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Exhibit R-2, RDT&E Budget Item Justification: PB 2024 Defense Health Agency **Date:** March 2023

Appropriation/Budget Activity 0130: <i>Defense Health Program I BA 2: RDT&E</i>	R-1 Program Element (Number/Name) PE 0603002DHA I <i>Medical Advanced Technology (AFRRI)</i>
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COST (\$ in Millions)	Prior Years	FY 2022	FY 2023	FY 2024 Base	FY 2024 OCO	FY 2024 Total	FY 2025	FY 2026	FY 2027	FY 2028	Cost To Complete	Total Cost
Total Program Element	1.022	0.351	0.366	0.373	0.000	0.373	0.380	0.388	0.396	0.404	Continuing	Continuing
242A: <i>Biodosimetry (USUHS)</i>	0.611	0.209	0.218	0.222	0.000	0.222	0.226	0.231	0.260	0.265	Continuing	Continuing
242B: <i>Radiation Countermeasures (USUHS)</i>	0.411	0.142	0.148	0.151	0.000	0.151	0.154	0.157	0.136	0.139	Continuing	Continuing

A. Mission Description and Budget Item Justification

For the Uniformed Services University of the Health Sciences/Armed Forces Radiobiology Research Institute (USUHS/AFRRI), is a unique Department of Defense asset, responsible for preserving and protecting the health and performance of U.S. military personnel operating in potential radiologically contaminated multi-domain conventional or hybrid battle spaces and urban environments; through research, education, and operational training that advance understanding of the effects of ionizing radiation in line with the 21st century dynamic threat landscape and national security threats posed by non-state actors, hostile state actors, and near-peer adversaries, as well as providing rapidly deployable radiation medicine expertise in response to a radiological or nuclear event domestically or abroad.

The uniqueness of USUHS/AFRRI comes from operating and maintaining state-of-the-art radiation facilities and dosimetry systems to support military relevant radiobiology research. These facilities enable researchers to conduct a wide range of radiobiology experiments in order to investigate militarily-relevant scenarios, and better understand radiation effects and potential mitigation strategies. A team of scientist, physicists, engineers, operators and technicians use proven and traceable dosimetry systems (e.g., ionization chambers, radiochromic film, thermoluminescent dosimeters) and consensus protocols to characterize radiation fields. Due to these facilities our researchers are able to experiment with photons (gamma-rays) which are intended to simulate fallout environments and are delivered by two cobalt-60 facilities - the high-level cobalt facility (HLCF), and for lower (chronic) doses and dose rates, the low-level cobalt facility (LLCF). These type of radiation sources are used for acute and chronic studies of materials, biologic specimens, and small and large animals. The LLCF also provides to our scientist low-dose rate gamma rays to simulate chronic exposure to low absorbed doses. Therefore, it also supports research focused on late or delayed radiation effects in biological specimens.

USUHS/AFRRI researchers are also able to use mixed-radiation fields (photons and neutrons) which are available from USUHS/AFRRI's Training, Research, Isotopes, General Atomics (TRIGA) reactor. The reactor is operated in either steady-state or pulsed mode to simulate a wide range of prompt exposure scenarios on a nuclear battlefield. The USUHS/AFRRI's TRIGA is the only one dedicated to military radiobiology research. The reactor produces a controlled, self-sustaining fission chain reaction in the reactor core which, in addition to the fuel elements and control rods (containing boron carbide), which includes a neutron start-up source (americium/beryllium). It is suspended under 4.9 m of water within a pool (an effective radiation shield) in a carriage assembly that allows movement of the core between two exposure rooms for experimental work with large-animal or other studies. The advantages of such a movable reactor core are that the quantity and character of the radiation that reaches the exposure facilities can be controlled, and more than one exposure facility can be used during reactor operations.

Our state-of-the-art radiation facilities are also able to provide a wide range of photon and electron irradiations for partial- and whole-body geometries by using a linear accelerator (LINAC) and a small animal radiation research platform (SARRP) providing a range of radiation types, energies, field sizes and dose rates and is extensively used to support standard cell configurations (i.e., 6-, 24- and 96-well plates), and targeted partial body irradiations of mice, minipigs, and nonhuman-primates (NHP) animal models. AFRRI's LINAC is used to produce, monitor, control and form photon or electron beams to the specified target. Whole-body irradiations are also possible

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depending on the animal size and desired dose rate. An Xstrahl SARRP facility is capable of operating at 220 kVp and 13 mA yielding a dose rate at the isocenter of approximately 2.6 Gy/min. Onboard portal camera and cone beam computed tomography (CT) imaging systems are used to ensure precise dose delivery. Lung- and gut-only irradiation protocols are approved and have been extensively used to support radiation countermeasure development in the mouse model. Other imaging support is provided by a Philips Brilliance CT big bore scanner. Some features of the scanner include an 85-cm bore size to accommodate larger research subjects, 60-cm true scan field of view and 16-slices per revolution. The above radiation sources and generators are used to support USUHS/AFRRI's current research focus areas which we will address in the following section.

Our scientific research goals includes maintaining a pool of highly qualified radiation biologists, and basic and applied research in identification and early development of measures to prevent, assess, and treat radiation injury. USUHS/AFRRI scientists conduct and publish research critical to the Department of Defense for force health protection and also contribute to the health and well-being of the population at large. USUHS/AFRRI research thrusts include development of diagnosis of radiation induced injury (biodosimetry), internalized radionuclides (internal contamination) and radiation countermeasures.

The program capitalizes on findings under PE 0602787HP, Medical Technology, and from industry and academia to advance novel medical countermeasures into and through pre-clinical studies toward newly licensed products. Research findings are mainly focused to advance the development and to produce the following: (1) To establish processes to permit rapid assessment of radiation exposed specimens using novel triage protocols; (2) To developed novel technologies using animal models in the study of radiation effects; (3) To investigate the overall radiation effect by internal contamination in the microbiome and anatomical tissue; (4) To find novel biomarkers, late effects and immunosuppression of radiation injury that can quantitate effects on combat performance decrements; (5) To identify novel therapeutic strategies that will support military operations within a nuclear or radiological environment minimizing ground troops short and long term adverse risk.

B. Program Change Summary (\$ in Millions)	<u>FY 2022</u>	<u>FY 2023</u>	<u>FY 2024 Base</u>	<u>FY 2024 OCO</u>	<u>FY 2024 Total</u>
Previous President's Budget	0.359	0.366	0.373	0.000	0.373
Current President's Budget	0.351	0.366	0.373	0.000	0.373
Total Adjustments	-0.008	0.000	0.000	0.000	0.000
• Congressional General Reductions	-	-			
• Congressional Directed Reductions	-	-			
• Congressional Rescissions	-	-			
• Congressional Adds	-	-			
• Congressional Directed Transfers	-	-			
• Reprogrammings	-	-			
• SBIR/STTR Transfer	-0.008	-			

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Exhibit R-2A, RDT&E Project Justification: PB 2024 Defense Health Agency										Date: March 2023		
Appropriation/Budget Activity 0130 / 2					R-1 Program Element (Number/Name) PE 0603002DHA / Medical Advanced Technology (AFRRI)				Project (Number/Name) 242A / Biodosimetry (USUHS)			
COST (\$ in Millions)	Prior Years	FY 2022	FY 2023	FY 2024 Base	FY 2024 OCO	FY 2024 Total	FY 2025	FY 2026	FY 2027	FY 2028	Cost To Complete	Total Cost
242A: <i>Biodosimetry (USUHS)</i>	0.611	0.209	0.218	0.222	0.000	0.222	0.226	0.231	0.260	0.265	Continuing	Continuing

A. Mission Description and Budget Item Justification

For the Uniformed Services University of the Health Sciences/Armed Forces Radiobiology Research Institute (USUHS/AFRRI), the Biodosimetry program addresses clinical symptoms of radiation exposure, reach back reference capabilities. Biodosimetry is the only method to detect, assess and estimate radiation dose exposure and is critical for military missions and saving lives. AFRRI prepared an in-depth Business Case Analysis and is strategically poised to establish the DoD's Advanced Biodosimetry Network (DABN), meeting the objective of US Senate Report SR 114-63. The established network would be complemented with the Diagnostic Biodosimetry Laboratory that aligns with the DoD Clinical Laboratory Improvement Program (CLIP). CLIP describes requirements within the respective DoD's Active and Reserve Components and facilities under their supervision to include oversight, inspections, proficiency testing (PT), personnel standards, and training in laboratories performing testing on human specimens so that clinical decisions can be made [reference DoDI 6440.02]". The Biodosimetry laboratory also received clinical specimens from the Fukushima radiation accident in 2011, showcasing USUHS/AFRRI's capabilities to support the DoD in case of an accidental radiation exposure or radiological terrorism scenario.

The Biodosimetry program capitalizes on findings under PE 0602787HP, Medical Technology, and from industry and academia to advance novel medical countermeasures into and through pre-clinical studies toward newly licensed products. Research findings are focused to advance the development and production of the following: (1) To establish clinically certified processes to permit rapid assessment of radiation exposed specimens; (2) To assess radiation exposure by developing and providing biological and biophysical dosimetry capabilities for acute, protracted, and prior radiation exposure; (3) To develop novel triage protocols for rapid assessment of radiation exposure; (4) To establish equipment triage automation to support the ability to manage mass-casualty radiation incidents around the globe.

B. Accomplishments/Planned Programs (\$ in Millions)

	FY 2022	FY 2023	FY 2024 Base	FY 2024 OCO	FY 2024 Total
Title: Biodosimetry (USUHS/AFRRI)	0.209	0.218	0.222	0.000	0.222
Description: The Biodosimetry program capitalizes on findings under PE 0602787HP, Medical Technology, and from industry and academia to advance novel medical countermeasures into and through pre-clinical studies toward newly licensed products.					
FY 2023 Plans:					
(1) To continue providing Department of Defense radiobiology – biodosimetry expert reach back support.					
(2) To participate in CBRNE/WMD NATO and military operations exercises.					
(3) To sustain laboratory clinical accreditation and competency in the cytogenetic biodosimetry service capability.					
(4) To implement quality control and quality assurance processes in order to preserve and ensure specimen testing and integrity supporting a transition of a research to clinical laboratory activities.					
(5) To sustain biodosimetry tools and biodosimetry expertise to support military relevant requirements.					

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Appropriation/Budget Activity 0130 / 2	R-1 Program Element (Number/Name) PE 0603002DHA / Medical Advanced Technology (AFRRI)	Project (Number/Name) 242A / Biodosimetry (USUHS)

B. Accomplishments/Planned Programs (\$ in Millions)	FY 2022	FY 2023	FY 2024 Base	FY 2024 OCO	FY 2024 Total
<p>(6) To establish processes to permit processing assessment of radiation exposure from specimens by testing the novel cytokinesis-block micronucleus assay (CBMN). The CBMN is a comprehensive system for measuring DNA damage, cytostasis and cytotoxicity. DNA damage events are scored specifically in once-divided binucleated (BN) cells and include (a) micronuclei (MNI), a biomarker of chromosome breakage and/or whole chromosome loss, (b) nucleoplasmic bridges (NPBs), a biomarker of DNA misrepair and/or telomere end-fusions, and (c) nuclear buds (NBUDs), a biomarker of elimination of amplified DNA and/or DNA repair complexes. Cytostatic effects are measured via the proportion of mono-, bi- and multinucleated cells and cytotoxicity via necrotic and/or apoptotic cell ratios. Further information regarding mechanisms leading to MNI, NPBs and NBUDs formation is obtained using centromere and/or telomere probes. The assay has the probability to be applied successfully for biomonitoring of in vivo genotoxic radiation exposure, in vitro radiation genotoxicity testing and in diverse research fields such as nutrigenomics and pharmacogenomics as well as a predictor of normal tissue and tumor radiation sensitivity and cancer risk.</p> <p>(7) To test the CBMN assay for triage automation and multivariable linear regression analysis to compare with already proven and globally accepted assays.</p> <p>(8) To establish a surge request procedure for cytogenetic analysis by developing sex and age-dependent CBMN dose-response calibrations curves and validate specimens cryopreservation protocols for delayed analysis using the metaphase-spread chromosome aberrations (i.e., DCA, PCC) assays.</p> <p>(9) To support the establishment of the Department of Defense Clinical Laboratory Improvement Program (CLIP) / Clinical Laboratory Improvement Amendments (CLIA) Clinical Biodosimetry laboratory with automated clinical specimen testing to manage mass-casualty radiation incidents around the globe.</p> <p>(10) To publish manuscripts and reports on research findings.</p> <p>FY 2024 Base Plans: FY 2024 plans are to continue efforts as outlined in FY 2023.</p> <p>FY 2024 OCO Plans: N/A</p> <p>FY 2023 to FY 2024 Increase/Decrease Statement: Pricing adjustment for inflation.</p>					
Accomplishments/Planned Programs Subtotals	0.209	0.218	0.222	0.000	0.222

C. Other Program Funding Summary (\$ in Millions) N/A

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Appropriation/Budget Activity 0130 / 2	R-1 Program Element (Number/Name) PE 0603002DHA / <i>Medical Advanced Technology (AFRRI)</i>	Project (Number/Name) 242A / <i>Biodosimetry (USUHS)</i>

C. Other Program Funding Summary (\$ in Millions)

Remarks

The program element 0602787DHA for AFRRI in addition to the three program elements: 0601115HP, 0602115HP, 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

Acquisition Strategy not required for Budget Activities 1, 2, 3, or 6 per DoD Financial Management Regulation (FMR) Volume 2B, Chapter 5, Paragraph 4.2.

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Appropriation/Budget Activity 0130 / 2					R-1 Program Element (Number/Name) PE 0603002DHA / Medical Advanced Technology (AFRRI)				Project (Number/Name) 242B / Radiation Countermeasures (USUHS)			
COST (\$ in Millions)	Prior Years	FY 2022	FY 2023	FY 2024 Base	FY 2024 OCO	FY 2024 Total	FY 2025	FY 2026	FY 2027	FY 2028	Cost To Complete	Total Cost
242B: Radiation Countermeasures (USUHS)	0.411	0.142	0.148	0.151	0.000	0.151	0.154	0.157	0.136	0.139	Continuing	Continuing

A. Mission Description and Budget Item Justification

Radiation Countermeasures (USUHS/AFRRI): For the Uniformed Services University of the Health Sciences/Armed Forces Radiobiology Research Institute (USUHS/AFRRI), 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, microbiome, gastrointestinal damage, neurobehavioral deficits, bone marrow damage), termed radiation combined injury (RCI). RCI's were observed at Hiroshima and Nagasaki, Japan, where 60-70% of victims received thermal burns concurrent with radiation injury. At the Chernobyl reactor meltdown, 10% of 237 victims exposed to radiation received thermal burns as well. In animal models of RCI including rat, guinea pig, dog, and swine, burns and wounds usually increase mortality after otherwise non-lethal radiation exposures. Consequences of RCI include acute myelosuppression, immune system inhibition, fluid imbalance, macro/microcirculation failure, massive cellular damage, and disruption of vital organ functions, which can lead to multiple organ dysfunction syndrome. There are different syndromes based on the time of manifestation in relation to radiation exposure; acute, delayed, late, and chronic syndromes. Acute radiation syndrome (ARS) is characterized by the differential response of the important organs to different doses of radiation. The ARS sub-syndromes include three major clinically-relevant pathologies; hematopoietic sub-syndrome (H-ARS), gastrointestinal sub-syndrome (GI-ARS), and neurovascular sub-syndrome (NV-ARS). Radiation countermeasures have been categorized as radioprotectors, radiomitigators, and therapeutics, based on the time of administration in relation to radiation exposure. The majority of countermeasures developed are for specific tissue injuries or specific syndromes. ARS is receiving the most attention, though other syndromes also need equal consideration.

Currently, treatments for ARS are limited; only the H-ARS has viable therapeutic options and even those are limited; Neupogen, Neulasta, Leukine, and Nplate. USUHS/AFRRI researchers made significant contributions in the initial development of the first three agents. These H-ARS treatments are genetically engineered recombinant growth factors or cytokines that were developed for other indication, were in clinic for long time, and recently repurposed for H-ARS. All U.S. Food and Drug Administration (FDA) approved agents for H-ARS are radiomitigators. No radioprotector, either for H-ARS or GI-ARS has yet been approved for human use.

Due to the increasing risk of nuclear and radiological terrorist attacks or accidents has renewed interest in developing radiation medical countermeasures. Our Radiation Countermeasures goals 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/or combination of FDA approved treatments 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.

It capitalizes on findings under PE 0602787HP, Medical Technology, and from industry and academia to advance novel medical countermeasures into and through pre-clinical studies toward newly licensed products. Research findings are focused to advance the understanding and to produce the following: (1) To identify new therapeutics candidates that show promising advancement for further development; (2) To develop novel technologies to minimize the use of animal models in the study

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of radiation countermeasure effects; (3) To investigate the overall radiation effect by countermeasures in various samples derived from animals for microbiome and anatomical tissue; (4) To find novel biomarkers, late effects and immunosuppression of radiation injury that can quantitate effects on combat performance decrements; (5) To identify novel therapeutic strategies that will support military operations within a nuclear or radiological environment minimizing ground troops short and long term adverse risk.

B. Accomplishments/Planned Programs (\$ in Millions)

	FY 2022	FY 2023	FY 2024 Base	FY 2024 OCO	FY 2024 Total
<p>Title: Radiation Countermeasures (USUHS)</p> <p>Description: Radiation Countermeasures (USUHS/AFRRI): For the Uniformed Services University of the Health Sciences/Armed Forces Radiobiology Research Institute (USUHS/AFRRI), 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, microbiome, gastrointestinal damage, neurobehavioral deficits, bone marrow damage), termed radiation combined injury (RCI). It capitalizes on findings under PE 0602787HP, Medical Technology, and from industry and academia to advance novel medical countermeasures into and through pre-clinical studies toward newly licensed products.</p> <p>FY 2023 Plans:</p> <p>(1) To continue ongoing studies using the cutaneous radiation injury in minipigs to analyze the skin microbiome before and after creation of clinically-relevant radiation lesions.</p> <p>(2) To perform transcriptomic studies with tissues of NHP exposed to radiation and treated with PEGylated interleukin-11.</p> <p>(3) To perform proteomic and metabolomic studies with serum samples of NHP exposed to radiation and treated with BBT-059.</p> <p>(4) To optimize and validate a proteomic protocol for validation of radiation biomarkers for countermeasure efficacy.</p> <p>(5) To study the dysfunctional signaling pathway resulting from countermeasure testing in NHP models.</p> <p>(6) Conduct microbiome studies with fecal samples of NHPs exposed to total-body (gamma-rays) and partial body (X-rays) radiation.</p> <p>(7) Conducted miRNA study using serum samples of irradiated NHPs.</p> <p>FY 2024 Base Plans: FY 2024 plans are to continue efforts as outlined in FY 2023.</p> <p>FY 2024 OCO Plans:</p>	0.142	0.148	0.151	0.000	0.151

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B. Accomplishments/Planned Programs (\$ in Millions)	FY 2022	FY 2023	FY 2024 Base	FY 2024 OCO	FY 2024 Total
N/A					
<i>FY 2023 to FY 2024 Increase/Decrease Statement:</i> Pricing adjustment for inflation.					
Accomplishments/Planned Programs Subtotals	0.142	0.148	0.151	0.000	0.151

C. Other Program Funding Summary (\$ in Millions)
N/A

Remarks
The program element 0602787DHA for AFRRI in addition to the three program elements: 0601115HP, 0602115HP, 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
Acquisition Strategy not required for Budget Activities 1, 2, 3, or 6 per DoD Financial Management Regulation (FMR) Volume 2B, Chapter 5, Paragraph 4.2.