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Exhibit R-2, RDT&E Budget Item Justification: PB 2023 Defense Health Agency **Date:** April 2022

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 2021	FY 2022	FY 2023 Base	FY 2023 OCO	FY 2023 Total	FY 2024	FY 2025	FY 2026	FY 2027	Cost To Complete	Total Cost
Total Program Element	1.015	0.352	0.359	0.366	0.000	0.366	0.373	0.380	0.388	0.396	Continuing	Continuing
242A: <i>Biodosimetry (USUHS)</i>	0.607	0.210	0.214	0.218	0.000	0.218	0.222	0.226	0.231	0.260	Continuing	Continuing
242B: <i>Radiation Countermeasures (USUHS)</i>	0.408	0.142	0.145	0.148	0.000	0.148	0.151	0.154	0.157	0.136	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 (?-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 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 computed tomography (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; (4) 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 2021</u>	<u>FY 2022</u>	<u>FY 2023 Base</u>	<u>FY 2023 OCO</u>	<u>FY 2023 Total</u>
Previous President's Budget	0.352	0.359	0.366	0.000	0.366
Current President's Budget	0.352	0.359	0.366	0.000	0.366
Total Adjustments	0.000	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	0.000	-			

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Exhibit R-2A, RDT&E Project Justification: PB 2023 Defense Health Agency										Date: April 2022		
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 2021	FY 2022	FY 2023 Base	FY 2023 OCO	FY 2023 Total	FY 2024	FY 2025	FY 2026	FY 2027	Cost To Complete	Total Cost
242A: <i>Biodosimetry (USUHS)</i>	0.607	0.210	0.214	0.218	0.000	0.218	0.222	0.226	0.231	0.260	Continuing	Continuing

A. Mission Description and Budget Item Justification

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 to produce the following: (1) To establish clinically certified processes to permit rapid assessment of radiation exposed specimens; (2) To access 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 2021	FY 2022	FY 2023 Base	FY 2023 OCO	FY 2023 Total
Title: Biodosimetry (USUHS/AFRRI)	0.210	0.214	0.218	0.000	0.218
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. Research findings are focused to advance the development and to produce the following: (1) To establish clinically certified processes to permit rapid assessment of radiation exposed specimens; (2) To access 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.					
In addition to the primary achievement of research objectives, the program educates Federal employees as a benefit to the public they serve through Federal service, through support to civil authorities, and in non-Federal professional and academic collaborations.					
FY21 Accomplishments: (1) Sustain efforts to establish a quality and assurance control plan for measurements of dose by cytogenetic chromosome aberration assay. (2) Continued the evaluation and validation of new radiation-responsive biomarkers in NHP and human models for biodosimetric diagnostic applications. (3) Established and extended the use of hematology biodosimetry algorithms for radiation-dose assessment using multiple cell-types biomarkers and animals.					

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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 2021	FY 2022	FY 2023 Base	FY 2023 OCO	FY 2023 Total
<p>(4) Established, optimized and validated radiation-induced DNA damage based on a quantitative long amplicon real-time PCR assay.</p> <p>(5) Developed a quantitative inhibition PCR assay of mitochondrial DNA using long- and short amplicon PCR using human samples.</p> <p>(6) Developed a quantitative inhibition PCR assay of mitochondrial DNA using long- and short amplicon PCR using mouse samples.</p> <p>(7) Extended the utility of the premature chromosome condensation (PCC) assay investigating the effects of PBI v/s TBI exposures to assess the fraction of the body exposed to radiation.</p> <p>(8) Validated the HIRI algorithm concept using animals (i.e., baboons, canine, and mice) dose-response databases for an extended time window up to 10 to 14 days after exposure.</p> <p>(9) Established a RICA algorithm for assessment of H-ARS severity using NHP radiation dose-response model based on CBC cell types biomarkers using the METREPOL system.</p> <p>(10) In 2019/2021, 15 manuscripts were published.</p> <p>FY 2022 Plans: FY 2022 and FY 2023 Plans: FY 2022 plans are to continue efforts as outlined in FY 2021 and to perform the following studies:</p> <p>(1) To establish processes to permit processing assessments of radiation exposure from specimens by testing the novel cytokinesis-block micronucleus cytome 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 have 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>(2) To test the CBMN assay for triage automation and multivariable linear regression analysis to compare with already proven and globally accepted assays.</p>					

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B. Accomplishments/Planned Programs (\$ in Millions)	FY 2021	FY 2022	FY 2023 Base	FY 2023 OCO	FY 2023 Total
<p>(3) 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>(4) To evaluate blood biomarkers to monitor radiation injury of radiation countermeasures.</p> <p>(5) To established the Department of Defense CLIP/CLIA Clinical Biodosimetry laboratory with automated clinical specimen testing to manage mass-casualty radiation incidents around the globe.</p> <p>FY 2023 Base Plans: FY 2023 plans are to continue efforts as outlined in FY 2022.</p> <p>FY 2023 OCO Plans: N/A</p> <p>FY 2022 to FY 2023 Increase/Decrease Statement: Pricing adjustment for inflation.</p>					
Accomplishments/Planned Programs Subtotals	0.210	0.214	0.218	0.000	0.218

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
USU optimizes these research funds to achieve its research objectives, often in partnership and collaboration with funding received from other DoD and interagency sources through Interagency Agreements and inter-service Support Agreements, which may be executed via Federal assistance agreements or contracts.

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Appropriation/Budget Activity 0130 / 2	R-1 Program Element (Number/Name) PE 0603002DHA / Medical Advanced Technology (AFRR)	Project (Number/Name) 242B / Radiation Countermeasures (USUHS)
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COST (\$ in Millions)	Prior Years	FY 2021	FY 2022	FY 2023 Base	FY 2023 OCO	FY 2023 Total	FY 2024	FY 2025	FY 2026	FY 2027	Cost To Complete	Total Cost
242B: Radiation Countermeasures (USUHS)	0.408	0.142	0.145	0.148	0.000	0.148	0.151	0.154	0.157	0.136	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 applied research for advanced development of biomedical strategies to prevent and treat health consequences from exposure to ionizing radiation. 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. Program objectives focus on preventing or mitigating the health consequences from exposures to ionizing radiation alone or in combination with other injuries, in the context of probable threats to US forces in current tactical, humanitarian and counterterrorism mission environments. Findings from basic and developmental research are integrated into highly focused advanced technology development studies yielding protective and therapeutic strategies.

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

	FY 2021	FY 2022	FY 2023 Base	FY 2023 OCO	FY 2023 Total
<p>Title: Radiation Countermeasures (USUHS)</p> <p>Description: Radiation Countermeasures (USU): For the Uniformed Services University of the Health Sciences (USU), this program supports applied research for advanced development of biomedical strategies to prevent and treat health consequences from exposure to ionizing radiation. 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. Program objectives focus on preventing or mitigating the health consequences from exposures to ionizing radiation alone or in combination with other injuries, in the context of probable threats to US forces in current tactical, humanitarian and counterterrorism mission environments. Findings from basic and developmental research are integrated into highly focused advanced technology development studies yielding protective and therapeutic strategies.</p> <p>In addition to the primary achievement of research objectives, the program educates Federal employees as a benefit to the public they serve through Federal service, through support to civil authorities, and in non-Federal professional and academic collaborations.</p> <p>FY21 Accomplishments:</p> <p>(1) There are several radiation countermeasures (BIO 300, TPOm, gamma-tocotrienol, BBT-059, PLX-R18, CDX 301) under advance development and few of them may be FDA approved in near future.</p>	0.142	0.145	0.148	0.000	0.148

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B. Accomplishments/Planned Programs (\$ in Millions)	FY 2021	FY 2022	FY 2023 Base	FY 2023 OCO	FY 2023 Total
<p>(2) Identified and evaluated the transcriptomic profiles of NHP brain compartments to profile the global transcriptomic changes in different brain compartments of NHPs exposed to radiation.</p> <p>(3) Performed the study of two new candidates EC-18 and YK-4-250.</p> <p>(4) Completed EC-18 study.</p> <p>(5) Completed 30 day survival efficacy for Myelo-001 and LA-GM-CFS</p> <p>(6) Performed safety study for YK-4-250</p> <p>(7) Performed 30 day survival efficacy study of EC-18 and YK-4-250.</p> <p>(8) Tested new candidates for basic toxicity and preliminary survival efficacy at a dose of LD70/30 to LD90/30.</p> <p>(9) In 2019/2021, 44 manuscripts were published.</p> <p>FY 2022 Plans: FY 2022 plans are to continue efforts as outlined in FY 2021 and to perform the following studies:</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 develop IL-18BP peptide as a radiation mitigator.</p> <p>(3) To perform transcriptomics studies with blood of NHP exposed to radiation and treated with PEGylated interleukin-11.</p> <p>(4) To perform proteomic and metabolomics studies with serum samples of NHP exposed to radiation and treated with BBT-059.</p> <p>(5) To optimize and validate a proteomic protocol for validation of radiation biomarkers for countermeasure efficacy.</p> <p>(6) To study the dysfunctional signaling pathway resulting from countermeasure testing in NHP models.</p> <p>FY 2023 Base Plans: FY 2023 plans are to continue efforts as outlined in FY 2022.</p> <p>FY 2023 OCO Plans: N/A</p> <p>FY 2022 to FY 2023 Increase/Decrease Statement: Pricing adjustment for inflation.</p>					
Accomplishments/Planned Programs Subtotals	0.142	0.145	0.148	0.000	0.148

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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

USU optimizes these research funds to achieve its research objectives, often in partnership and collaboration with funding received from other DoD and interagency sources through Interagency Agreements and inter-service Support Agreements, which may be executed via Federal assistance agreements or contracts.