Exhibit R-2, RDT&E Budget Item Justification: PB 2020 Defense Health Agency	Date: February 2019
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 2018	FY 2019	FY 2020 Base	FY 2020 OCO	FY 2020 Total	FY 2021	FY 2022	FY 2023	FY 2024	Cost To Complete	Total Cost
Total Program Element	9.329	1.282	1.356	1.383	-	1.383	1.411	1.439	1.468	1.497	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)*	1.879	0.272	0.277	0.283	-	0.283	0.289	0.295	0.301	0.307	Continuing	Continuing
241B: *Internal Contamination (USUHS)*	0.979	0.143	0.146	0.149	-	0.149	0.152	0.155	0.158	0.161	Continuing	Continuing
241C: *Radiation Countermeasures (USUHS)*	6.347	0.867	0.933	0.951	-	0.951	0.970	0.989	1.009	1.029	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 2018	FY 2019	FY 2020 Base	FY 2020 OCO	FY 2020 Total
Previous President's Budget	1.331	1.356	1.383	-	1.383
Current President's Budget	1.282	1.356	1.383	-	1.383
Total Adjustments	-0.049	0.000	0.000	-	0.000
• Congressional General Reductions	-	-			
• Congressional Directed Reductions	-	-			
• Congressional Rescissions	-	-			
• Congressional Adds	-	-			
• Congressional Directed Transfers	-	-			
• Reprogrammings	-	-			
• SBIR/STTR Transfer	-0.049	-			

Exhibit R-2A, RDT&E Project Justification: PB 2020 Defense Health Agency			Date: February 2019
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 2018	FY 2019	FY 2020 Base	FY 2020 OCO	FY 2020 Total	FY 2021	FY 2022	FY 2023	FY 2024	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)

N/A

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 2020 Defense Health Agency			Date: February 2019
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 2018	FY 2019	FY 2020 Base	FY 2020 OCO	FY 2020 Total	FY 2021	FY 2022	FY 2023	FY 2024	Cost To Complete	Total Cost
241A: *Biodosimetry (USUHS)*	1.879	0.272	0.277	0.283	-	0.283	0.289	0.295	0.301	0.307	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 2018	FY 2019	FY 2020
Title: Biodosimetry (USUHS)	0.272	0.277	0.283
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.			

Exhibit R-2A, RDT&E Project Justification: PB 2020 Defense Health Agency		Date: February 2019
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 2018	FY 2019	FY 2020
-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 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 2018 Accomplishments: - Evaluated several radiation-responsive protein biomarkers for early-phase and organ-specific damage in animal total-body irradiation (TBI) models: In mouse (with minimal supportive care) and nonhuman primate (with minimal and full medical supportive care consisting of G-CSF or Neupogen® [filgrastim], antibiotics, blood transfusions, etc.]) in order to predict as early as possible the radiation-induced multi-organ involvement (MOI) and multi-organ failure (MOF) and late effects of exposure and acute radiation sickness (ARS) outcome in two animal models to support FDA regulatory requirement. -Demonstrated in mouse TBI studies that the evaluated biomarker profiles show no gender-effect as well as no dose-rate effect within a broad range (0.02 to ~2 Gy/min) reflecting the fact that the radiation dose prediction might be done strictly based on biomarker level regardless to the exposure dose-rate. -Identified several biomarkers of gastrointestinal (GI) injury: citrulline, citrullinated proteins (CP), bactericidal permeability increasing (BPI) protein, lipopolysaccharide binding protein (LBP), procalcitonin (PCT), intestinal fatty acid binding protein (I-FABP), diamine oxidase (DAO or histaminase) in mouse and nonhuman primate (NHP) TBI models. -Plasma citrulline and citrullinated proteins were identified as early biomarkers of radiation-induced gastrointestinal damage and a potential new biomarkers of late-effect kidney failure.			

Exhibit R-2A, RDT&E Project Justification: PB 2020 Defense Health Agency		Date: February 2019
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 2018	FY 2019	FY 2020
-Citrullinated proteins were demonstrated as a new predicative radiation-responsive biomarker in animal models for a prediction of the ARS outcome (AFRRI US Patent Number 9,063,148 issued on 6/23/2015). -Evaluated biochemical profiles in NHP TBI model revealed elevations in individual enzymes that reflect radiation-damage to the respective organs (i.e., salivary glands, pancreas, liver, muscles, kidney, etc.). -Confirmed that the specific biomarker levels correlate with a severity of radiation damage to different organs evaluated in complete necropsies performed in NHPs. Although, those findings need to evaluate in partial-body animal studies using either SARRP or LINAC. -Evaluated the IL-18 level in urine of NHPs total-body irradiated with 60Co gamma-rays and demonstrated its great utility as a non-invasive early prognostic indicator of survival facilitated rapid detection of radiation exposure that might be suitable for field-deployable biodosimetry point-of-care to determine the exposure dose in a few minutes. -Demonstrated that the urine IL-18 levels combined with other biomarkers measured in blood provided highly discriminatory power, specificity and sensitivity of radiation exposure. -Created ARS severity score response categories in mouse and NHP TBI gamma-rays studies reveled good similarities with one created in radiation accident victims. -Completed comparison of some results/data from the NHP dose-response TBI (gamma- and x-rays) studies with data collected in radiation accident victims and radiation therapy patients and revealed good similarities. -Evaluated and demonstrated the different responses of mouse hematopoietic and immune cells to low-moderate doses (0.1, 0.5, 1.0, 3.0, and 5.0 Gy) of total-body γ-irradiation (TBI). Radiation < 1 Gy can significantly damage hematopoietic stem and progenitor cells; low dose radiation-induced decrease of stem cell factor (SCF) in mouse BM and increase in circulating proinflammatory factors may be responsible for the enhanced sensitivity of hematopoietic stem and progenitor cells to radiation. -Developed a novel method, using long-range quantitative PCR to determine radiation-induced nuclear and mitochondria DNA damage. -Demonstrated the circulating microRNA (miR)-30 and miR-34 as radiation biomarkers in mice which can also be used to track radiation-induced apoptosis in human and mouse cells. - Established the severity of mortality and platelet depletion dependence on radiation doses and dose rates. - Established the severity of lymphocyte depletion and concentrations of biomarkers G-CSF, IL-18, Flt-3 ligand dependence on radiation doses. -Established two radiation dose-response calibration curves (60Co-gamma rays at 0.6 Gy/min and 0.1 Gy/min) for automated scoring of dicentrics chromosome aberrations (DCA) that enable rapid radiation dose assessment. These studies contribute towards DoDs radiological medical preparedness by validating enhanced throughput capability via automated scoring software and laboratory competency. -Reported on radiation dose-responses for both total-body and partial-body irradiation up to 30 Gy using the premature chromosome condensation (PCC) assay using multiple endpoints (i.e., excess fragments, rings, length ratio, and dicentrics). On-going studies are evaluating the accuracy of these various endpoints using the PCC assay using blind samples.			

Exhibit R-2A, RDT&E Project Justification: PB 2020 Defense Health Agency		Date: February 2019
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 2018	FY 2019	FY 2020
-Participated as a satellite scoring laboratory in the RENEB (Realizing the European Network in Biodosimetry) RENEB ILC II exercise involving the analysis of 500 spreads in each of three samples. Preliminary analysis showed samples that our results were to be within in the acceptable range. Participated in intra- and inter-laboratory DCA/dose assessment comparison exercises with Health Canada. (Dr. Ruth Wilkins). This exercise involved the use of 10 human blood samples (exposed to various radiation doses) received from Health Canada that were cultured, stained, and scored for dicentrics using their requested triage scoring approach (n=50). Data analysis is on-going. -Initiated studies to compare total-body and partial-body radiation exposures using the mouse model system to evaluate candidate radiation biomarkers (i.e., proteomic, miRNA) to assess organ specific injury. - Reported new research findings that increases in biomarkers from blood after mixed field irradiation and gamma irradiation depended on radiation doses but not radiation dose rates. The effects also were not affected by genders. The observation is essential for establishing the biomarkers for triage and radiation dose assessment. One paper on this subject was published in Radiation Research 189:634-643, 2018. ***FY 2019 Plans:*** FY 2019 plans continue efforts as outlined in FY 2018. In addition, efforts continue for 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 (60Co gamma ray, low-LET) exposure. Additionally, the following are included this plan: - Explore the mechanisms of low-moderate doses of radiation-mediated adverse effects based on the results obtained from FY18's studies. - Evaluate and identify the molecular targets and cellular "initiating events" after low-moderate doses of radiation exposure in multiple organs and tissues of mouse and human cells. - Evaluate and identify the sensitivity of different organ to low-moderate doses of gamma radiation-induced oncogene expression and development of malignancy in in vivo and ex vivo model. - Evaluate using long-range quantitative PCR method to determine DNA damage in human and animal blood cells and assess radiation injury after different doses of gamma radiation. -Determine the mechanisms by which IL-18 induces vascular endothelium damage and multiple organ injury in mouse model and in vitro cell lines, as well as to evaluate the radioprotection/mitigation efficacy of anti-IL-18. -Perform dose response studies to measure dicentric chromosomal aberrations in irradiated lymphocytes after exposure to mixed neutron mimicking those from an improvised nuclear device at relevant distances from the epicenter. -Sustain research efforts to optimize cytogenetic assays for rapid dose assessment as well as rapid assessment the fraction of the body exposed in a radiation casualty.			

Exhibit R-2A, RDT&E Project Justification: PB 2020 Defense Health Agency		Date: February 2019
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 2018	FY 2019	FY 2020
-Identify and optimize miRNA biomarkers for specific radiation sensitive organ systems (i.e., gastrointestinal system, pulmonary system, etc.). ***FY 2020 Plans:*** FY 2020 plans continue efforts as outlined in FY 2019. ***FY 2019 to FY 2020 Increase/Decrease Statement:*** Pricing Adjustment.			
Accomplishments/Planned Programs Subtotals	0.272	0.277	0.283

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 FY2019

-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.

- Explore the mechanisms of low-moderate doses of radiation-mediated adverse effects based on the results obtained from FY18's studies.
- Evaluate and identify the molecular targets and cellular "initiating events" after low-moderate doses of radiation exposure in multiple organs and tissues of mouse.
- Evaluate and identify the sensitivity of different organ to low-moderate doses of gamma radiation-induced oncogene expression and development of malignancy.
- Evaluate using long-range quantitative PCR method to determine DNA damage in human and animal blood cells and assess radiation injury after different doses of gamma radiation, as well as to evaluate the efficacy of radiation countermeasures.

-Investigate the mechanisms by which IL-18 induces vascular endothelium damage and multiple organ and tissue injury.

-Apply proteomic markers in various combinations in multivariate or logistic regression models for predicting radiation dose and/or ARS severity.

-Demonstrate the use of centromeric probes and rapid in situ hybridization in the PCC assay to score dicentrics to enhance the robustness of dose assessment capability over a broad dose range.

By FY2020

Exhibit R-2A, RDT&E Project Justification: PB 2020 Defense Health Agency		Date: February 2019
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 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.
-Investigate the mechanisms by which IL-18 induces vascular endothelium damage and multiple organ and tissue injury.
- Explore the mechanisms of low-moderate doses of radiation-mediated tissue injury in experimental mice.
- Evaluate and identify the molecular targets and cellular “initiating events” after low-moderate doses of radiation exposure in multiple organs and tissues of mouse.
- Explore the mechanisms by which low-moderate doses of gamma radiation-induced malignancy in radiosensitive tissues using mouse model.
- Establish an accurate and sensitive method using long-range quantitative PCR method to determine DNA damage in human and animal blood cells after mixed-field (neutron and photons) radiation exposure, as well as to evaluate the efficacy of radiation countermeasures.
-Validate use of the cytogenetic biodosimetry suite of assays for radiation dose assessment in annual exercises.

Exhibit R-2A, RDT&E Project Justification: PB 2020 Defense Health Agency			Date: February 2019
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 2018	FY 2019	FY 2020 Base	FY 2020 OCO	FY 2020 Total	FY 2021	FY 2022	FY 2023	FY 2024	Cost To Complete	Total Cost
241B: *Internal Contamination (USUHS)*	0.979	0.143	0.146	0.149	-	0.149	0.152	0.155	0.158	0.161	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 2018	FY 2019	FY 2020
Title: Internal Contamination (USUHS)	0.143	0.146	0.149

Description: Radioactive material can enter the body by a variety of pathways including ingestion, inhalation, and wound contamination. While some internalized isotopes will be naturally eliminated from the body, many others are not. They remain immobile or are transported and deposited to other organs where they continually irradiate the surrounding tissue. This chronic internal radiation exposure can cause unrepairable cellular damage eventually leading to death. This Program uses innovative approaches to address this pressing health concern.

FY 2018 Plans:
Continue cytotoxicity testing 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 agent 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 2018 Accomplishments:
-Molecularly imprinted polymers prepared using ternary and silica-based protocols, with zinc as the surrogate template, were able to bind cobalt from simulated serum and intestinal fluids.
-Molecularly imprinted polymers prepared using silica-based protocols, with copper as the surrogate template, were able to bind uranium from simulated serum and intestinal fluids.

Exhibit R-2A, RDT&E Project Justification: PB 2020 Defense Health Agency		Date: February 2019
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 2018	FY 2019	FY 2020
-Molecularly imprinted polymers prepared using europium as a surrogate template for strontium and rubidium as a surrogate template for cesium were unable to bind the appropriate metals. -No metal binding was observed in simulated gastric fluid because of the pH-sensitive nature of the metal: polymer interaction. -Molecularly imprinted polymer preparations demonstrated low cytotoxicity and did not result in the hemolysis of isolated rat red blood cells. ***FY 2019 Plans:*** FY2019 plans continue efforts as outlined in FY 2018. In addition, plans include the design optimization and feasibility studies to test and evaluate the potential for chemically-modified dendrimeric structures as promising radionuclide decorporation agents. ***FY 2020 Plans:*** FY2020 plans include initiation of feasibility of incorporating non-toxic plant-based metal chelators into a dendrimeric structure for use as potential radionuclide decorporation agents. ***FY 2019 to FY 2020 Increase/Decrease Statement:*** Pricing Adjustment.			
Accomplishments/Planned Programs Subtotals	0.143	0.146	0.149

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 FY2019

-Initiate study into feasibility of chemically-modified dendrimeric structures as radionuclide decorporation agents.

By FY2020

-Continue feasibility study on the use of chemically-modified dendrimeric structures as radionuclide decorporation agents and determine if further investigation is warranted.

Exhibit R-2A, RDT&E Project Justification: PB 2020 Defense Health Agency			Date: February 2019
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 2018	FY 2019	FY 2020 Base	FY 2020 OCO	FY 2020 Total	FY 2021	FY 2022	FY 2023	FY 2024	Cost To Complete	Total Cost
241C: *Radiation Countermeasures (USUHS)*	6.347	0.867	0.933	0.951	-	0.951	0.970	0.989	1.009	1.029	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 2018	FY 2019	FY 2020
Title: Radiation Countermeasures (USUHS)	0.867	0.933	0.951
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.			

Exhibit R-2A, RDT&E Project Justification: PB 2020 Defense Health Agency		Date: February 2019
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 2018	FY 2019	FY 2020
-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 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 2018 Accomplishments: -Demonstrated that MAPK inhibitors can both increase and decrease production of radiation induced inflammatory cytokines and chemokines secreted by murine macrophages. This broadens the types of regulator interventions potentially available for controlling inflammation. -Published peer reviewed manuscript describing how commercially available gene reporter cells can be used to assay Type I interferons (IFNα/β). Potentially this can be a lower cost method with utility to screening large sample sets or high through put experimental approaches. -Established a material transfer agreement (MTA) with pharmaceutical drug sponsors to test a select list of drug candidates for radiation countermeasures development.			

Exhibit R-2A, RDT&E Project Justification: PB 2020 Defense Health Agency		Date: February 2019
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 2018	FY 2019	FY 2020
-Completed acute toxicity study of four drug candidates. The candidates are (1) EPX-217 from Epitek, Inc, (2) MultiStem from Athersys, Inc., (3) Ketone ester from National Institute of Health, and (4) Xisomab 3G3 from Aronora Inc. These prescreened drug candidates were obtain through an interagency agreement (IAA) with the National Institute of Allergy and Infectious Diseases (NIAID) to test their survival efficacy following total body irradiation (TBI). -Completed acute toxicity study of PLX-R18 (Pluristem therapeutics Inc.) and BP-C2 (Meabco A/S) drug molecules. -Completed thirty day efficacy study with PLX-R18 in H-ARS mouse model, the result shows ~45% survival benefit with the drug. A confirmation study is being planned; recently PLX-R18 has received Investigational new drug (IND) status by FDA. - Completed evaluation of MAPK/ERK (Extracellular Signal-regulated Kinase) signaling pathway, RT²Profiler PCR Array and TGFß / BMP Signaling Pathway. Completed assay of RT² Profiler PCR Array with spleen from irradiated animals with and without the radiation drug candidate (BBT-059) to determine the biological target of BBT-059 in the aforementioned cellular these pathways. -Completed analysis of blood and major organs and tissues including eye and brain harvested at 1, and 6 months post-TBI to a lethal dose of radiation in order to assess DEARE (Delayed effects of acute radiation exposure) in surviving animals treated with two radiation drug candidates (BBT-059 and TPOm). - Completed global profile of cellular gene responses (i.e. transcriptomic changes) in CD34+ cell populations exposed to different doses of ionizing radiation (IR) to determine the gene signature biomarkers for dose-dependent effects of IR for radiation drug. - Reported on the underlying mechanisms of ghrelin as a potential drug to mitigate multi-organ injury involving radiation exposure. The findings shows that Ghrelin can potentially be used as therapeutic for treating radiation injury alone or in combination with physical trauma. Two papers on hematopoietic mitigation and brain bleeding inhibition have been published in Cell Biosci 8:27, 2018 and International Journal of Molecular Science 18:1693, 2017. ***FY 2019 Plans:*** FY 2019 plans continue efforts as outlined in FY 2018. This also includes continued discovery effort in partnership with NIAID, NIH and other collaborators to advance radiobiology knowledge products and medical material products to meet the military requirements for radiation countermeasures and risk assessment and biodosimetry capabilities and their technology readiness levels for future advanced development. ***FY 2020 Plans:*** FY 2020 plans continue efforts as outlined in FY 2019 plans. ***FY 2019 to FY 2020 Increase/Decrease Statement:*** Pricing Adjustment.			
Accomplishments/Planned Programs Subtotals	0.867	0.933	0.951

Exhibit R-2A, RDT&E Project Justification: PB 2020 Defense Health Agency		Date: February 2019
Appropriation/Budget Activity 0130 / 2	**R-1 Program Element (Number/Name)** PE 0602787DHA / *Medical Technology (AFRRI)*	**Project (Number/Name)** 241C / *Radiation Countermeasures (USUHS)*

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 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.

- Evaluate the radiation-induced IL-18 expression and activation in multiple tissues and organs using mouse model.

-Conduct experiments to test the hypothesis that IL-18 binding protein (IL-18BP) or anti-IL-18 antibody can protect /mitigate human cells (in vitro) and mouse (in vivo) after lethal doses of total-body gamma irradiation (TBI).

-Develop IL-18 binding protein as a novel radiation mitigative/treatment countermeasure in mouse model.

- Test IL-18BP and G-CSF drug combination as a protection and/or mitigation/treatment drug after gamma radiation exposure.

- Test IL-18BP and G-CSF drug combination as a protection and/or mitigation/treatment drug after mixed-field (neutron and photons) radiation exposure.

Exhibit R-2A, RDT&E Project Justification: PB 2020 Defense Health Agency		Date: February 2019
Appropriation/Budget Activity 0130 / 2	**R-1 Program Element (Number/Name)** PE 0602787DHA / *Medical Technology (AFRRI)*	**Project (Number/Name)** 241C / *Radiation Countermeasures (USUHS)*

By FY 2020
-Continue studies in developing IL-18 BP as a novel radiation mitigative/treatment countermeasure in mouse model using different mouse strain.
- Test further IL-18BP and G-CSF combination as a protection and/or mitigation/treatment drug after gamma radiation exposure.
- Test further IL-18BP and G-CSF combination as a protection and/or mitigation/treatment drug after mixed-field (neutron and photons) radiation exposure.
- Complete measuring 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.
- Complete measuring cytokines in spleen and bone marrow of mice after mixed field irradiation to study differential effects of genders and radiation dose rate.
- Complete correlating radiation-induced cellular biomarkers such as mTOR-AKT and MAPK signaling network and ATP production after in vitro radiation-burn combined injury.
- Complete evaluating 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.