Exhibit R-2a, RDT&E Project Justification							Date: February 2003	
Appropriation/Budget Activity RDT&E, D BA 3				Project Name and Number Medical Advanced Technology, PE 0603002D8Z				
Cost ($ in millions)	2002	2003	2004	2005	2006	2007	2008	2009
Medical Advanced Technology/ P506	2.066	0.000	5.028	2.065	2.542	2.594	2.645	2.697

A. Mission Description and Budget Item Justification:

(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 opportunistic infections. 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.

B. Accomplishments/Planned Program

	2002	2003	2004	2005
5-AED Preclinical Studies	0.323	0	1.830	0.752

2002: Extended pharmacokinetic, toxicologic, and pathologic assessments of 5-androstenediol as an injectable radioprotectant using a canine animal model. Early results substantiate findings of the pilot study showing that 5-AED is well tolerated at doses of 20 mg/kg or below; effectively enhances myelopoiesis, mobilizes and elevates circulating levels of vital blood cells (neutrophils, granulocytes and platelets), and yields pharmacokinetic and hematological profiles suggestive of a broad radioprotective time window.
2003: Establish product development office, quality assurance oversight function and contract consultation to support FDA regulatory compliance for drug transition. Initiate preclinical safety and toxicity assessments (GLP-based toxicity studies) of 5-androstenediol using both small (rodents) and large animal (canine) models in preparation for investigational new drug (IND) application to the FDA.
2004: Plan and execute radioprotective drug (5-AED) efficacy studies in a second large model (nonhuman primates); prepare and submit IND application to FDA/CDER.
2005: Plan and execute clinical phase 1 trial with radioprotective drug, 5-AED.

	2002	2003	2004	2005
Trans-oral-mucosal 5-AED	0.153	0	0.508	0.209

2002: Initiated toxicity and pharmacokinetic assessments of trans-oral-mucosal delivery of 5-androstenediol in a small animal model. Developed experimental plans and procedures for comparable work in a large canine model.
2003: Initiate efficacy and safety testing of 5-androstenediol radioprotectant using a second, trans-oral mucosal route of drug administration in small rodents (mice).
2004: Initiate efficacy and safety testing of 5-androstenediol radioprotectant using a second, trans-oral mucosal route of drug administration in large animals (canines and/or primates).
2005: Initiate GLP-based safety and toxicity assessments of 5-androstenediol radioprotectant using a second, trans-oral mucosal route of drug administration in large animals (canines and/or primates).

	2002	2003	2004	2005
Therapeutic Cytokine Combination	0.200	0	0.372	0.153

2002: Completed a pilot efficacy study of the therapeutic cytokine combination, IL-11 plus G-CSF, in the canine animal model. Planned extended study, and developed and tested critical testing procedures for key hematopoietic endpoints in support of the extended study.
2003: Initiate efficacy experiments in a large animal model (canines) of a combined cytokine (IL-11, plus G-CSF) treatment protocol.
2004: Initiate efficacy experiments in a second large animal model (nonhuman primates) of combined cytokine (IL-11, plus G-CSF) treatment protocol.
2005: Initiate GLP-based safety and toxicity assessments of combined treatment protocol in small and large animal models; Develop and submit IND application to FDA/CDER.

	2002	2003	2004	2005
Antiemetic Treatment	0.075	0	0	0

2002: Completed a large animal (canine) study designed to reduce the toxicity (nausea) of aminothiol prophylaxis by supplemental anti-emetic treatment.

	2002	2003	2004	2005
Automated Cytogenetic Biodosimetry	0.112	0	0.513	0.211

2002: Upgraded bright-field and fluorescent-based microscopy systems supporting cytogenetic biodosimetry studies. Improved image resolution some 16-fold using a high resolution color camera in bright field satellite scoring station with software compatible with Windows 2000 OS. Initiated studies to automate sample processing and to enhance chromosome separation on metaphase spreads to facilitate development of a fully automated lymphocyte metaphase dicentric assay with high-sample throughput capability suitable for radiation dose assessments in mass casualty situations. Employed updated versions of the dicentric assay in several real-world radiation accident cases to validate improvements, and initiated actions to transition the update assay.
2003: Continue use of cytogenetic-based biodosimetry system to expand radiation calibration curves (i.e. low-dose rate gamma and fission neutron radiation) and support development efforts to automate analysis of PCC for Advanced Technology Demonstration.
2004: Continue studies to expand radiation calibration curves and dose rate effects.
2005: Employ system to assess radiation doses in accident victims and complete Advanced Technology Demonstration.

	2002	2003	2004	2005
Biodosimetry Assay Validation	0.195	0	0.106	0.043

2002: Continued *in vivo* validation of the newly patented premature chromosome condensation (PCC) assay using samples from radiation accidents, radiation therapy patients and animal studies. Participated in international scientific collaboration comparing utility of novel cytological bioassay with conventional chromosome aberration bioassay involving samples from patients exposed in the Feb 2000 radiation accident in Thailand. Initiated studies in an animal model to determine persistency of the biomarker relative to time post-irradiation.
2003: Continue *in vivo* validation of the newly patented premature chromosome condensation (PCC) assay using samples from radiation accidents and radiation therapy patients and from animal studies. Continue collaborative and in-house *in vivo* murine studies to validate most promising molecular biomarkers.
2004: Complete analysis of samples from more than 10 radiotherapy patients, publish/present data from radiation accident cohort study and evaluate suitability of color pigment technique for automation. Continue *in vivo* validation of RT-PCR assay for gene expression biomarkers using samples from radiation accidents and radiation therapy patients and from animal studies relative to other battlefield toxicants of military relevance known or expected to have genotoxic effects.
2005: Complete analysis of samples from more than 20 radiotherapy patients, provide comparative data for PCC and dicentric assays, complete time-course studies to determine persistency of damage in the PCC assay.

	2002	2003	2004	2005
Molecular Biomarkers	0.045	0	0.271	0.111

2002: Continued studies to optimize and validate multiple molecular biomarker strategy using analytical platforms suitable for field-based biodosimetry systems. Developed internal reference and external calibration standards for relative and absolute quantification of gene expression and protein biomarkers.
2003: Initiated collaborative studies to 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. Continue studies to optimize sample processing of molecular biomarkers for field-based analysis.
2004: Continue key studies to define reagents to stabilize molecular biomarkers after blood draw for field- and clinical-based analysis. Complete initial phase studies evaluating the specificity of proposed radiation responsive molecular biomarkers.
2005: Initiate field testing of radiation responsive molecular biomarkers.

	2002	2003	2004	2005
Biodosimetry Assessment Tool	0.045	0	0.095	0.039
2002: Updated the Biodosimetry Assessment Tool (BAT) software application to include new data (onset of vomiting) based on historical data from criticality accidents. Distributed web-based beta version of the BAT software program for radiation casualty management. Extracted data from the human radiation accident registry, in collaboration with Radiation Emergency Assistance Center /Training Site (Oak Ridge, TN) scientists, to build a radiation calibration curve for combined depletion kinetics of both lymphocytes and monocytes in peripheral blood to support fielding of a small-footprint blood cell counter in deployed military laboratories. **2003:** Complete minor BAT software application upgrades to complete version # 1 release. Develop beta version of 1st responder radiological assessment triage (FRAT) software application based on the Palm OS. Continue studies to update lymphocyte depletion kinetics utility for dose predictions based on neutron criticality accidents. **2004:** Maintain Windows-based OS BAT software application. Incorporate plan upgrades to body-map and report function to include graphical display of time course bioassay data. Release version 1.0 of FRAT software application. **2005:** Maintain Windows OS BAT and Palm OS FRAT software application.				
	2002	2003	2004	2005
Antimicrobial Efficacy	0.020	0	0	0
2002: Completed background investigations and developed research and animal use protocols to initiate new studies to assess the efficacy of six specific antimicrobial agents – quinolones (gatifloxacin, ciprofloxacin), macrolides (clarithromycin), doxycycline, penicillin, and clindamycin – in treating combined exposures to sublethal gamma radiation and infectious microbes.				
	2002	2003	2004	2005
Pneumonia and Sepsis	0.220	0	0	0
2002: Established rodent model to demonstrate increased susceptibility to pneumonia and progression to Gram-negative sepsis after sublethal doses of gamma-photon radiation.				
	2002	2003	2004	2005
Genistein Evaluation	0.303	0	0	0
2002: Completed animal studies showing that genistein is a weak biological response modifier against sepsis caused by an endemic pathogenic intestinal infection after low doses of gamma-photon radiation.				
	2002	2003	2004	2005
Embedded DU and Tungsten	0.375	0	0.473	0.194
2002: Continued *in vivo* carcinogenicity and immunotoxicity studies with embedded DU and tungsten alloys. Determined from a pilot study that male mice implanted with DU or tungsten alloys can transmit genetic damage to offspring. Identified several new analytical techniques designed to improve sensitivity of methodology for the rapid detection of DU in urine. Completed protocol development to increase sensitivity of mass spectrometric detection of DU in biological samples. **2003:** Continue basic cancer and immunotoxicity studies with embedded DU and tungsten alloys. Produce research results to update surgical treatment protocols for DU shrapnel and other DU exposure guidelines. **2004:** Begin development of *in vitro* inhalation model for DU and tungsten toxicity as a possible substitute for animal studies. Improve sensitivity of colorimetric test for uranium in biological fluids and environmental samples in order to advance possible kit technology. Continue basic cancer and immunotoxicity studies with embedded DU and tungsten alloys. Produce research results to update surgical treatment protocols for DU shrapnel and DU exposure guidelines. **2005:** Complete basic rodent studies assessing carcinogenicity and immunotoxicity of embedded DU and tungsten alloys. Produce research results to update surgical treatment protocols for DU shrapnel and DU exposure guidelines.				
	2002	2003	2004	2005
Infection Therapies	0	0	0.860	0.353

2003: Identify from several newly FDA approved antimicrobiol agents those showing the greatest efficacy for treating radiation-induced infections in a whole-body gamma irradiated rodent model, and begin assembling data sets to support FDA approval of these drugs for a new indication. Assess the effectiveness of the phytoestrogen genistein for managing infections from exogenous pathogens following sublethal irradiation in a mouse model, and begin assembling data sets to support FDA approval for use as a food supplement.
2004: Identify potential BRM, which provides 50% survival following a low-end lethal radiation dose.
2005: Identify potential combination of most efficacious antimicrobial agent and BRM, which provides 95% survival following a low-end lethal radiation dose.

C. Other Program Funding Summary: N/A.
D. Acquisition Strategy. N/A.
E. Major Performers: Armed Forces Radiobiology Research Institute, Bethesda, MD.