Exhibit R-2, RDT&E Budget Item Justification: PB 2014 Defense Health Program	DATE: March 2013
APPROPRIATION/BUDGET ACTIVITY 0130: *Defense Health Program* BA 2: *RDT&E*	R-1 ITEM NOMENCLATURE PE 0602787HP: *Medical Technology (AFRRI)*

COST ($ in Millions)	All Prior Years	FY 2012	FY 2013#	FY 2014 Base	FY 2014 OCO ##	FY 2014 Total	FY 2015	FY 2016	FY 2017	FY 2018	Cost To Complete	Total Cost
Total Program Element	-	3.558	1.193	1.216	-	1.216	1.241	1.286	1.307	1.331	Continuing	Continuing
241A: *Biodosimetry (USUHS)*	-	0.726	0.244	0.248	-	0.248	0.253	0.262	0.267	0.272	Continuing	Continuing
241B: *Internal Contamination (USUHS)*	-	0.376	0.127	0.129	-	0.129	0.132	0.138	0.140	0.143	Continuing	Continuing
241C: *Radiation Countermeasures (USUHS)*	-	2.456	0.822	0.839	-	0.839	0.856	0.886	0.900	0.916	Continuing	Continuing

FY 2013 Program is from the FY 2013 President's Budget, submitted February 2012

The FY 2014 OCO Request will be submitted at a later date

A. Mission Description and Budget Item Justification

For the Uniformed Services University of the Health Sciences (USUHS), Armed Forces Radiobiology Research Institute (AFRRI), 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 in current tactical, humanitarian and counterterrorism 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. Advances in assessment, prognostication, and therapy in case of actual or suspected radiation exposures will enhance triage, treatment decisions and risk assessment in operational settings.

B. Program Change Summary ($ in Millions)	FY 2012	FY 2013	FY 2014 Base	FY 2014 OCO	FY 2014 Total
Previous President's Budget	3.602	1.193	1.216	-	1.216
Current President's Budget	3.558	1.193	1.216	-	1.216
Total Adjustments	-0.044	0.000	0.000	-	0.000
• Congressional General Reductions	-	-			
• Congressional Directed Reductions	-	-			
• Congressional Rescissions	-	-			
• Congressional Adds	-	-			
• Congressional Directed Transfers	-	-			
• Reprogrammings	-	-			
• SBIR/STTR Transfer	-0.044	-			

Exhibit R-2, RDT&E Budget Item Justification: PB 2014 Defense Health Program	DATE: March 2013
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Change Summary Explanation

FY 2012: Realignment from DHP RDT&E, PE 0602787-Medical Technology (AFRRI) (-$0.044 million) to DHP RDT&E PE 0605502-Small Business Innovation Research (SBIR) Program (+$0.044 million).

FY 2013: No Change

FY 2014: No Change

Exhibit R-2A, RDT&E Project Justification: PB 2014 Defense Health Program			DATE: March 2013
APPROPRIATION/BUDGET ACTIVITY 0130: *Defense Health Program* BA 2: *RDT&E*	R-1 ITEM NOMENCLATURE PE 0602787HP: *Medical Technology (AFRRI)*	PROJECT 241A: *Biodosimetry (USUHS)*	

COST ($ in Millions)	All Prior Years	FY 2012	FY 2013#	FY 2014 Base	FY 2014 OCO ##	FY 2014 Total	FY 2015	FY 2016	FY 2017	FY 2018	Cost To Complete	Total Cost
241A: *Biodosimetry (USUHS)*	-	0.726	0.244	0.248	-	0.248	0.253	0.262	0.267	0.272	Continuing	Continuing

FY 2013 Program is from the FY 2013 President's Budget, submitted February 2012

The FY 2014 OCO Request will be submitted at a later date

A. Mission Description and Budget Item Justification

Biodosimetry (USUHS): For the Uniformed Services University of the Health Sciences (USUHS), the mission and research objectives for biodosimetry are to assess radiation exposure by developing and providing biological and biophysical dosimetry capabilities for acute, protracted, and prior radiation exposures; to identify proper medical treatment of injuries to military personnel to sustain warfighting capabilities; and to reduce dose detection threshold and automate assays to permit a robust and rapid capability.

B. Accomplishments/Planned Programs ($ in Millions)	FY 2012	FY 2013	FY 2014
Title: Biodosimetry (USUHS)	0.726	0.244	0.248

FY 2012 Accomplishments:

- Determined that epigenetic changes in an in vitro model depend on the radiation quality and may be a new biomarker of radiation exposure quality.
- Determined that intra-chromosomal inversions – cytogenetic aberrations can discriminate between internalized uranium exposure and nitrogen mustard in an in vivo model.
- Extended the time- and dose-window for use in the combination of multiple protein biomarkers and hematological parameters using a murine (several mouse strains) radiation model (60Co gamma-rays total-body irradiation to 0-14 Gy and time-points 6h - 7d after irradiation) for the radiation dose and injury assessment as well as for the survival prognosis; extended the radiation biomarker panel.
- Sustained efforts to establish an animal model for evaluation of candidate bioassays to assess partial-body exposures.
- Evaluated the use of lymphocytes and neutrophil to lymphocyte ratio as diagnostic indicators of radiation exposure using murine model system.
- Completed report on the evaluation of the combination of multiple protein biomarkers, hematological parameters, and clinical signs ranging 1d – 30d in total-body irradiated.
- Evaluated the subset of biomarkers affected by wounding in mouse radiation model (60Co gamma-rays total-body irradiation to 0-14 Gy and time-points 6h - 7d after irradiation) for radiation dose assessment.
- Successfully completed the “blinded” study for radiation dose assessment and dose-dependent discrimination of study animal groups using a mouse radiation model (60Co gamma-rays total-body irradiation to 0-14 Gy and time-points 6h - 7d after irradiation).

Exhibit R-2A, RDT&E Project Justification: PB 2014 Defense Health Program		DATE: March 2013
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B. Accomplishments/Planned Programs ($ in Millions)	FY 2012	FY 2013	FY 2014
- New radiation-responsive biomarkers were discovered. Provided inputs and invention disclosure to the HJF Joint Office of Technology (JOTT) on AFRRI's significant contributions to the provisional patent application entitled: "BIODOSIMETRY PANELS AND METHODS". - Provided contributions of necessary proof-of-concept dose-response data to transition combined proteomic and hematologic concept for further development of diagnostic devices (i.e., hand-held, field deployable) and to facilitate obtaining necessary FDA approval.			
FY 2013 Plans: - Continue efforts on the further evaluation of new radiation-responsive biomarkers in animal models and extend the utility of the newly developed molecular biomarker assay system for individual biodosimetry. - Identify specific epigenetic changes that can discriminate high-dose from low-dose radiation exposure. - Evaluate the enhancement for radiation dose assessment using a combination of hematological and protein biomarkers in two FDA-approved animal models. - Initiate preparation of report for FDA on combined utility of hematological and protein biomarkers for biodosimetry applications. - Extend murine partial-body radiation studies to evaluate late-phase and gastrointestinal injury radiation biomarkers. - Incorporate radiation bioinformatics (radioinformatics) capabilities, to include computational methods and data management tools to advance data collection, analysis, interpretation, and reporting of large data sets. - Create the ARS category score system based on multiple biodosimetric endpoints (i.e., peripheral blood cell counts and radiation-responsive protein expression profile), taking into account animal body weight, and temperature in the mouse radiation model. - Investigate the effect of exposure to different doses of radiation (6-14 Gy) on survival of mice in order to find associations between protein expression profiles, hematology parameters, body weight, and hematopoietic and GI sub-syndromes of the acute-radiation sickness (ARS). - Investigate dose-rate effect for low (photons) and high (mixed field neutrons and photons) Linear Energy Transfer (LET) for protein biomarkers in Total-Body Irradiation (TBI) animal models up to 7 days post irradiation. - Investigate combined utility of hematological and protein biomarkers for biodosimetry applications high (mixed field of neutrons and photons) LET total-body irradiations in TBI animal models. - Continue to study radiation-responsive biomarkers and clinical signs after radiation combined injury in mice. Investigate effects of combined injury (irradiation in combinations with wounds or burns) on candidate panel of protein biomarkers in mouse model up to 7 days post irradiation and trauma. - Investigate the gender and age effects on evaluated panel of protein biomarkers in mouse model up to 7 days post irradiation. - Sustain efforts to provide necessary proof-of-concept dose-response data to transition combined proteomic and hematological concept for further development of diagnostic devices (i.e., hand-held, field deployable) and obtain necessary FDA approval.			

Exhibit R-2A, RDT&E Project Justification: PB 2014 Defense Health Program		DATE: March 2013
APPROPRIATION/BUDGET ACTIVITY 0130: *Defense Health Program* BA 2: *RDT&E*	R-1 ITEM NOMENCLATURE PE 0602787HP: *Medical Technology (AFRRI)*	PROJECT 241A: *Biodosimetry (USUHS)*

B. Accomplishments/Planned Programs ($ in Millions)	FY 2012	FY 2013	FY 2014
- Continue to evaluate the protein biomarkers, hematological parameters, and clinical signs ranging 1 day to 30 days in total-body irradiated wounded mice at non-lethal, sub-lethal, and lethal radiation doses. - Establish Dosimetry map for protracted (Low-Dose-Rate) 60Co irradiation for murine model; initiate comparison studies between LDR and prompt radiation on selected biomarkers in murine models. ***FY 2014 Plans:*** - Contribute to the further evaluation of discovered new radiation-responsive biomarkers in animal models. - Prepare report for FDA on combined utility of hematological and protein biomarkers for biodosimetry applications in two FDA-required animal models. - Continue to provide necessary proof-of-concept dose-response data to transition combined proteomic and hematological concept for further development of diagnostic devices (i.e., hand-held, field deployable) and obtain necessary FDA approval. - Begin to develop the protocol for evaluating newly discovered protein biomarkers for use in human radiation accident cases. - Begin to evaluate the protein biomarkers, hematological parameters, and clinical signs ranging 1d – 30d in partial-body irradiated wounded mice at non-lethal, sub-lethal, and lethal radiation doses.			
Accomplishments/Planned Programs Subtotals	0.726	0.244	0.248

C. Other Program Funding Summary ($ in Millions)

N/A

Remarks

D. Acquisition Strategy

N/A

E. Performance Metrics

By FY 2012

– Evaluate the combination of multiple protein biomarkers and hematological parameters in murine (several mouse strains) radiation model for the radiation dose and injury assessment as well as for survival prognosis.
- Expand the panel of radiation-responsive protein biomarkers.
- Evaluate the subset of radiation biomarkers affected by wounding.
- Determine whether epigenetic changes during leukemogenesis can be used as neoplastic prognostic markers.

By FY 2013

Exhibit R-2A, RDT&E Project Justification: PB 2014 Defense Health Program		DATE: March 2013
APPROPRIATION/BUDGET ACTIVITY 0130: *Defense Health Program* BA 2: *RDT&E*	R-1 ITEM NOMENCLATURE PE 0602787HP: *Medical Technology (AFRRI)*	PROJECT 241A: *Biodosimetry (USUHS)*

- Further evaluate new radiation-responsive biomarkers for ARS sub-syndromes in animal models. Demonstrate accurate radiological detection from biological samples into quartiles of doses 0-1 Gy, 1-3 Gy, 3-6 Gy, 6-10 Gy, and greater than 10 Gy.
- Incorporate radiation bioinformatics (radioinformatics) capabilities, to include computational methods and data management tools to advance data collection, analysis, interpretation, and reporting of large data sets.
- Create the ARS category score system based on multiple biodosimetric endpoints (i.e., peripheral blood cell counts and radiation-responsive protein expression profile), taking into account animal body weight, and temperature in the mouse radiation model.
- Initiate assessment of partial-body radiation murine models over the protracted time period.
- Investigate the dose-rate effect for low and high LET total-body irradiations for protein biomarkers. Investigate combined utility of hematological and protein biomarkers for biodosimetry applications high (mixed field neutrons and photons) LET total-body irradiations in TBI animal models.
- Investigate the combined injury (irradiation in combination with wounds or burns) effects from the evaluation panel of protein biomarkers.
- Further evaluate the dose assessment protein biomarker panel, the hematological panel, and clinical sign ranging 1 day to 30 days after total-body irradiation with wound trauma at 1 Gy, 5.5 Gy, and 9.75 Gy.
- Investigate the gender and age effects as well as the partial-body irradiation effects on the evaluated panel of protein biomarkers.

By FY 2014

- Characterize partial-body radiation murine models over the protracted time period and compare results with prompt irradiation on selected biomarkers.
- Provide necessary proof-of-concept dose-response data to transition combined proteomic and hematological concept for further development of diagnostic devices (i.e., hand-held, field deployable) and obtain the necessary FDA approval. Prepare preliminary report for FDA on combined utility of hematological and protein biomarkers for biodosimetry applications in two FDA-required animal models.
- Begin to develop the protocol on evaluated and newly developed protein biomarkers for use in human radiation accident cases.
- Begin to evaluate the protein biomarkers, hematological parameters, and clinical signs ranging 1d – 30d in partial-body irradiated wounded mice at non-lethal, sub-lethal, and lethal radiation doses.

Exhibit R-2A, RDT&E Project Justification: PB 2014 Defense Health Program			DATE: March 2013
APPROPRIATION/BUDGET ACTIVITY 0130: *Defense Health Program* BA 2: *RDT&E*	R-1 ITEM NOMENCLATURE PE 0602787HP: *Medical Technology (AFRRI)*	PROJECT 241B: *Internal Contamination (USUHS)*	

COST ($ in Millions)	All Prior Years	FY 2012	FY 2013#	FY 2014 Base	FY 2014 OCO ##	FY 2014 Total	FY 2015	FY 2016	FY 2017	FY 2018	Cost To Complete	Total Cost
241B: *Internal Contamination (USUHS)*	-	0.376	0.127	0.129	-	0.129	0.132	0.138	0.140	0.143	Continuing	Continuing

FY 2013 Program is from the FY 2013 President's Budget, submitted February 2012

The FY 2014 OCO Request will be submitted at a later date

A. Mission Description and Budget Item Justification

Internal Contamination (USUHS): For the Uniformed Services University of the Health Sciences (USUHS), the mission and research objective for Internal Contamination is to determine whether the short-term and long-term radiological and toxicological risks of embedded metals warrant changes in the current combat and post-combat fragment removal policies for military personnel. Additionally, the biological effects of internalization of radioactive elements from Radiological Dispersal Devices (RDDs) and depleted uranium weapons, as well as therapeutic approaches to enhance the elimination of radionuclides from the body are being investigated.

B. Accomplishments/Planned Programs ($ in Millions)	FY 2012	FY 2013	FY 2014
Title: Internal Contamination (USUHS)	0.376	0.127	0.129
FY 2012 Accomplishments: - Determined that exposure to depleted uranium can cause direct DNA damage to male reproductive tissues in a rodent model system. - Determined that leukemic transformation by depleted uranium exposure involves non-targeted radiation damage in a rodent model system. - Determined that epigenetic changes manifested as global DNA alterations and genetic changes manifested as chromosomal instability are associated with depleted uranium-induced leukemia. - Demonstrated that molecularly imprinted polymers synthesized to likely radiological dispersal device material selectively bind these metals in artificial biofluids. - Showed that embedded fragments of surrogate radiological dispersal device material exhibit widely varying solubility characteristics in a rodent model system. - Initiated characterization of renal tumors observed in depleted uranium-implanted laboratory rats.			
FY 2013 Plans: - Develop combinatorial approaches to depleted uranium-induced transformation using a combination of drugs to target the properties of the epigenetic machinery. - Assess the ability of molecularly imprinted polymers to bind to potential internal contamination risks using an in vitro model system.			

Exhibit R-2A, RDT&E Project Justification: PB 2014 Defense Health Program		DATE: March 2013
APPROPRIATION/BUDGET ACTIVITY 0130: *Defense Health Program* BA 2: *RDT&E*	R-1 ITEM NOMENCLATURE PE 0602787HP: *Medical Technology (AFRRI)*	PROJECT 241B: *Internal Contamination (USUHS)*

B. Accomplishments/Planned Programs ($ in Millions)	FY 2012	FY 2013	FY 2014
- Continue characterization of depleted uranium-associated rat renal tumors. ***FY 2014 Plans:*** - Determine the efficacy of molecularly imprinted polymers on reducing the body burden of internalized radionuclides using a rodent model system. - Test novel leukemia countermeasures to determine if chemoprevention mechanism involves modification of chromatin regulation in depleted uranium-induced leukemia in vivo. - Validate combinatorial approach of depleted uranium-induced damage to cellular epigenetic machinery using an in vivo model. - Initiate investigation, using depleted uranium-implanted laboratory rodents, into early biomarkers of depleted uranium-induced renal neoplasia.			
Accomplishments/Planned Programs Subtotals	0.376	0.127	0.129

C. Other Program Funding Summary ($ in Millions)

N/A

Remarks

D. Acquisition Strategy

N/A

E. Performance Metrics

By FY 2013
- Continue characterization of depleted uranium-associated rat renal tumors.
- Evaluate ability of molecularly imprinted polymers to bind potential internal contamination risks.

By FY 2014
-Complete assessment of combinatorial approach for assessing depleted uranium-induced damage.
-Conclude evaluation of molecularly imprinted polymers as decorporation agents.

By FY 2015
- Initiate in vivo study into early biomarkers of depleted uranium-induced renal tumors.
-Complete in vivo study on the mechanism of depleted uranium-induced leukemia.

Exhibit R-2A, RDT&E Project Justification: PB 2014 Defense Health Program			DATE: March 2013
APPROPRIATION/BUDGET ACTIVITY 0130: *Defense Health Program* BA 2: *RDT&E*	R-1 ITEM NOMENCLATURE PE 0602787HP: *Medical Technology (AFRRI)*	PROJECT 241C: *Radiation Countermeasures (USUHS)*	

COST ($ in Millions)	All Prior Years	FY 2012	FY 2013#	FY 2014 Base	FY 2014 OCO ##	FY 2014 Total	FY 2015	FY 2016	FY 2017	FY 2018	Cost To Complete	Total Cost
241C: *Radiation Countermeasures (USUHS)*	-	2.456	0.822	0.839	-	0.839	0.856	0.886	0.900	0.916	Continuing	Continuing

FY 2013 Program is from the FY 2013 President's Budget, submitted February 2012

The FY 2014 OCO Request will be submitted at a later date

A. Mission Description and Budget Item Justification

Radiation Countermeasures (USUHS): For the Uniformed Services University of the Health Sciences (USUHS), this program supports developmental, mission-directed research to investigate new concepts and approaches that will lead to advancements in biomedical strategies for preventing, treating, assessing and predicting the health effects of human exposure to ionizing radiation as well as combined with injuries(burns, wounds, hemorrhage). Research ranges from exploration of biological processes likely to form the basis of technological solutions, to initial feasibility studies of promising solutions. Program objectives focus on mitigating the health consequences from exposures to ionizing radiation that represent the highest probable threat to U.S. forces in current tactical, humanitarian and counterterrorism 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.

B. Accomplishments/Planned Programs ($ in Millions)	FY 2012	FY 2013	FY 2014
Title: Radiation Countermeasures (USUHS)	2.456	0.822	0.839
FY 2012 Accomplishments: - Determined that in the bone marrow microenvironment, cell-cell communication is critical to development of radiation leukemia, providing evidence of a new target for radiation-leukemia prevention. - Determined that epigenetic mechanisms are dysregulated during radiation-induced leukemia and may be a target for new therapies. - Determined that chromosomal instability (genetic change) is associated with radiation-induced leukemia. - Determined that Phenylbutyrate treatment can prevent neoplastic transformation and genomic instability of bronchial airway cells. - Demonstrated that delta-tocotrienol (DT3) has significant radioprotective effects on survival of mice hematopoietic and gastrointestinal (GI) system. - DT3 protected mouse and human hematopoietic progenitors from gamma-irradiation through extracellular signal-regulated kinase and mammalian target of rapamycin signaling. - Demonstrated that DT3 protected intestinal mucosal barrier from high dose radiation damage and blocked sepsis and bacterial translocation in high dose-irradiated mice. - Demonstrated that Genistein, a naturally occurring isoflavone, protects hematopoietic system from gamma radiation and prevents radiation-induced elevation of pro-inflammatory factors in mouse model.			

Exhibit R-2A, RDT&E Project Justification: PB 2014 Defense Health Program		DATE: March 2013
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B. Accomplishments/Planned Programs ($ in Millions)	FY 2012	FY 2013	FY 2014
- Investigated mechanisms of self-defense in radiation-injured human hematopoietic microenvironment cells and demonstrated the role of REDDI1 (regulated in development and DNA damage responses), a novel survival factor, in human osteoblasts after gamma radiation. - Examined and compared radiation-induced microRNA profiles in human hematopoietic progenitor cells and hematopoietic niche cells. - Tocopheral succinate (TS) mobilizes large numbers of progenitor cells in the peripheral blood by inducing high levels of Granulocyte Colony-Stimulating Factor (G-CSF). - TS-mobilized progenitors significantly protect mice when administered as late as 48h post-irradiation with 11 Gy and also mitigates radiation injury in gut. - Demonstrated that human primary lung epithelial cells produce colony stimulating factors in response to TS stimulation. - Developed procedure for quantifying whole transcriptomic signatures associated with G-CSF transcript upregulation after TS exposure. - Initiated ex vivo culture of murine bone marrow endothelial cells (BMEC) for in vivo studies of their efficacy as a radiation countermeasure. - Showed human endothelial cells (EC) support bone marrow hematopoietic function after irradiation in vitro. - Demonstrated significant radioprotective effects of 17-DMAG on bone marrow, mediated by increasing hematopoietic cells and mesenchymal stem cells. A manuscript was contingently accepted by International Journal of Radiation Biology for publication. - Demonstrated radioprotective effects of 17-DMAG on ileum and lung, mediated by reducing epithelial apoptosis and crypt autophagy. - Found that Alxn4100TPO displayed significant therapeutic efficacy after radiation combined injury by increasing the platelet formation. - Found that ciprofloxacin displayed significant therapeutic efficacy after radiation combined injury by increasing erythrocyte generation and cellular ATP production. Manuscripts are in preparations. - Established an animal model of radiation combined with hemorrhage, which showed that hemorrhage enhanced radiation damage to the bone formation and maintenance.			
FY 2013 Plans: - Determine whether Phenylbutyrate-induced suppression of neoplastic transformation of bronchial tissue is radiation quality- or dose-dependent and whether epigenetic or genetic processes are predominant. - Evaluation the mitigative and therapeutic effects of DT3 (24h post-irradiation) in gamma-irradiated mice. - Evaluate the radioprotective and mitigative/therapeutic effects of tilorone hydrochloride in in vivo animal model. - Evaluate intracellular signaling pathways in mechanisms of efficacy of tilorone hydrochloride. - Analysis of progenitor cell engraftment in bone marrow and blood after whole body irradiation followed by transfusion with blood products from TS-treated mice.			

Exhibit R-2A, RDT&E Project Justification: PB 2014 Defense Health Program		DATE: March 2013
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B. Accomplishments/Planned Programs ($ in Millions)	FY 2012	FY 2013	FY 2014
- By analyzing transcriptomic signatures after TS stimulation and modulation of colony-stimulating factor production using functional genomics, we plan to determine the mechanism and necessary molecular components by which TS mediates colony-stimulating factor production. - Determine role of Wnt signaling pathway in hematopoietic recovery in bone marrow and spleen from sub-lethally irradiated mice. - Show effect of GT3 in Wnt signaling pathway regulation during hematopoietic recovery after radiation in mouse hematopoietic tissues (bone marrow and spleen). - Establish 3 dimensional coculture in vitro model. - Initiate ex vivo culture of murine BMEC for in vivo studies. - Test hypothesis that EC/EPC improves animal survival after gamma irradiation. - Test hypothesis that Ang/Tie2 pathway is involved in animal survival after gamma irradiation. - Test functional roles of Ang/Tie2 pathway in hematopoietic support after irradiation. - Evaluate eleven novel radiation countermeasure candidates in mice. - Evaluate intracellular signaling pathways in mechanisms of efficacy of GT3 and DT3. - The mechanisms of 17-DMAG as a countermeasure against radiation combined with hemorrhage will be elucidated in GI system. - Bone pathophysiology will be evaluated in radiation combined with hemorrhage in presence of absence of 17-DMAG. - The efficacy of a combined pharmaceutical regimen against radiation combined with hemorrhage will be evaluated. - Determine effectiveness of combined therapy of G-CSF and Alxn4100TPO, to prevent, mitigate, or inhibit the long-term deleterious responses to radiation combined injury. - Elucidate the underlying mechanisms of therapeutic effects of G-CSF and Alxn4100TPO after radiation combined injury. - Evaluate the micro-RNA profile in mouse serum after radiation alone and combination with wound trauma.			
FY 2014 Plans: - Determine whether protection of the bone marrow environment epigenetic changes following radiation can prevent radiation leukemia. - Evaluate radioprotective and mitigative/therapeutic effects of tilorone hydrochloride in an in vivo animal model. - Evaluate intracellular signaling pathways in mechanisms of efficacy of tilorone hydrochloride in different mouse tissues after radiation. - Evaluate intracellular signaling pathways in mechanisms of efficacy of DT3 in different mouse tissues after radiation. - Determine role of niche and hedgehog signaling in hematopoietic recovery following sub-lethal dose of radiation (in vitro and in vivo study). - Evaluation of radioprotective efficacy of GT3-Lipid nanocarriers in mice. - Test hypothesis that EC and endothelial progenitor cells (EPC) from Gottingen minipig are altered after radiation. - Test functions of irradiated EC and EPC from Gottingen minipig.			

Exhibit R-2A, RDT&E Project Justification: PB 2014 Defense Health Program		DATE: March 2013
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B. Accomplishments/Planned Programs ($ in Millions)	FY 2012	FY 2013	FY 2014
- Continue to evaluate intracellular signaling pathways and cytokine profiles in mechanisms of efficacy of G-CSF and Alxn4100TPO in irradiated wounded mice. - Continue to evaluate micro-RNA profiles in mouse serum after both radiation alone and combination with wound trauma with treatment with countermeasures.			
Accomplishments/Planned Programs Subtotals	2.456	0.822	0.839

C. Other Program Funding Summary ($ in Millions)

N/A

Remarks

D. Acquisition Strategy

N/A

E. Performance Metrics

By FY 2012

- Screen a minimum of two additional promising new countermeasures.
- Use newly purchased linear accelerator to open new areas of inquiry in partial body and organ-specific pathophysiology and countermeasure response.
- Complete toxicological comparison of tocols to identify lead candidate.
- Characterized levels of radiation biomarkers using a large cohort of healthy human adults to establish a multivariate biomarker baseline.
- Develop at least one new candidate model/method for high throughput drug screening.
- Develop at least one new countermeasure for radiation combined injury.
- Complete establishing the animal model of radiation combined with hemorrhage.

By FY 2013

- Complete elucidation of mechanisms of 17-DMAG as a countermeasure in radiation injury combined with trauma, burns, or hemorrhagic shock.
- Complete tocol mechanistic studies focused on lead candidate.
- Continue partial body and organ specific model development.
- Continue refinement of identified new candidate drug screening model/method.
- Unfold part of underlying mechanisms of therapeutic effects of G-CSF and Alxn4100TPO after radiation combined injury.
- Complete evaluation of the micro-RNA profile in mouse serum after radiation alone and combination with wound trauma.

Exhibit R-2A, RDT&E Project Justification: PB 2014 Defense Health Program		DATE: March 2013
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By FY 2014

- Determine whether protection of bone marrow environment epigenetic changes following radiation can prevent radiation leukemia.
- Evaluate radioprotective and mitigative/therapeutic effects of tilorone hydrochloride in in vivo animal model.
- Complete evaluation of intracellular signaling pathways and cytokine profiles in mechanisms of efficacy of G-CSF and Alxn4100TPO in irradiated wounded mice.
- Complete partial evaluation of micro-RNA profiles in mouse serum after both radiation alone and combination with wound trauma and treatment with countermeasures.