

**Defense Health Program
Fiscal Year 2006/FY 2007 Budget Estimates
Exhibit R-2, DHP Budget Item Justification**

Date: January 2005
R-1 Item Nomenclature: 2
Medical Technology (AFRRI) - 0602787HP

Appropriation/Budget Activity
Defense Health Program/BA-2

COST (\$ in Millions)	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008	FY 2009	FY 2010	FY 2011
	<u>Actual</u>	<u>Estimate</u>						
Total PE 0602787HP Cost	0.000	0.000	3.166	3.236	3.306	3.381	3.417	3.553
Medical Technology/P505 Subtotal Cost	0.000	0.000	3.166	3.236	3.306	3.381	3.417	3.553

A. Mission Description and Budget Item Justification:

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 human exposure to ionizing radiation. Program objectives focus on mitigating the health consequences from exposures to ionizing radiation that represent the highest probable threat to U.S. 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.

The program has three primary goals: (1) rational development of prophylactic and therapeutic strategies based on fundamental knowledge of radiation-induced path physiology and on leveraging advances in medicine and biotechnology from industry and academia; (2) development of novel biological markers and delivery for rapid, field-based individual dose assessment; and (3) understanding toxic consequences from exposure to internal contamination from isotopes such as uranium.

B. Program Change Summary:

COST (\$ in Millions)	FY 2004	FY 2005	FY 2006	FY 2007
	<u>Actual</u>	<u>Estimate</u>	<u>Estimate</u>	<u>Estimate</u>
FY06 Budget Estimate Submission RDT&E	0.000	0.000	0.000	0.000
FY06 Budget Estimates RDT&E	0.000	0.000	3.166	3.236
Total Adjustments	0.000	0.000	3.166	3.236
Congressional Program actions				
Congressional rescissions				
Congressional increases				
Reprogramming	0.000	0.000	3.166	3.236
SBIR/STTR Transfer				
Internal Transfer				

NOTE: Program transfers effective FY 2006 from RDT&E Defense Agencies, Budget Activity 3, Program Element 0602787D8Z to RDT&E Defense Health Program, Budget Activity 2, Program Element 0602787HP.

C. Other Program Funding Summary: Not applicable.

D. Acquisition Strategy: Not applicable.

E. Performance Metrics:

By FY 2006 identify at least 6 drugs or therapeutic approaches that are promising for treatment of radiation injury.
By FY 2008 identify at least 2 new biodosimetric approaches to determine individual radiation exposure.
By FY 2010 develop decision criteria for antibiotic use after radiation injury.

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Exhibit R-2a, DHP Project Justification**

Date: January 2005
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Medical Technology (AFRRI) - 0602787HP
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Appropriation/Budget Activity
Defense Health Program/BA-2

Project Number and Title: Medical Techonology/P505

A. Mission Description and Budget Item Justification:

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.

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).

NOTE: Program transfers effective FY 2006 from RDT&E Defense Agencies, Budget Activity 3, Program Element 0602787D8Z to RDT&E Defense Health Program, Budget Activity 2, Program Element 0602787HP.

B. Accomplishments/Planned Program:

Cost (in \$ Millions)	FY 2004	0.326	FY 2006	FY 2007
Mechanisms of 5-AED Radioprotection	0	0	0.154	0.004

FY 2004 Accomplishments: To address the FDA requirement for an understanding of the mechanisms responsible for 5-AED's radio protective actions, demonstrated that 5-AED modulates the spleen levels of several cytokines, which mediate signals of the immune system.
FY 2005 Plans: Initiate experiments on effects of 5-AED on the function of peritoneal macrophages, a critical, non-circulating component of the immune system. Continue to assess changes in cytokines in the spleen.
FY 2006 Plans: Complete assays on actions of 5-AED in irradiated and non-irradiated rodents on oxidative burst and phagocytosis of peritoneal macrophages. Provide initial assessment of relationship between changes in cytokines and functional mechanisms of 5-AED.
FY 2007 Plans: Complete assessment of relationship between changes in cytokines and functional mechanisms of 5-AED.

Cost (in \$ Millions)	FY 2004	FY 2005	FY 2006	FY 2007
Radioprotective effects of isoflavones and vitamin derivatives	0	0	0.326	0.317

FY 2004 Accomplishments: Previously, demonstrated that the soybean derived isoflavone genistein has radio protective effects. Improved the vehicle for administration of the isoflavones and determined the dose response curve for radioprotection by genistein in rodents. Determined the optimal time for administration of genistein for radioprotection. Completed the screening of tocopherol isomers - alpha, gamma, and delta-tocopherol for radioprotection; alpha and delta-tocopherols were found to be equally effective while gamma-tocopherol was less effective. Assessed the effects of alpha-tocopherol on radiation-induced thrombocytopenia (reduced the duration) and neutropenia (marginal improvement in recovery).
FY 2005 Plans: Establish the dose-response relationship for a second soy isoflavone, daidzein, for radiation protection and determine the optimal time for administration. Evaluate the hematological effects of genistein with radiation exposure. Assess antimicrobial properties of genistein. Determine the dose-reduction factor of the most effective isomer of tocopherol. Compare pharmacokinetics of this isomer given subcutaneously in irradiated and non-irradiated mice.
FY 2006 Plans: Evaluate combinations of genistein and daidzein to determine the optimal ratio. Using this optimal ratio determine the best time course for administration. Determine the effect of the most efficacious isomer of tocopherol on neutropenia and thrombocytopenia and assess the cytokine messengers after radiation and tocopherol treatment.
FY 2007 Plans: Assess behavioral toxicity of the optimal isoflavone formulation and begin cytological toxicity testing. Determine pharmacokinetics of the isoflavones. Initiate GLP toxicity testing of the most effective isomer of tocopherol.

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**Appropriation/Budget Activity
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Cost (in \$ Millions)	FY 2004	FY 2005	FY 2006	FY 2007
Radioprotectants/Therapeutics Screening	0	0	0.872	0.975

FY 2004 Accomplishments: Continued systematic screening of potential radioprotectant and therapeutic compounds under a drug screen protocol. Among the drugs tested in FY2004 was a promising DHEA derivative that is effective in an oral preparation. Drugs that show potential will be targeted for further development. Evaluated drug release from liposomes using in vitro and in vivo (pharmacokinetic) assays.

FY 2005 Plans: Continued systematic survey of potential radioprotectant and therapeutic compounds under a drug screen protocol. There are currently about 20 drugs in the queue for analysis. Among those with the highest priority are CpG oligonucleotides, statins, SOD mimics, dipeptidyl peptidase inhibitors, and truncated flagellin.

FY 2006 Plans: New drugs continue to come to the attention of the Institute for assessment. These agents will be evaluated for their ability to prevent and/or treat radiation injury. Approaches to screening new agents will be improved.

FY 2007 Plans: Continue to assess the new pharmaceutical agents that come to the attention of the Institute. These agents will be evaluated for their ability to prevent and/or treat radiation injury. Continue to refine approaches to screening new agents.

Cost (in \$ Millions)	FY 2004	FY 2005	FY 2006	FY 2007
PCC Cytogenetic Assay	0	0	0.174	0.223

FY 2004 Accomplishments: Optimized the temperature and humidity conditions for the premature chromosome condensation (PCC) aberration assay that permits rapid analysis of radiation exposure across a broad dose range from interphase lymphocytes of peripheral blood. Optimized the PCC induction protocol for small blood volumes.

FY 2005 Plans: Continue to improve sample preparation by promoting signal transduction mechanisms for inducing PCC in peripheral blood lymphocytes. These efforts will improve the efficiency of the assay.

FY 2006 Plans: Optimize the color pigment technique that will be used for fluorescent in situ hybridization (FISH) method for detecting chromosome aberrations in multiple chromosomes. Optimize the multicolor FISH protocol that will allow detection and quantification of radiation-induced chromosome aberrations in multiple chromosomes. This approach will increase the sensitivity of the assay.

FY 2007 Plans: With the optimized process evaluate capability to detection and quantification of partial-body exposures.

Cost (in \$ Millions)	FY 2004	FY 2005	FY 2006	FY 2007
Molecular Biomarkers- DNA mutations	0	0	0.187	0.224

FY 2004 Accomplishments: Developed real-time PCR for detection of DNA mutations (common mitochondria DNA deletion) in genomic DNA samples providing a significant advance in quantitative assessment of target sequences. Initiated studies to optimize the real-time and cytological DNA mutation bioassay to detect low-frequency DNA mutations.

FY 2005 Plans: Develop and evaluate modified deletion primers for quantitative fluid phase PCR bioassay in Human Peripheral Blood Lymphocytes (HPBL). Begin evaluation of low level multiplex detection.

FY 2006 Plans: Develop cytological assay using PCR to measure mtDNA deletions in HPBL. Perform in vitro dose-response studies for fluid-phase PCR assay in HPBL.

FY 2007 Plans: Evaluate in vitro inter-individual variation for both cytological and PCR DNA mutation bioassays.

Cost (in \$ Millions)	FY 2004	FY 2005	FY 2006	FY 2007
Blood-Based Cell and Protein Markers	0	0	0.285	0.285

FY 2004 Accomplishments: Optimized the micro assay to measure concentration of a specific marker protein (GADD45) in human blood samples. Characterized the relationship for GADD45 levels with radiation dose and post-exposure time, demonstrating feasibility of approach.

FY 2005 Plans: Initiate in vitro studies evaluating radiation-responsive blood protein biomarkers involving other protein targets. Initiate protein biomarker studies to evaluate inter-individual, partial body, and combined agent effects.

FY 2006 Plans: Define effects of inter-individual variation. Improve assay through stabilization of protein biomarkers after blood draw.

FY 2007 Plans: Define effects of the confounders such as partial body exposures, and combined agent effects.

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Cost (in \$ Millions)	FY 2004	FY 2005	FY 2006	FY 2007
Late-Arising Radiation Injuries	0	0	0.142	0.159

FY 2004 Accomplishments: Determined that phenylacetate and epigallocatechin (EGCG) can effectively suppress radiation-induced human cell transformation in vitro (i.e., block development of pre-cancerous cells).

FY 2005 Plans: Initiate radiation leukemogenesis studies with phenylacetate and EGCG.

FY 2006 Plans: Complete radiation leukemogenesis with EGCG. Evaluate potential of new compounds to counter late radiation injury.

FY 2007 Plans: Complete radiation leukemogenesis with phenylacetate. Initiate assessment of new compounds on human cell transformation.

Cost (in \$ Millions)	FY 2004	FY 2005	FY 2006	FY 2007
New Approaches to Treatment of Post Radiation Infection	0	0	0.529	0.509

FY 2004 Accomplishments: Identified the bacterial species that cause sepsis in lethally irradiated animal. Initiated in vitro studies on properties of probiotics (microbes that can be ingested to combat pathogenic bacteria of the gut). Determined that *Lactobacillus reuteri* is not susceptible to ciprofloxacin.

FY 2005 Plans: Determine the effects of the quinolones against a polymicrobial infection from endogenous pathogens with lethal doses of radiation. Evaluate the effectiveness of *L. reuteri* as a probiotic protective agent when mice are challenged with *S. sonnei* and sub-lethal radiation exposure.

FY 2006 Plans: Evaluate the effectiveness of *L. reuteri* as a probiotic protective agent when mice are challenged with *S. sonnei* and lethal radiation exposure. Assess effect of probiotic on hematological parameters associated with the radiation injury.

FY 2007 Plans: Evaluate any new antibiotics on post-radiation infection. Assess effects of probiotic treatment on immune system function. Initiate assessment of the capability of inactivated *L. reuteri* to promote survival after radiation injury.

Cost (in \$ Millions)	FY 2004	FY 2005	FY 2006	FY 2007
Host-Defense Mechanisms	0	0	0.304	0.317

FY 2004 Accomplishments: Differentiated at least two mechanisms by which certain prospective radioprotectants protect mammalian cells from virally-induced cell death.

FY 2005 Plans: Evaluate the effect of antioxidants and radioprotectants including genistein on changes induced by virus infection and radiation exposure using cell survival, apoptotic markers, and cytokine production as endpoints. Assess a variety of pathways that can result in cell death with and without viral infection in an effort to uncover cellular processes targeted by therapeutic drugs.

FY 2006 Plans: Continue analysis of pathways and mechanisms. Assess effects of radiation therapeutic agents on these pathways.

FY 2007 Plans: As basic understanding of radiation injury expands and knowledge regarding mechanisms of cell damage and death grow, develop appropriate assays to assess the mechanisms of action of radioprotectant and therapeutic agents.

Cost (in \$ Millions)	FY 2004	FY 2005	FY 2006	FY 2007
Internal contamination - Health Effects and countermeasures	0	0	0.193	0.223

FY 2004 Accomplishments: Ingestion, inhalation, and wounds are routes of internal contamination with radioisotopes following use of a radiological weapon. In FY2005 a project will be initiated to examine the health consequences of this kind of exposure with the intent of developing new therapeutic agents.

FY 2005 Plans: Initiate studies to evaluate the effects of radioisotopes on a macrophage cell line in vitro to model the response of the lung macrophages to inhaled contaminants. To understand how late carcinogenic consequences develop after internal contamination and to develop effective countermeasures, studies will be initiated to evaluate the contribution of radiation (v. the chemical nature of the contaminant) to genomic instability and transformation.

FY 2006 Plans: Assess the effects of internal contaminants on macrophage function (oxidative burst and phagocytosis). Complete the analysis of genomic instability and transformation and begin to assess countermeasures.

FY 2007 Plans: Continue assessment of countermeasures.

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C. Other Program Funding Summary: Not applicable.

D. Acquisition Strategy: Not applicable.

E. Major Performers: Armed Forces Radiobiology Research Institute, Bethesda, MD.