| Exhibit R-2, RDT&E Budget Item Justification: PB 2024 Defense Health Agency | | | | | | | | | | | Date: March 2023 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Appropriation/Budget Activity<br>0130: *Defense Health Program I* BA 2: *RDT&E* | | | | | R-1 Program Element (Number/Name)<br>PE 0602787DHA *I Medical Technology (AFRRI)* | | | | | | | |
| **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 | 4.101 | 1.417 | 1.468 | 1.497 | 0.000 | 1.497 | 1.528 | 1.557 | 1.588 | 1.619 | Continuing | Continuing |
| 241A: *Biodosimetry (USUHS)* | 0.849 | 0.290 | 0.301 | 0.307 | 0.000 | 0.307 | 0.313 | 0.319 | 0.325 | 0.331 | Continuing | Continuing |
| 241B: *Internal Contamination (USUHS)* | 0.447 | 0.153 | 0.158 | 0.161 | 0.000 | 0.161 | 0.164 | 0.167 | 0.170 | 0.173 | Continuing | Continuing |
| 241C: *Radiation Countermeasures (USUHS)* | 2.805 | 0.974 | 1.009 | 1.029 | 0.000 | 1.029 | 1.051 | 1.071 | 1.093 | 1.115 | 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 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.

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 develop novel technologies to minimize the use of 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) | FY 2022 | FY 2023 | FY 2024 Base | FY 2024 OCO | FY 2024 Total |
|---|---|---|---|---|---|
| Previous President's Budget | 1.439 | 1.468 | 1.497 | 0.000 | 1.497 |
| Current President's Budget | 1.417 | 1.468 | 1.497 | 0.000 | 1.497 |
| Total Adjustments | -0.022 | 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 | -0.022 | - | | | |

| Exhibit R-2A, RDT&E Project Justification: PB 2024 Defense Health Agency | | | Date: March 2023 |
|---|---|---|---|
| Appropriation/Budget Activity<br>0130 / 2 | R-1 Program Element (Number/Name)<br>PE 0602787DHA / *Medical Technology (AFRRI)* | Project (Number/Name)<br>241A / *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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 241A: *Biodosimetry (USUHS)* | 0.849 | 0.290 | 0.301 | 0.307 | 0.000 | 0.307 | 0.313 | 0.319 | 0.325 | 0.331 | 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.

| B. Accomplishments/Planned Programs ($ in Millions) | FY 2022 | FY 2023 | FY 2024 Base | FY 2024 OCO | FY 2024 Total |
|---|---|---|---|---|---|
| ***Title:*** Biodosimetry (USUHS) | 0.290 | 0.301 | 0.307 | 0.000 | 0.307 |
| ***Description:*** Biodosimetry (USUHS/AFRRI): 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.<br><br>***FY 2023 Plans:***<br>(1) To establish biodosimetry research effort to identify, optimize, and validate candidate multiparameter-based biodosimetry assays applicable for military applications in both field deployable as well as reach-back reference laboratory for triage and definitive radiation injury and dose assessment.<br>(2) To investigate the use of a real-time PCR assay to quantify persistent radiation-induced DNA damage in human mitochondria DNA using long-cycle PCR methodology useful for biodosimetry applications.<br>(3) To evaluate blood biomarkers to monitor radiation injury of radiation countermeasures.<br>(4) To establish dual staining using two different fluorescence probes and to implement those in the automated cytokinesis blocked micronuclei assay. | | | | | |

| Exhibit R-2A, RDT&E Project Justification: PB 2024 Defense Health Agency | | Date: March 2023 |
|---|---|---|
| **Appropriation/Budget Activity**<br>0130 / 2 | **R-1 Program Element (Number/Name)**<br>PE 0602787DHA / *Medical Technology (AFRRI)* | **Project (Number/Name)**<br>241A / *Biodosimetry (USUHS)* |

| B. Accomplishments/Planned Programs ($ in Millions) | FY 2022 | FY 2023 | FY 2024 Base | FY 2024 OCO | FY 2024 Total |
|---|---|---|---|---|---|
| (5) To investigate the use of immuno-assay fluorescent staining of human centromeric proteins to enhance accurate detection of radiation-induced dicentric chromosomes using both metaphase spreads and premature chromosome condensation assays.<br>(6) To establish radiation dosimetry characterized mixed (neutron and gamma rays) field radiation fields and implement a laboratory intercomparison study with human blood samples to both establish necessary radiation calibration curves and blind test samples for radiation dose assessment.<br>(7) To publish manuscripts and report on research findings.<br>***FY 2024 Base Plans:***<br>FY 2024 plans are to continue efforts as outlined in FY 2023.<br>***FY 2024 OCO Plans:***<br>N/A<br>***FY 2023 to FY 2024 Increase/Decrease Statement:***<br>Pricing adjustment for inflation. | | | | | |
| **Accomplishments/Planned Programs Subtotals** | 0.290 | 0.301 | 0.307 | 0.000 | 0.307 |

**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.

| Exhibit R-2A, RDT&E Project Justification: PB 2024 Defense Health Agency | | | Date: March 2023 |
|---|---|---|---|
| Appropriation/Budget Activity<br>0130 / 2 | R-1 Program Element (Number/Name)<br>PE 0602787DHA / *Medical Technology (AFRRI)* | Project (Number/Name)<br>241B / *Internal Contamination (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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 241B: *Internal Contamination (USUHS)* | 0.447 | 0.153 | 0.158 | 0.161 | 0.000 | 0.161 | 0.164 | 0.167 | 0.170 | 0.173 | Continuing | Continuing |

**A. Mission Description and Budget Item Justification**

Internal Contamination (USUHS): For the Uniformed Services University of the Health Sciences/Armed Forces Radiobiology Research Institute (USUHS/AFRRI), the stated goal of the Internal Contamination and Metal Toxicity Program is to determine whether the short- and long-term radiological and toxicological risks of inhaled, ingested, or embedded metals warrant changes in the fragment removal policies for military personnel and, in the case of internalized radiological hazards, to investigate treatment strategies to enhance elimination of these metals from the body. To that end, our current research priorities are to investigate the health effects of embedded military relevant metals with the aim of identifying a battery of biomarkers to indicate the potential of adverse health effects so that proper treatment paradigms, including surgical removal of the fragment, can be undertaken at the appropriate time. Results from this research will also inform military decision-makers as to whether the fragment removal policy for particular metals needs to be reassessed. In the event that these embedded fragments are radioactive, a thorough understanding of the biokinetics of the metal is essential. Treatment strategies to enhance the elimination of internalized radionuclides are also being investigated, with innovative approaches such as chemical molecularly imprinted polymers and dendrimer complexes at the forefront. Outside collaborations with private industry also provides opportunities to identify and screen novel countermeasures for internal contamination.

Research findings are focused to advance the development and to produce the following: (1) effective therapeutics to enhance the elimination of internalized radionuclides; (2) chemically synthesized imprinted polymers with high specific metal binding capabilities (3) novel chemical synthesis and in vitro systems to determine cytotoxicity issues in order to minimize the use of animal models in the study.

| B. Accomplishments/Planned Programs ($ in Millions) | FY 2022 | FY 2023 | FY 2024 Base | FY 2024 OCO | FY 2024 Total |
|---|---|---|---|---|---|
| ***Title:*** Internal Contamination (USUHS) | 0.153 | 0.158 | 0.161 | 0.000 | 0.161 |
| ***Description:*** Internal Contamination (USUHS): 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 organic chemical synthesis (Molecularly Imprinted Polymer (MIPs), the novel development of gastrointestinal organ-on-chip technology and studies on the gut microbiome approaches to address this pressing health concern. First, MIPs have been shown to be highly-efficient and specific metal chelators. In order to expand the applicability of this approach, we synthesize chelation moieties onto dendritic polymer (dendrimers). Dendrimers are non-toxic, highly branched three-dimensional structures whose synthesis can be tightly controlled to yield a product of precise shape and size, thus, becoming highly-specific metal binders and can be tested as therapeutic agents | | | | | |

| Exhibit R-2A, RDT&E Project Justification: PB 2024 Defense Health Agency | | Date: March 2023 |
|---|---|---|
| **Appropriation/Budget Activity**<br>0130 / 2 | **R-1 Program Element (Number/Name)**<br>PE 0602787DHA / *Medical Technology (AFRRI)* | **Project (Number/Name)**<br>241B / *Internal Contamination (USUHS)* |

| B. Accomplishments/Planned Programs ($ in Millions) | FY 2022 | FY 2023 | FY 2024 Base | FY 2024 OCO | FY 2024 Total |
|---|---|---|---|---|---|
| for internalized radionuclides. Second, the development of organ-on-chip technology will lead to minimized use of animal models in the study of internal radiation effects. The model utilizes intestinal cell types and three dimensional architecture to mimic intestinal physiology and pathology. This novel 3D culture system will mimic the in vivo animal model and provide new stratagem to investigate the radiation induced gastrointestinal syndrome. This program also explores the internal radiation effects on the gut microbiome, understanding that alterations in the microbiome will share similar pathologic characteristics such as reduced bacterial diversity and the emergence of opportunistic pathogens that provide diagnostics and therapeutic targets. Determining the effect of ionizing radiation on altering the gut microbiome will reveal the effect on physiology, cell survival, inflammation, cytokine expression and metabolism.<br><br>***FY 2023 Plans:***<br>(1) The Department of Defense and Department of Veterans Affair recognized the need for a better understanding of the health effects of embedded metal fragments and enhanced health surveillance of personnel suffering from such injuries. In response, the Department of Defense Health Affairs issued a directive instructing surgeons to save any excised fragments for further analysis so that the metals could be identified. In addition, the directive compiled a list of “metals of concern” to enhance patient follow-up with the establishment of the Toxic Embedded Fragment Center at the Baltimore VA Medical Center in order to follow-up with service members. These developments led to further collaborations between USUHS/AFRRI and the Baltimore DVA, University of Maryland School of Medicine, U.S. FDA, and the University of Kentucky resulting in receiving support by a Congressionally Directed Medical Research Program (CDMRP) funded project.<br>(2) Research team will validate signaling pathways by western blot and compare protein expression with age matched control minipig tissues.<br>(3) Research team will perform enzyme-linked immunosorbent assay (ELISA) for protein markers for gut leakage/intestinal permeability to support disruption of gut microflora to confirm the data from microbiome analysis.<br>(4) Team will continue with validation of small molecules for gut organ-on-chip model in murine model.<br>(5) An ongoing study to determine the effect of aurin tricarboxylic acid (ATA), a potential countermeasure against internal contamination continues (NIH funding).<br>(6) An effort to expand AFRRI/USUHS research on internal contamination to include toxic chemicals and metals inhaled in burn pits is planned.<br><br>***FY 2024 Base Plans:*** | | | | | |

| Exhibit R-2A, RDT&E Project Justification: PB 2024 Defense Health Agency | | Date: March 2023 |
|---|---|---|
| **Appropriation/Budget Activity**<br>0130 / 2 | **R-1 Program Element (Number/Name)**<br>PE 0602787DHA / *Medical Technology (AFRRI)* | **Project (Number/Name)**<br>241B / *Internal Contamination (USUHS)* |

| B. Accomplishments/Planned Programs ($ in Millions) | FY 2022 | FY 2023 | FY 2024 Base | FY 2024 OCO | FY 2024 Total |
|---|---|---|---|---|---|
| FY 2024 plans continue efforts as outlined in FY 2023.<br>***FY 2024 OCO Plans:***<br>N/A<br>***FY 2023 to FY 2024 Increase/Decrease Statement:***<br>Pricing adjustment for inflation. | | | | | |
| **Accomplishments/Planned Programs Subtotals** | 0.153 | 0.158 | 0.161 | 0.000 | 0.161 |

**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.

| Exhibit R-2A, RDT&E Project Justification: PB 2024 Defense Health Agency | | | Date: March 2023 |
|---|---|---|---|
| Appropriation/Budget Activity<br>0130 / 2 | R-1 Program Element (Number/Name)<br>PE 0602787DHA / *Medical Technology (AFRRI)* | Project (Number/Name)<br>241C / *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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 241C: *Radiation Countermeasures (USUHS)* | 2.805 | 0.974 | 1.009 | 1.029 | 0.000 | 1.029 | 1.051 | 1.071 | 1.093 | 1.115 | 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 or CNS-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. A new program and approach has been added to address non-lethal or low-dose radiation health effects that could compromise combat operations if left undiagnosed. Once potential health effects are identified, countermeasures for these non-lethal health effects will be addressed.

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 indications 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 range 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.

| Exhibit R-2A, RDT&E Project Justification: PB 2024 Defense Health Agency | | Date: March 2023 |
|---|---|---|
| **Appropriation/Budget Activity**<br>0130 / 2 | **R-1 Program Element (Number/Name)**<br>PE 0602787DHA / *Medical Technology (AFRRI)* | **Project (Number/Name)**<br>241C / *Radiation Countermeasures (USUHS)* |

| B. Accomplishments/Planned Programs ($ in Millions) | FY 2022 | FY 2023 | FY 2024 Base | FY 2024 OCO | FY 2024 Total |
|---|---|---|---|---|---|
| ***Title:*** Radiation Countermeasures (USUHS) | 0.974 | 1.009 | 1.029 | 0.000 | 1.029 |
| ***Description:*** For the Uniformed Services University of the Health Sciences/Armed Forces Radiobiology Research Institute (USUHS/AFRRI), the Radiation Countermeasures 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. Research findings are focused to advance the understanding and to produce the following: (1) To identify new therapeutic candidates that show promising advancement for further development; (2) To develop novel technologies to minimize the use of animal models in the study of radiation countermeasure effects; (3) To investigate the overall radiation effect by countermeasures 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.<br><br>***FY 2023 Plans:***<br>(1) To complete methylome and proteome studies and identify early epigenomic steps post-radiation caused by LDR/LDR neutron exposure to murine stem cells populations as potential low dose exposure markers using multiple analytical bioinformatics programs.<br>(2) To down-select potential gut-organ-on-chip small molecule and test for efficacy in murine model.<br>(3) To screen one potential prophylactic countermeasure in the partial body irradiation model with 2.5% sparing of bone marrow.<br>(4) To perform neutron/gamma radiation with single 3D cell culture.<br>(5) To perform neutron/gamma radiations with endothelium/immune cell 3D cultures.<br>(6) To determine DRF for promising candidates.<br>(7) To determine hematological end points to assess recovery from H-ARS.<br>(8) To analyze specimens of the jejunum after lethal irradiation in mice treated with FDA-approved therapeutics.<br>(9) To identify other animal models where various anatomical sites (e.g. intestinal, oral, cutaneous, pulmonary, and urinary, etc) can be interrogated for microbiome alterations.<br>(10) To test IL-18BP efficacy using the in vitro Caco2 IL-18 receptor knockout cell line and 3D cell culture.<br>(11) To optimize the gastro-intestinal organ-on-chip model using intestinal cell lines to mimic the 3D architecture of the intestinal physiology. | | | | | |

| Exhibit R-2A, RDT&E Project Justification: PB 2024 Defense Health Agency | | Date: March 2023 |
|---|---|---|
| **Appropriation/Budget Activity**<br>0130 / 2 | **R-1 Program Element (Number/Name)**<br>PE 0602787DHA / *Medical Technology (AF RRI)* | **Project (Number/Name)**<br>241C / *Radiation Countermeasures (USUHS)* |

| B. Accomplishments/Planned Programs ($ in Millions) | FY 2022 | FY 2023 | FY 2024 Base | FY 2024 OCO | FY 2024 Total |
|---|---|---|---|---|---|
| (12) To define biomarkers of neurobehavioral deficits following low-dose exposure.<br>(13) To identify circulating miRNAs at different time points following low-dose irradiation.<br>(14) To determine the relationship between circulating miRNAs and neurobehavioral deficits.<br>(15) To identify miRNA in exosomes from radiation exposed human primary cell lines that target CXCR4 receptor in recipient cells that facilitate proliferation or neutrophil progenitors using high-throughput methods.<br>(16) To determine the effect of exosome-packed selected miRNA on the release of neutrophils from BM cells using in vitro BM model, and their interactions with G-CSF and GM-CSF, with gamma radiation.<br>(17) To identify additional health effects from low dose mixed field radiation.<br>(18) To identify additional health effects from chronic low dose gamma “Fallout” type radiation.<br>(19) To establish a partial body irradiation with 5% BM protection (PBI/BM5) mouse model, and study the radiation-induced multiple organ injuries including gastrointestinal (GI), Lung, heart, brain and kidney using the PBI/BM5 model.<br>(20) To evaluate the mitigative effects of IL-18BP on survival of radiation-induced GI injury using PBI/BM5 mouse model.<br>(21) To identify the effects of intestinal microbiota and their metabolites on radiation-induced injury in a mouse model.<br>(22) To test if gut-microbiome-derived L-histidine treatment after irradiation combined with wound injury increases survival and organ repair.<br>(23) To test if gut-microbiome-derived L-histidine treatment before or after irradiation combined with wound injury changes ATP production and mitochondrial remodeling.<br>***FY 2024 Base Plans:***<br>FY 2024 plans continue efforts as outlined in FY 2023.<br>***FY 2024 OCO Plans:***<br>N/A<br>***FY 2023 to FY 2024 Increase/Decrease Statement:***<br>Pricing adjustment for inflation. | | | | | |
| **Accomplishments/Planned Programs Subtotals** | 0.974 | 1.009 | 1.029 | 0.000 | 1.029 |

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

N/A

| Exhibit R-2A, RDT&E Project Justification: PB 2024 Defense Health Agency | | Date: March 2023 |
|---|---|---|
| **Appropriation/Budget Activity**<br>0130 / 2 | **R-1 Program Element (Number/Name)**<br>PE 0602787DHA / *Medical Technology (AFRRI)* | **Project (Number/Name)**<br>241C / *Radiation Countermeasures (USUHS)* |

**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.