsis following irradiation in a rodent model. Characterized intestinal microflora found in heart-blood following lethal doses of radiation in a rodent model.				
	2002	2003	2004	2005
Novel Antimicrobial Therapies	0.565	0	0	0
2002: Initiated new studies in a rodent model to develop novel antimicrobial therapies for radiation-induced microbial sepsis.				
	2002	2003	2004	2005
Efficacy of Ciprofloxacin	0.445	0	0	0
2002: Determined that ciprofloxacin provides significant efficacy against gastrointestinal infection by *Shigella sonnei* in a sublethally irradiated rodent model.				
	2002	2003	2004	2005
Embedded DU and Tungsten	1.615	0	1.658	1.820
2002: Completed studies of female reproductive effects of embedded DU. Continued studies of carcinogenicity and immunotoxicity of DU and tungsten alloys in cultured cells and rodents. Determined from a pilot study that male mice implanted with DU or tungsten alloys can transmit genetic damage to offspring. **2003:** Continue basic *in vitro* and *in vivo* studies of carcinogenicity and immunotoxicity of DU and tungsten alloys. Initiate investigation of whether paternally embedded DU or tungsten alloy in results in transmission of genetic damage to offspring in rodents. **2004:** Expand *in vitro* studies to understand mechanisms of DU and tungsten alloy carcinogenicity. Establish *in vitro* inhalation model for DU and tungsten toxicity. Improve sensitivity of colorimetric test for uranium in biological fluids and environmental samples. Continue basic studies of carcinogenicity and immunotoxicity of DU and tungsten alloys in rodents. **2005:** Complete basic rodent studies assessing carcinogenicity and immunotoxicity of embedded DU and tungsten alloys. Continue *in vitro* studies.				
	2002	2003	2004	2005
Late-Arising Radiation Injuries	0	0	0.663	0.728
2003: Survey select pharmacologics/therapeutics with defined normal tissue protective effects against late-arising radiation injuries using newly developed "critical target" cellular assays. **2004:** Assay efficacious pharmacologics/therapeutics that specifically block and/or limit expression of key cellular indicators of late-arising radiation-induced pathologies using newly developed gene response and genetic assays. **2005:** Confirm and validate cellular and molecular markers of late-arising radiation injury and protective action of the selected pharmacologic(s) by direct correlations with both temporal and frequency patterns of expressed late-effects in irradiated animals.				

	2002	2003	2004	2005
Endogenous Bacterial Sepsis Therapies	0	0	1.290	1.416
2003: Complete studies to identify most efficacious antimicrobial strategies for treating radiation-induced sepsis from endogenous pathogens following high dose whole-body gamma irradiation in a rodent model. Initiate studies to determine benefit of probiotic bacteria and biological response modifiers in preventing or alleviating radiation-induced translocation of normal enteric bacteria in a rodent model following high doses of radiation. **2004:** Determine benefit of probiotics and BRMs in preventing and alleviating radiation-induced enteric infections in a rodent model. Demonstrate efficacy of the probiotic *Lactobacillus reuteri* and the BRM beta-1,3-glucan. The objective is to achieve 50% survival following a low-end lethal radiation dose combined with a lethal bacterial challenge. **2005:** Demonstrate efficacy of the BRMs genistein and 5-androstenediol in preventing and alleviating radiation-induced enteric infections in a rodent model. The objective is to achieve 50% survival following a low-end lethal radiation dose combined with a lethal bacterial challenge. Complete studies in rodent model to identify the best combination treatment strategy for radiation-induced infections. The objective is to achieve 95% survival using a combined BRM/antibiotic treatment strategy following low-end lethal irradiation.				
	2002	2003	2004	2005
Exogenous Microbial Infection Therapies	0	0	0.774	0.849
2003: Initiate studies to assess the effectiveness of probiotic bacteria in the prevention of infections from exogenous (endemic) pathogens following sublethal irradiation. Assess the therapeutic effectiveness of the soy isoflavon, genistein, delivered orally for the management of exogenous pathogens following whole-body exposure to sublethal radiation. **2004:** Continue studies to assess the efficacy of antimicrobial agents in preventing death or incapacitation from endemic pathogens in the irradiated host. **2005:** Evaluate potential combination of most efficacious antimicrobial agent and BRM, which provides 95% survival following a sub-lethal radiation dose for management of an exogenous pathogen.				
	2002	2003	2004	2005
Host-Defense Mechanisms	0	0	0.424	0.465
2003: Using the macrophage-influenza virus A experimental model, identify and characterize patterns of host-defense modulation at the molecular level following sublethal irradiation and infection. **2004:** Evaluate RNA array based methods for characterizing host-defense response at the molecular level following sublethal irradiation and infection **2005:** Initiate animal model study to assess molecular markers of sublethal irradiation and infection. Initiate non-invasive optical diagnostic methods for mapping the pattern of partial body radiation exposures using changes in dermal and sub-dermal morphological markers.				
C. Other Program Funding Summary: N/A. **D. Acquisition Strategy. N/A.** **E. Major Performers: Armed Forces Radiobiology Research Institute, Bethesda, MD.**				