Exhibit R-2, RDT&E Budget Item Justification: PB 2021 Defense Health Agency											Date: February 2020	
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 2019**	**FY 2020**	**FY 2021 Base**	**FY 2021 OCO**	**FY 2021 Total**	**FY 2022**	**FY 2023**	**FY 2024**	**FY 2025**	**Cost To Complete**	**Total Cost**
Total Program Element	10.611	1.307	1.383	1.411	-	1.411	1.439	1.468	1.497	1.527	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)*	2.151	0.277	0.283	0.289	-	0.289	0.295	0.301	0.307	0.313	Continuing	Continuing
241B: *Internal Contamination (USUHS)*	1.122	0.146	0.149	0.152	-	0.152	0.155	0.158	0.161	0.164	Continuing	Continuing
241C: *Radiation Countermeasures (USUHS)*	7.214	0.884	0.951	0.970	-	0.970	0.989	1.009	1.029	1.050	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 2019	FY 2020	FY 2021 Base	FY 2021 OCO	FY 2021 Total
Previous President's Budget	1.356	1.383	1.411	-	1.411
Current President's Budget	1.307	1.383	1.411	-	1.411
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 2021 Defense Health Agency			Date: February 2020
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 2019	FY 2020	FY 2021 Base	FY 2021 OCO	FY 2021 Total	FY 2022	FY 2023	FY 2024	FY 2025	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

Exhibit R-2A, RDT&E Project Justification: PB 2021 Defense Health Agency			Date: February 2020
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 2019	FY 2020	FY 2021 Base	FY 2021 OCO	FY 2021 Total	FY 2022	FY 2023	FY 2024	FY 2025	Cost To Complete	Total Cost
241A: *Biodosimetry (USUHS)*	2.151	0.277	0.283	0.289	-	0.289	0.295	0.301	0.307	0.313	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 2019	FY 2020	FY 2021
Title: Biodosimetry (USUHS)	0.277	0.283	0.289
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 2019 Accomplishments: - Reported on a proteomic algorithm to predict hematological acute radiation syndrome (H-ARS) severity using a baboon radiation model; these findings support the utility of point-of-care proteomic devices to triage radiation casualties identifying individuals at risk of life-threatening exposures and requiring immediate medical treatment. -- Initiated studies to expose blood lymphocytes to LINAC electrons in lieu of fission neutrons. - Evaluated the utility of length ratio of chromosomes using automated scoring as an endpoint using the premature chromosome condensation (PCC) assay to rapidly assess the radiation dose and fraction of the body exposed. -- Continued efforts to apply centromeric sequence protein nucleic acid (PNA) probes to identify dicentric chromosomes using the PCC assay. -- Reported findings demonstrating differential effects of mixed-field (i.e., 5.5 neutrons to gamma rays) vs. gamma rays on hematology blood count changes following exposure to radiation. Established a consensus baboon radiation database using mixed field and gamma ray exposure for H-ARS severity. Developed an algorithm to predict H-ARS severity based on blood cell count changes, independent of whether exposures were from mixed-field or gamma rays only. These results support the concept to employ H-ARS severity assessment using blood cell counts to assess radiation exposure following nuclear incident. - Completed experimental studies on effects of low-to-moderate doses of gamma radiation on mouse hematopoietic system.			

Exhibit R-2A, RDT&E Project Justification: PB 2021 Defense Health Agency		Date: February 2020
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 2019	FY 2020	FY 2021
- Demonstrated that 0.5 Gy of total-body γ-irradiation (TBI) is a threshold dose for hematopoietic and immune system injury in CD2F1 mice. - Developed a novel method to measure radiation-induced DNA damage in cells using long range quantitative PCR. - Demonstrated that IL-18 is a useful radiation biomarker for radiation injury. ***FY 2020 Plans:*** - 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. - Predict radiation dose absorbed by different organs by identifying and evaluating 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. - 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. - Explore further the mechanisms of low-moderate doses of radiation-mediated injury in experimental mice and human and mouse cells. - Explore the mechanisms by which low-moderate doses of gamma radiation-induced malignancy in radiosensitive tissues using mouse model and in vitro human and mouse cells. - Develop 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. -Investigate the mechanisms by which IL-18 induces vascular endothelium damage and multiple organ and cell injury in in vivo and ex vivo studies. -Enhance rapid dose and injury assessment using the biodosimetry suite of assays. -Analyze tissues collected from male and female mice exposed to either mixed field radiation or Co-60 radiation including different radiation doses and dose rates. ***FY 2021 Plans:*** FY 2021 plans continue efforts as outlined in FY 2020 in addition to the following: -- Evaluate the use of the hematological algorithms using archived animal and human databases to provide prognostic diagnostic capability of radiation injury assessment. -- Compare various PCC endpoints for their utility to predict the fraction of the body exposed to radiation to determine those that could best provide rapid and accurate diagnostic information. - Evaluate utility of long range QPCR (LR-QPCR) and primer extension blockade enabled QPCR (PEBE-QPCR) to quantitatively measure radiation-induced DNA damage in mammalian cells			

Exhibit R-2A, RDT&E Project Justification: PB 2021 Defense Health Agency		Date: February 2020
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 2019	FY 2020	FY 2021
- Develop IL-18 as a useful biomarker to monitor and track the lesions from radiation exposure and the efficacy of radiation-mitigation. - Investigate the mechanisms by which IL-18 signaling induces mouse tissue and cell injury after radiation and IL-18BP's mitigative effects. ***FY 2020 to FY 2021 Increase/Decrease Statement:*** Pricing adjustment for inflation.			
Accomplishments/Planned Programs Subtotals	0.277	0.283	0.289

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 2021 Defense Health Agency			Date: February 2020
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 2019	FY 2020	FY 2021 Base	FY 2021 OCO	FY 2021 Total	FY 2022	FY 2023	FY 2024	FY 2025	Cost To Complete	Total Cost
241B: *Internal Contamination (USUHS)*	1.122	0.146	0.149	0.152	-	0.152	0.155	0.158	0.161	0.164	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 2019	FY 2020	FY 2021
Title: Internal Contamination (USUHS)	0.146	0.149	0.152
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 2019 Accomplishments: AFRRI/USUHS Report AFR-B5-3530: Molecularly Imprinted Polymers for Internal Radionuclide Decontamination. ***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 2021 Plans:*** FY 2021 plans continue efforts as outlined in FY 2020 in addition to the following: initiation of feasibility studies of incorporating non-toxic plant-based metal chelators into a dendrimeric structure for use as potential radionuclide decorporation agents. ***FY 2020 to FY 2021 Increase/Decrease Statement:*** Pricing adjustment for inflation.			
Accomplishments/Planned Programs Subtotals	0.146	0.149	0.152

C. Other Program Funding Summary ($ in Millions)

N/A

Exhibit R-2A, RDT&E Project Justification: PB 2021 Defense Health Agency		Date: February 2020
Appropriation/Budget Activity 0130 / 2	**R-1 Program Element (Number/Name)** PE 0602787DHA / *Medical Technology (AFRRI)*	**Project (Number/Name)** 241B / *Internal Contamination (USUHS)*

C. Other Program Funding Summary ($ in Millions)

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 2021 Defense Health Agency			Date: February 2020
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 2019	FY 2020	FY 2021 Base	FY 2021 OCO	FY 2021 Total	FY 2022	FY 2023	FY 2024	FY 2025	Cost To Complete	Total Cost
241C: *Radiation Countermeasures (USUHS)*	7.214	0.884	0.951	0.970	-	0.970	0.989	1.009	1.029	1.050	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 2019	FY 2020	FY 2021
Title: Radiation Countermeasures (USUHS)	0.884	0.951	0.970
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 2019 Accomplishments: - Reported translational research findings on Ghrelin therapy for mitigation of small intestine injury by sustaining granulocyte-colony stimulating factor (G-CSF), keratinocyte chemoattractant (KC) and macrophage inflammatory protein 1-alpha (MIP-1α), and decreased interleukin-18 (IL-18) in small intestine after combined radiation injury (CI). Ghrelin mitigating small intestinal injury induced by CI was confirmed by histology examination and reduction of cell death biomarker in small intestine. - Reported research findings on radiation injury (RI) and CI induced brain hemorrhage in cerebrum and cerebellum by reducing circulating platelets and brain energy production and increasing brain inflammation and cell death signals,			

Exhibit R-2A, RDT&E Project Justification: PB 2021 Defense Health Agency		Date: February 2020
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 2019	FY 2020	FY 2021
- Demonstrated in an animal model that combinational therapy of Ghrelin and Neulasta inhibited brain hemorrhage from RI and CI by recovering energy production, inhibiting inflammation, and blocking cell death signals in brain as well as increasing platelets in circulation. -Reported animal test/evaluation findings on radiation drug candidate, BBT-059, developed by Bolder Biotechnology, protected mice from radiation-induced gastro-intestinal injury, significantly increased serum citrulline, reduced inflammatory serum amyloid A (SAA) levels and bacterial translocation in liver and spleen. In addition, research findings showed that animals treated with BBT-059 survived up to 12 months post-radiation exposure from lethal and supra-lethal dose (delayed effects of acute radiation exposure, DEARE) with no histological changes in major organs including heart, kidney, brain, and liver. -Reported animal test/evaluation findings on radiation drug candidate, PLX-R18, developed by Pluristem Therapeutics, demonstrated significant increase in 30-day survival when it was administered two doses on day 1 pre and day 3 post-radiation. In addition, research findings showed that PLX-R18 protected mice from radiation induced hematopoietic acute radiation syndrome, significantly accelerated recovery of peripheral blood and bone marrow progenitor cells. - Completed animal test toxicity study of IL-18BP as a putative radiation drug and found no toxicity after subcutaneous (SC) injection from 0.25 mg/kg to 5.0 mg/kg to CD2F1 mice. - Demonstrated that a single injection of rhIL-18BP (1.5mg/kg) to mice at 24 h, 48 or 72 h post-total-body irradiation (TBI) exhibited a delayed mortality time in comparison with vehicle control-treated mice. In addition, IL-18BP (1.5 mg/kg, 48 h post-radiation) significantly increased bone marrow hematopoietic stem and progenitor cell clonogenicity and blood platelet number in mice after 9 or 10 Gy (LD70/30 and LD90/30) TBI. Also, two doses injection of rhIL-18BP (1.5mg/kg) to mice at 48 h and 5 days post-9 Gy TBI significantly increased 30-day survival of mice in compression of vehicle-control injected and irradiated mice. -Completed studies on the radiation-dependent effects on the human HSC proteome by in vitro methods; a few but promising radiation-induced protein biomarkers have been identified. -Generated additional translational information on radiation-induced biomarker signature using samples obtained from irradiated large animal model. This work is being done using transcriptomics and metabolomics/lipidomics platforms. -Successfully initiated a radiation induced microbiome study using irradiated murine model samples This work will continue by using bacterial DNA analysis as well as metabolomics/lipidomics. ***FY 2020 Plans:*** FY 2020 plans are: - Initiate a new proposed project to investigate molecular mechanisms underlying the differential responses to high-linear energy transfer (LET) radiation between males and females. - Examine and analyze organ injury in small intestine and bone marrow of mice exposed to mixed-field radiation. - Start proteomic analysis of 25 cytokines/chemokines and C3 in bone marrow, spleen and small intestine. - Assess pathological changes in major organs in one and six months post-total body radiation (TBI) in male and female C57BL/6 mice.			

Exhibit R-2A, RDT&E Project Justification: PB 2021 Defense Health Agency		Date: February 2020
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 2019	FY 2020	FY 2021
- Continue to evaluate radiation-induced biomarker signature using large animal model samples and state of the art techniques: transcriptomics, metabolomics/lipidomics. - Continue to evaluate radiation induced microbiome using irradiated murine model samples. This will be done using transcriptomics and metabolomics/lipidomics platforms. - Establish Gut-on-chip model to minimize the use of animals in radiation biology research. ***FY 2021 Plans:*** FY2021 plans continue efforts as outlined in FY2020 in addition to the following: - Further investigate radiation effects on the molecular pathway of AKT-MAPK cross talk. - Evaluate long-term differential expression of micro-RNAs in C57BL/6 mice (male and female) and mini-pig after radiation. - Determine the DEARE (delayed effects of acute radiation exposure) effects on the gut microbiome compositions and host-microbiome relationship and identify gender differences. - Evaluate the pharmacokinetic of IL-18BP in mouse. - Evaluate the radiation mitigative effects of IL-18BP in different mouse model. - Determine the dose reduction factor (DRF) of IL-18BP in irradiated mice. - Evaluate the effects and mechanisms of IL-18BP on survival of mouse gastrointestinal systems after lethal doses of TBI. ***FY 2020 to FY 2021 Increase/Decrease Statement:*** Pricing adjustment for inflation.			
Accomplishments/Planned Programs Subtotals	0.884	0.951	0.970

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