Exhibit R-2, RDT&E Budget Item Justification: PB 2019 Defense Health Agency	Date: February 2018
Appropriation/Budget Activity 0130: *Defense Health Program I* BA 2: *RDT&E*	**R-1 Program Element (Number/Name)** PE 0602787DHA *I Medical Technology (AFRRI)*

COST ($ in Millions)	Prior Years	FY 2017	FY 2018	FY 2019 Base	FY 2019 OCO	FY 2019 Total	FY 2020	FY 2021	FY 2022	FY 2023	Cost To Complete	Total Cost
Total Program Element	8.133	1.196	1.331	1.356	-	1.356	1.383	1.411	1.439	1.468	Continuing	Continuing
020: *CSI - Congressional Special Interests*	0.124	0.000	0.000	0.000	-	0.000	0.000	0.000	0.000	0.000	Continuing	Continuing
241A: *Biodosimetry (USUHS)*	1.634	0.245	0.272	0.277	-	0.277	0.283	0.289	0.295	0.301	Continuing	Continuing
241B: *Internal Contamination (USUHS)*	0.851	0.128	0.143	0.146	-	0.146	0.149	0.152	0.155	0.158	Continuing	Continuing
241C: *Radiation Countermeasures (USUHS)*	5.524	0.823	0.916	0.933	-	0.933	0.951	0.970	0.989	1.009	Continuing	Continuing

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 preventing or 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 2017	FY 2018	FY 2019 Base	FY 2019 OCO	FY 2019 Total
Previous President's Budget	1.242	1.331	1.356	-	1.356
Current President's Budget	1.196	1.331	1.356	-	1.356
Total Adjustments	-0.046	0.000	0.000	-	0.000
• Congressional General Reductions	-	-			
• Congressional Directed Reductions	-	-			
• Congressional Rescissions	-	-			
• Congressional Adds	-	-			
• Congressional Directed Transfers	-	-			
• Reprogrammings	-	-			
• SBIR/STTR Transfer	-0.046	-			

Congressional Add Details ($ in Millions, and Includes General Reductions)	FY 2017	FY 2018
Project: 020: *CSI - Congressional Special Interests*		
Congressional Add: *472A – Program Increase: Restore Core Research Funding Reduction (USUHS)*	0.000	-

Exhibit R-2, RDT&E Budget Item Justification: PB 2019 Defense Health Agency	Date: February 2018
Appropriation/Budget Activity 0130: *Defense Health Program I* BA 2: *RDT&E*	**R-1 Program Element (Number/Name)** PE 0602787DHA *I Medical Technology (AFRRI)*

Congressional Add Details ($ in Millions, and Includes General Reductions)	FY 2017	FY 2018
Congressional Add Subtotals for Project: 020	0.000	-
Congressional Add Totals for all Projects	0.000	-

Exhibit R-2A, RDT&E Project Justification: PB 2019 Defense Health Agency			Date: February 2018
Appropriation/Budget Activity 0130 / 2	R-1 Program Element (Number/Name) PE 0602787DHA / *Medical Technology (AFRRI)*	Project (Number/Name) 020 / *CSI - Congressional Special Interests*	

COST ($ in Millions)	Prior Years	FY 2017	FY 2018	FY 2019 Base	FY 2019 OCO	FY 2019 Total	FY 2020	FY 2021	FY 2022	FY 2023	Cost To Complete	Total Cost
020: *CSI - Congressional Special Interests*	0.124	0.000	0.000	0.000	-	0.000	0.000	0.000	0.000	0.000	Continuing	Continuing

A. Mission Description and Budget Item Justification

The FY15 DHP Congressional Special Interest (CSI) funding is directed toward core research initiatives in Program Element (PE) 0602787 - Medical Technology (AFRRI). Because of the CSI annual structure, out-year funding is not programmed.

B. Accomplishments/Planned Programs ($ in Millions)	FY 2017	FY 2018
Congressional Add: 472A – Program Increase: Restore Core Research Funding Reduction (USUHS)	0.000	-
FY 2017 Accomplishments: [*** PLEASE ENTER CONGRESSIONAL ADD TEXT FOR PRIOR YEAR. ***]		
Congressional Adds Subtotals	0.000	-

C. Other Program Funding Summary ($ in Millions)

N/A

Remarks

D. Acquisition Strategy

N/A

E. Performance Metrics

N/A

Exhibit R-2A, RDT&E Project Justification: PB 2019 Defense Health Agency			Date: February 2018
Appropriation/Budget Activity 0130 / 2	R-1 Program Element (Number/Name) PE 0602787DHA / *Medical Technology (AFRRI)*	Project (Number/Name) 241A / *Biodosimetry (USUHS)*	

COST ($ in Millions)	Prior Years	FY 2017	FY 2018	FY 2019 Base	FY 2019 OCO	FY 2019 Total	FY 2020	FY 2021	FY 2022	FY 2023	Cost To Complete	Total Cost
241A: *Biodosimetry (USUHS)*	1.634	0.245	0.272	0.277	-	0.277	0.283	0.289	0.295	0.301	Continuing	Continuing

A. Mission Description and Budget Item Justification

For the Uniformed Services University of the Health Sciences (USU), 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 preventing or 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. Accomplishments/Planned Programs ($ in Millions)	FY 2017	FY 2018	FY 2019
Title: Biodosimetry (USUHS)	0.245	0.272	0.277
Description: For the Uniformed Services University of the Health Sciences (USU), 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 for all relevant military applications.			
FY 2018 Plans: Establish a suite of biodosimetry assays, techniques, and standard operating procedures to support analysis of chromosomal aberrations for assessing radiation injury and dose. Establish dose-response curve for dicentric yields, that is, frequencies of chromosome aberrations in irradiated lymphocytes using automated dicentric scoring software utility. Perform dose response studies to measure dicentric chromosomal aberrations in irradiated lymphocytes after exposure to mixed neutron and photon radiation fields mimicking those from an improvised nuclear device at relevant distances from the epicenter. Identify radiation-responsive biological markers (aka biomarkers) such as microRNAs and proteins that are organ-specific in a mouse model of partial-body radiation exposure. Participate in annual performance evaluation of established techniques and procedures for radiation biodosimetry to demonstrate accuracy in dose assessment methodology such as cytogenetic assays for detecting chromosomal aberrations; implement new approaches through reassessment to enhance throughput capability for processing and scoring of chromosomal aberrations. Establish partial-body animal radiation mouse model of acute radiation syndrome (ARS) using low linear energy transfer(LET)/photon exposure from the small animal radiation research platform (SARRP) and assess organ-specific radiation injury biomarkers similar to ones performed earlier in low-linear energy transfer (LET) Total-body irradiation (TBI) mouse model. Establish partial-body animal radiation models (mouse and nonhuman primates (NHPs)) using low-LET/photon exposure with the SARRP for mice and with the linear accelerator (LINAC) radiation platform for NHPs in order to assess organ-specific radiation injury biomarkers evaluated earlier in low-LET TBI studies. Establish mouse TBI model			

Exhibit R-2A, RDT&E Project Justification: PB 2019 Defense Health Agency		Date: February 2018
Appropriation/Budget Activity 0130 / 2	**R-1 Program Element (Number/Name)** PE 0602787DHA / *Medical Technology (AFRRI)*	**Project (Number/Name)** 241A / *Biodosimetry (USUHS)*

B. Accomplishments/Planned Programs ($ in Millions)	FY 2017	FY 2018	FY 2019
for combined hematological and proteomic biodosimetry approach following mixed-field (neutrons and photons, high-LET) in addition to one already established and evaluated for a pure photon (60 Co gamma ray, low-LET) exposure. Evaluate IL-18 and IL-12, small protein signaling agents as dual radiation biomarkers in non-human primate urine sampling for assessment of radiation injury and doses, severity and lethality after TBI. Develop microRNAs profile as biomarkers of radiation injury and dose by sampling urine from gamma-irradiated NHPs using microRNAs microarray and quantitative real-time polymerase chain reaction (RT-PCR) methods. Compare microRNAs profiles in gamma-irradiated mouse serum and NHPs urine and identify sensitive and accurate radiation biomarkers. Evaluate effects of low and moderate doses of gamma-radiation from hematopoietic and immune system of mice (in vivo) and human cells (in vitro). Further evaluate mechanisms of radiation-induced lymphocyte damage. Further evaluate additional hematology and leukemia biomarkers during leukemogenesis that are differentially expressed at early and late phases of transformation. Identify additional epigenetic changes that discriminate between differences in dose rate at low doses (<10 cGy). ***FY 2019 Plans:*** FY 2019 plans continue efforts as outlined in FY 2018 in addition to establishing a mouse Total-body irradiation (TBI) model for combined hematological (blood cells) and proteomic (proteins) biodosimetry approach following the mixed-field (neutron and photons) along with one already established and evaluated for a pure photon (60 Co gamma ray, low-LET) exposure. ***FY 2018 to FY 2019 Increase/Decrease Statement:*** N/A			
Accomplishments/Planned Programs Subtotals	0.245	0.272	0.277

C. Other Program Funding Summary ($ in Millions)

N/A

Remarks

The program element 0602787DHA for AFRRI in addition to the three program elements: 0601115HPPE, 0602115HPPE, and 0603115HP are coordinated and integrated into the portfolio management by the Joint Program Committee-7/ Radiation Health Effects Research Program (RHERP).

D. Acquisition Strategy

N/A

E. Performance Metrics

By FY 2017
-Perform initial analysis of multiple parameter biodosimetry assessment using murine partial-body exposure model.
-Establish use of automated metaphase finder to enhance throughput for processing samples and automated scoring of dicentrics.

Exhibit R-2A, RDT&E Project Justification: PB 2019 Defense Health Agency		Date: February 2018
Appropriation/Budget Activity 0130 / 2	**R-1 Program Element (Number/Name)** PE 0602787DHA / *Medical Technology (AFRRI)*	**Project (Number/Name)** 241A / *Biodosimetry (USUHS)*

-Evaluate correlations between levels of radiation biomarkers (IL-18, IL-18BP and miR-34) and survival rates in individual mice 1 to 40 days after radiation.
-Report on further analysis of IL-18 and develop algorithm using IL-18 as significant variable for use in combination with archived complete blood count and serum chemistry data (from same NHP dataset) for estimating radiation injury.
-Develop biomarkers which can identify “treatment-point” in individual mice after radiation injury.
-Identify the network of miRNAs and their targeted mRNAs in radiation-induced apoptotic signal pathways.
-Continue evaluating new early-phase and organ-specific damage radiation-responsive biomarkers in animal models.
-Continue comparing and correlating hematology, blood serum chemistry, protein biomarkers and necropsy results in NHP dose-response study to evaluate radiation damage to specific organs.
-Continue comparing results/data from NHP dose-response TBI (photon/low LET) studies with data collected from radiation accident victims and radiation therapy patients.
-Continue refining combination of radiation biomarkers in blood with best balance of discrimination, sensitivity and specificity.
-Continue evaluating the predictive radiation-responsive biomarkers in animal models for prediction of ARS severity and outcome.
-Measure specific methylation and histone changes using Reverse transcription polymerase chain reaction (RT-PCR) technique in murine spleen samples from low dose and high dose radiation exposure studies.
By FY2018
-Characterize partial-body animal radiation models (murine) using animals involving low-LET exposure with AFRRI small-animal irradiator (for mice) to identify organ-specific radiation injury biomarkers evaluated earlier in low-LET TBI studies.
-Initiate studies to characterize cytogenetic chromosomal aberration yields following exposure to neutron and photon mixed field sources.
-Perform mass-casualty exercise to test throughput capability in dose assessment by cytogenetics.
-Continue scoring dicentric aberrations following exposure to neutron and photon mixed field exposures.
-Establish partial-body animal radiation models (mouse and NHP) using low-LET photon exposure with AFRRI small-animal irradiator (for mice) and LINAC (for NHPs) to identify organ-specific radiation injury biomarkers evaluated earlier in low-LET TBI studies.
-Establish mouse TBI model for combined hematological and proteomic biodosimetry following mixed-field (neutrons and photons, high-LET) in addition to one already established and evaluated for a pure photon (60Co gamma-rays, low-LET) exposure.
-Develop miRNA profile for urine of gamma-irradiated NHPs urine using miRNA microarray and quantitative RT-PCR.
-Evaluate IL-18 and IL-12 as dual radiation biomarkers in NHP urine.
-Evaluate effects of low-moderate doses of gamma-radiation on hematopoietic and immune cell injury to understand the molecular targets and cellular “initiating events” after low-moderate doses of radiation exposure in these cells.
-Develop miRNA profile and identify sensitive and accurate biomarkers in mouse and human hematopoietic and immune cells after low-moderate doses radiation exposure.
-Evaluate effects of low-moderate doses of radiation on induced proinflammatory factor activation in mouse thymus, BM and spleen cells and human CD34+ cells.
-Ascertain mechanisms by which low-moderate doses of radiation induce stress responses in mouse and human immune and hematopoietic cells, and lymphocyte depletion.
-Initiate murine leukemia model to concomitantly predict leukemia development based on epigenetic markers identified in FY16 and FY17.
By FY2019

Exhibit R-2A, RDT&E Project Justification: PB 2019 Defense Health Agency		Date: February 2018
Appropriation/Budget Activity 0130 / 2	**R-1 Program Element (Number/Name)** PE 0602787DHA / *Medical Technology (AFRRI)*	**Project (Number/Name)** 241A / *Biodosimetry (USUHS)*

-Establish a mouse TBI model for combined hematological and proteomic biodosimetry approach following the mixed-field (neutrons and photons, high-LET) in addition to one already established and evaluated for a pure photon (60Co gamma-rays, low-LET) exposure.
- Evaluate the acute and delayed effects of low-moderate doses of total body radiation exposure and develop biomarkers to identify the acute and long-term of these low-moderate doses radiation injury in mouse model.
By FY2020
-Establish a mouse partial-body irradiation model for combined hematological and proteomic biodosimetry approach following the mixed-field (neutrons and photons, high-LET) in addition to one already established and evaluated for a pure photon (60Co gamma-rays, low-LET) exposure.
-Identify and evaluate the organ-specific radiation injury biomarkers evaluated earlier in low-LET total-body irradiation studies and partial-body biodosimetry in mouse partial-body irradiation model.
By FY21
- Establish a partial-body nonhuman primate (NHP) radiation model using the LINAC to identify the organ-specific radiation injury proteomic and serum chemistry biomarkers evaluated earlier in low-LET TBI studies.
By FY22
- Identify and evaluate the organ-specific radiation injury biomarkers evaluated earlier in low-LET total-body irradiation studies and partial-body organ-specific biodosimetry in NHP partial-body irradiation model (using LINAC).
- Prepare preliminary report for FDA on combined utility of combined hematological, proteomic and serum chemistry biomarkers in mouse and NHP partial-body irradiation models for organ-specific biodosimetry applications in two FDA-required animal models.

Exhibit R-2A, RDT&E Project Justification: PB 2019 Defense Health Agency			Date: February 2018
Appropriation/Budget Activity 0130 / 2	R-1 Program Element (Number/Name) PE 0602787DHA / *Medical Technology (AFRRI)*	Project (Number/Name) 241B / *Internal Contamination (USUHS)*	

COST ($ in Millions)	Prior Years	FY 2017	FY 2018	FY 2019 Base	FY 2019 OCO	FY 2019 Total	FY 2020	FY 2021	FY 2022	FY 2023	Cost To Complete	Total Cost
241B: *Internal Contamination (USUHS)*	0.851	0.128	0.143	0.146	-	0.146	0.149	0.152	0.155	0.158	Continuing	Continuing

A. Mission Description and Budget Item Justification

Internal Contamination (USU): For the Uniformed Services University of the Health Sciences (USU), 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 2017	FY 2018	FY 2019
Title: Internal Contamination (USUHS)	0.128	0.143	0.146
Description: For the Uniformed Services University of the Health Sciences (USU), 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.			
FY 2018 Plans: Continue cytotoxicity testing, to predict potential toxic effects in whole animals, of surrogate-templated molecularly imprinted polymers for extraction of radionuclide contaminants; begin assessment of extracorporeal decorporation techniques to determine blood purification and chelation efficiencies of the polymers in a laboratory rat model. Design feasibility study to assess potential of chemically-modified dendrimeric structures as radionuclide decorporation agents and to optimize the efficiency of the designed polymers as decorporation agents. Continue assessment of dendrimeric structures for further optimization as a promising radionuclide decorporation agents in regard to desired properties such as specificity, binding strength and lower cytotoxicity. Initiate a study to determine if non-toxic plant-based metal chelators can be effectively used as radionuclide decorporation agents for the treatment of internal radionuclide contamination.			
FY 2019 Plans: FY2019 plans continue efforts as outlined in FY 2018 in addition to design optimization and feasibility studies to test and evaluate the potential for chemically-modified dendrimeric structures as promising radionuclide decorporation agents			
FY 2018 to FY 2019 Increase/Decrease Statement:			

Exhibit R-2A, RDT&E Project Justification: PB 2019 Defense Health Agency		Date: February 2018
Appropriation/Budget Activity 0130 / 2	**R-1 Program Element (Number/Name)** PE 0602787DHA / *Medical Technology (AFRRI)*	**Project (Number/Name)** 241B / *Internal Contamination (USUHS)*

B. Accomplishments/Planned Programs ($ in Millions)	FY 2017	FY 2018	FY 2019
N/A			
Accomplishments/Planned Programs Subtotals	0.128	0.143	0.146

C. Other Program Funding Summary ($ in Millions)

N/A

Remarks

The program element 0602787DHA for AFRRI in addition to the three program elements: 0601115HPPE, 0602115HPPE, and 0603115HP are coordinated and integrated into the portfolio management by the Joint Program Committee-7/ Radiation Health Effects Research Program (RHERP).

D. Acquisition Strategy

N/A

E. Performance Metrics

By FY 2017
-Complete molecularly imprinted polymer binding specificity studies; initiate cytotoxicity assessments.
By FY2018
-Complete cytotoxicity and extracorporeal decorporation assessments of surrogate-templated molecularly imprinted polymers.
By FY2019
-Initiate study into feasibility of chemically-modified dendrimeric structures as radionuclide decorporation agents.
By FY2020
-Complete feasibility study on the use of chemically-modified dendrimeric structures as radionuclide decorporation agents and determine if continued investigation is warranted.
By FY2021
-Initiate investigation into the applicability of non-toxic plant-based chelators as radionuclide decorporation agents using in vitro model systems.

Exhibit R-2A, RDT&E Project Justification: PB 2019 Defense Health Agency			Date: February 2018
Appropriation/Budget Activity 0130 / 2	R-1 Program Element (Number/Name) PE 0602787DHA / *Medical Technology (AFRRI)*	Project (Number/Name) 241C / *Radiation Countermeasures (USUHS)*	

COST ($ in Millions)	Prior Years	FY 2017	FY 2018	FY 2019 Base	FY 2019 OCO	FY 2019 Total	FY 2020	FY 2021	FY 2022	FY 2023	Cost To Complete	Total Cost
241C: *Radiation Countermeasures (USUHS)*	5.524	0.823	0.916	0.933	-	0.933	0.951	0.970	0.989	1.009	Continuing	Continuing

A. Mission Description and Budget Item Justification

Radiation Countermeasures (USU): For the Uniformed Services University of the Health Sciences (USU), this program supports developmental, mission directed research to investigate new concepts and approaches that will lead to advancements in biomedical strategies for preventing and treating the health effects of human exposure to ionizing radiation as well as radiation combined with injuries (burns, wounds, hemorrhage), termed combined injury (CI). 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 preventing and mitigating the health consequences from exposures to ionizing radiation, in the context of probable threats 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 2017	FY 2018	FY 2019
Title: Radiation Countermeasures (USUHS)	0.823	0.916	0.933
Description: For the Uniformed Services University of the Health Sciences (USU), this program supports developmental, mission directed research to investigate new concepts and approaches that will lead to advancements in biomedical strategies for preventing and treating the health effects of human exposure to ionizing radiation as well as radiation combined with injuries (burns, wounds, hemorrhage), termed combined injury (CI). 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 preventing and mitigating the health consequences from exposures to ionizing radiation, in the context of probable threats 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.			
FY 2018 Plans: Test and evaluate five or more new compounds in mouse model for the development of new radiation protection (prophylactic) countermeasures. Conduct mechanism of action studies to elucidate the cell signaling transduction pathways for promising drug substances and products as potential radiation countermeasures using cell-based assays for their characterization. Conduct animal studies to evaluate BBT-059, a PEGylated protein analog in a mouse model for radiation countermeasures development. Test and evaluate promising drug substances and products as radiation countermeasures to determine their efficacy and safety in irradiated gut and/or lung mouse model used for studying radiation biology. Evaluate long term effects of acute radiation exposure in surviving mice after exposure to lethal dose of radiation. Evaluate survival effects of ghrelin as a drug substance for radiation treatment in animal model for acute radiation syndrome (ARS). Continue to evaluate and down-select lead drug substances and			

Exhibit R-2A, RDT&E Project Justification: PB 2019 Defense Health Agency		Date: February 2018
Appropriation/Budget Activity 0130 / 2	**R-1 Program Element (Number/Name)** PE 0602787DHA / *Medical Technology (AFRRI)*	**Project (Number/Name)** 241C / *Radiation Countermeasures (USUHS)*

B. Accomplishments/Planned Programs ($ in Millions)	FY 2017	FY 2018	FY 2019
products and drug combinations that are effective at radiation doses producing hematopoietic (H-ARS) or gastrointestinal (GI-ARS) syndrome and identify those that are effective in treating radiation combined (e.g. burn, wound, etc.) injury in animal model of ARS. Test and evaluate drug substances and products for radiation countermeasures development against mixed-field (neutron and photon) radiation exposure mimicking those from an improvised nuclear device at relevant distances from the epicenter. Conduct further studies to elucidate the mechanism of action of promising drug substances and drug products against mixed-field radiation exposure using cell-based assays for their characterization. Further evaluate radiation sensitivity and variation among different animal models (species). Conduct exploratory studies on radiation effects when combined with insults from viruses or bacteria on the immune system and elucidate the ensuing reactive oxygen species (ROS) produced by cellular metabolism and how by using broad MAPkinase pharmacological inhibitors, antioxidants and modulators, highly selective inhibitors, etc. provide a potential treatment or drug for the radiation combined insults. Establish panel of gene reporter cells system and methodologies to identify potential on and off therapeutic biological targets towards a novel strategy for developing new radiation countermeasures. Continue evaluation of radiation-induced leukemia in murine model to concomitantly predict leukemia development based on epigenetic markers identified previously in FY16 and FY17 at low and high doses of radiation exposure and determine the dual benefit of administering radiation countermeasures (drug substance) for both acute and delayed effects of ionizing radiation exposure. ***FY 2019 Plans:*** FY 2019 plans continue efforts as outlined in FY 2018 in addition to continued discovery effort to advance radiobiology knowledge products and continued development of radiobiology research products for radiation countermeasures and biodosimetry capabilities and assessment of the technology readiness levels of promising material solutions or products for advanced development. ***FY 2018 to FY 2019 Increase/Decrease Statement:*** N/A			
Accomplishments/Planned Programs Subtotals	0.823	0.916	0.933

C. Other Program Funding Summary ($ in Millions)

N/A

Remarks

The program element 0602787DHA for AFRRI in addition to the three program elements: 0601115HPPE, 0602115HPPE, and 0603115HP are coordinated and integrated into the portfolio management by the Joint Program Committee-7/ Radiation Health Effects Research Program (RHERP).

D. Acquisition Strategy

N/A

Exhibit R-2A, RDT&E Project Justification: PB 2019 Defense Health Agency		Date: February 2018
Appropriation/Budget Activity 0130 / 2	**R-1 Program Element (Number/Name)** PE 0602787DHA / *Medical Technology (AFRRI)*	**Project (Number/Name)** 241C / *Radiation Countermeasures (USUHS)*

E. Performance Metrics

By FY 2017

-Identify novel radiation countermeasures from drug screening and development. Continue to identify dynamic changes in circulatory blood cell counts, bone marrow cellularity and ileum structure morphology after radiation-wound combined injury (CI).

-Complete evaluation of cells signals such mTOR-AKT signaling and MAPK signaling in ileum and ileal morphology after exposure to gamma-radiation combined with hemorrhage.

-Complete assessment of cytokine profiles in serum and ileum after ghrelin therapy in order to find key cytokines as biomarkers associated with ileal recovery after CI.

-Begin to measure other biomarkers such as CRP, C3, IgM, PGE2, and Flt-3 ligand in serum of minipigs and mice model for acute radiation syndrome after Co-60 irradiation at various dose rates.

-Complete assessment of timing and duration of effects of MAPK cell signaling pathway inhibitors on inflammatory response by macrophages exposed to ionizing radiation.

-Complete assessment of ex vivo human macrophage response to ionizing radiation alone (IR), microbial infection, and to a combination both IR and microbial exposure.

-Complete assessment of transcription factor reporter cells to test biological response modulators of gene activation induced by IR, microbial agonists, and combined exposure to both insults.

-Complete development of oxidation-sensitive drug delivery system at rate corresponding to level of oxidants present within microenvironment of cell system.

-Complete development of multi-photon-responsive nanocarrier designed to respond to UV light, near infrared (NIR), and infrared light exposure.

-Complete assessment of nanoparticle constructs' ability to modulate macrophage inflammatory responses to a combination of ionizing radiation and microbial agonist exposures.

-Identify and measure early epigenomics steps in post-radiation process caused by low doses of gamma radiation and at low dose rates to stem cell populations.

-Identify specific histone modifications associated with low LET radiation (gamma or x-ray) and compare to high LET radiation (alpha or neutron) in low doses at different dose rates of exposure.

-Measure effects of low doses (<100 cGy) at different dose rates (34 µGy to 10 cGy/min) on neural stem (NSC) cell potential, DNA damage, histone acetylation/ methylation, and DNA methylation.

-Compare radiation qualities of different radiation sources (e.g. x-ray/LINAC, gamma, alpha particle, and neutrons) for radiobiology studies.

-Measure effects of low doses (<100 cGy) at different dose rates (34 µGy to 10 cGy/min) on mesenchymal stem cell (MSC) potential, DNA damage, histone acetylation/ methylation, and DNA methylation.

-Measure effects of low doses of gamma (<100 cGy) at different dose rates (34 µGy to 10 cGy/min) on MSC in vivo, evaluating DNA damage, histone acetylation/ methylation, and DNA methylation. Measure effects of low doses of alpha particles (<100 cGy) at different dose rates (34 µGy to 10 cGy/min) on MSC in vivo.

By FY 2018

-FY 2018 performance metrics build on measures outlined in FY 2017 in addition to initiating murine leukemia model and characterizing multiple epigenetic markers in serum to include white blood cells (WBCs) after exposure to low and high doses of radiation as well as at a low versus high dose rate (frequency).

-Start mouse lifespan studies on radiation-induce acute radiation syndrome (ARS) and evaluate countermeasures treatment effects to assess ARS progression to delayed radiation effects such as leukemia and thymic tumors.

-Elucidate the molecular pathways involved in the radioprotection by promising drug substances/products like TPOm and BBT-059 for countermeasures development.

Exhibit R-2A, RDT&E Project Justification: PB 2019 Defense Health Agency		Date: February 2018
Appropriation/Budget Activity 0130 / 2	**R-1 Program Element (Number/Name)** PE 0602787DHA / *Medical Technology (AFRRI)*	**Project (Number/Name)** 241C / *Radiation Countermeasures (USUHS)*

-Elucidate the efficacy of the drug substance, small molecule PrC-210 on the recovery observed from radiation-induced depletion of peripheral blood cells and bone marrow progenitor cells. Test and evaluate new potential drug substances and products for radiation countermeasures development.

By FY 2019

-FY 2019 performance metrics build on measures outlined in FY 2018 and include continued assessment of leukemia progression concomitantly with measurement of multiple epigenetic markers in serum and WBCs using microarray technology.

-Further assess leukemia progression in mice that recovered from ARS but continued receiving countermeasures against late effects of radiation exposure; use necropsy examination to determine the cause of death at later stages.

-Test and evaluate promising drug substances and products for radiation countermeasures development against in mixed field (neutron and photon) radiation exposure.

-Test and evaluate promising drug substances and products for radiation countermeasures development for Radiation-Induced Gastrointestinal Syndrome (GI-ARS) in mice using the small animal radiation research platform (SARRP).

-Conduct mouse studies to elucidate the delayed effects of acute lethal radiation exposure in drug treated survivors.

-Continue to measure radiation-induced biomarkers such as cytokines, CRP, C3, IgM, PGE2, and Flt-3 ligand in serum of mice after Co-60 irradiation at various dose rates.

-Continue to measure cytokines in spleen and bone marrow of mice after mixed field irradiation to study differential effects of genders and radiation dose rate.

-Correlate radiation-induced cellular biomarkers such as mTOR-AKT and MAPK signaling network and ATP production after in vitro radiation-burn combined injury.

-Evaluate mTOR-AKT signaling and MAPK signaling in ex vivo culture of bone marrow mesenchymal cells and in vitro small intestine cells after exposure to gamma-radiation combined with burn trauma to determine survival signaling pathways.

-Complete assessment of MAPK pathway inhibitors in their effectiveness to alter the inflammatory response in macrophages exposed to radiation.

-Complete assessment of ex vivo culture of human macrophage cells response to ionizing radiation, viral infection and combined injury.

-Complete determination of the effect of ionizing radiation on cellular signaling pathways that control production of Type I interferon signaling in inflammation response.

-Evaluate radiation quality effects on gene reporter cells. Evaluate results from pilot studies of cells with high oxidative and virus resistance.