Exhibit R-2, RDT&E Budget Item Justification: FY 2018 Defense Health Agency											Date: May 2017	
Appropriation/Budget Activity 0130: *Defense Health Program* / BA 2: *RDT&E*					R-1 Program Element (Number/Name) PE 0602787DHA / *Medical Technology (AFRRI)*							
COST ($ in Millions)	**Prior Years**	**FY 2016**	**FY 2017**	**FY 2018 Base**	**FY 2018 OCO**	**FY 2018 Total**	**FY 2019**	**FY 2020**	**FY 2021**	**FY 2022**	**Cost To Complete**	**Total Cost**
Total Program Element	7.002	1.131	1.242	1.331	-	1.331	1.356	1.383	1.411	1.439	Continuing	Continuing
020: *CSI - Congressional Special Interests*	0.124	0.000	0.000	0.000	-	0.000	0.000	0.000	0.000	0.000	Continuing	Continuing
241A: *Biodosimetry (USUHS)*	1.403	0.231	0.254	0.272	-	0.272	0.277	0.283	0.289	0.295	Continuing	Continuing
241B: *Internal Contamination (USUHS)*	0.730	0.121	0.133	0.143	-	0.143	0.146	0.149	0.152	0.155	Continuing	Continuing
241C: *Radiation Countermeasures (USUHS)*	4.745	0.779	0.855	0.916	-	0.916	0.933	0.951	0.970	0.989	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 2016	FY 2017	FY 2018 Base	FY 2018 OCO	FY 2018 Total
Previous President's Budget	1.222	1.242	1.331	-	1.331
Current President's Budget	1.131	1.242	1.331	-	1.331
Total Adjustments	-0.091	0.000	0.000	-	0.000
• Congressional General Reductions	-	-			
• Congressional Directed Reductions	-	-			
• Congressional Rescissions	-	-			
• Congressional Adds	-	-			
• Congressional Directed Transfers	-	-			
• Reprogrammings	-	-			
• SBIR/STTR Transfer	-0.091	-			

Congressional Add Details ($ in Millions, and Includes General Reductions)	FY 2016	FY 2017
Project: 020: *CSI - Congressional Special Interests*		
Congressional Add: *472A – Program Increase: Restore Core Research Funding Reduction (USUHS)*	0.000	-

Exhibit R-2, RDT&E Budget Item Justification: FY 2018 Defense Health Agency	Date: May 2017
Appropriation/Budget Activity 0130: *Defense Health Program I* BA 2: *RDT&E*	**R-1 Program Element (Number/Name)** PE 0602787DHA *I Medical Technology (AFRRI)*

Congressional Add Details ($ in Millions, and Includes General Reductions)	FY 2016	FY 2017
Congressional Add Subtotals for Project: 020	0.000	-
Congressional Add Totals for all Projects	0.000	-

Change Summary Explanation

FY 2016: Realignment from Defense Health Program, Research, Development, Test and Evaluation (DHP RDT&E), PE 0602787-Medical Technology (AFRRI) (-$0.091 million) to DHP RDT&E PE 0605502-Small Business Innovation Research (SBIR) / Small Business Technology Transfer (STTR) Program (+$0.091 million).

FY 2017: No Change.

FY 2018: No Change.

Exhibit R-2A, RDT&E Project Justification: FY 2018 Defense Health Agency			Date: May 2017
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 2016	FY 2017	FY 2018 Base	FY 2018 OCO	FY 2018 Total	FY 2019	FY 2020	FY 2021	FY 2022	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)	FY 2016	FY 2017
Congressional Add: 472A – Program Increase: Restore Core Research Funding Reduction (USUHS)	0.000	-
FY 2016 Accomplishments: No Funding Programmed.		
Congressional Adds Subtotals	0.000	-

C. Other Program Funding Summary ($ in Millions)

N/A

Remarks

D. Acquisition Strategy

N/A

E. Performance Metrics

N/A

Exhibit R-2A, RDT&E Project Justification: FY 2018 Defense Health Agency			Date: May 2017
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 2016	FY 2017	FY 2018 Base	FY 2018 OCO	FY 2018 Total	FY 2019	FY 2020	FY 2021	FY 2022	Cost To Complete	Total Cost
241A: *Biodosimetry (USUHS)*	1.403	0.231	0.254	0.272	-	0.272	0.277	0.283	0.289	0.295	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 2016	FY 2017	FY 2018
Title: Biodosimetry (USUHS)	0.231	0.254	0.272
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 2016 Accomplishments: Sustained studies evaluating radiation-responsive biomarkers in animal models for early-phase and organ-specific bioindicators. Provided necessary proof-of-concept dose-response data to transition combined proteomic and hematological concept for further development of diagnostic devices (i.e., hand-held, field deployable). Reported on hematology and blood serum chemistry data collected in NHP radiation study with limited- and full-supportive care (G-CSF, antibiotics, blood transfusions, etc.) to evaluate radiation damage to specific organs. Continued efforts to establish robust cytogenetic biodosimetry capability; initiated studies to characterize length ratio (ratio of longest to smallest chromosome) using premature chromosome condensation assay in irradiated lymphocytes. Evaluated diagnostic utility of urinary radiation biomarkers using radiation doses (0 Gy, 1 Gy, 3.5 Gy, 5.0 Gy, 6.5 Gy and 8.5 Gy) in nonhuman primate model between 1-30 days post-irradiation; Completed analysis of urinary amylase and CRP where results were not correlated with radiation dose; Measured changes in urine IL-18 expression up to 5 days post-irradiation, showing diagnostic usefulness for distinguishing radiation exposure. Evaluated 5 of total 18 proposed new radiation-responsive protein biomarkers in mouse and nonhuman primate (NHP) total-body irradiation (TBI) models for early-phase and organ-specific damage. Plasma citrullinated proteins were evaluated as potential new biomarkers of epithelial radiation-induced small bowel damage in animal models using commercially available antibodies and assays developed at AFRRI by Dr. Ossetrova (Ossetrova NI. “Immunoassays for Citrullinated Proteins”, PCT/US2009/061660, filed on October 22, 2009, claiming priority to U.S. Provisional Application No. 61/107,446, filed on October 22, 2008. US Patent Number 9,063,148 issued on 6/23/2015).			

Exhibit R-2A, RDT&E Project Justification: FY 2018 Defense Health Agency		Date: May 2017
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 2016	FY 2017	FY 2018
Citrullinated proteins evaluated as new predictive radiation-responsive biomarkers in animal model acute radiation sickness (ARS). Completed analyses of hematology and blood serum chemistry collected in NHP dose-response study with limited and full supportive care (i.e., G-CSF or Neupogen® [filgrastim], antibiotics, blood transfusions, etc.) to evaluate radiation damage to specific organs. Completed analyses of necropsies performed on NHPs in studies with limited and full supportive care (i.e., G-CSF or Neupogen® [filgrastim], antibiotics, blood transfusions, etc.) to determine radiation dose-dependent damage to different organs/tissues and correlate those results with levels of already evaluated tissue/organ-specific protein biomarkers. Some results/data from NHP dose-response TBI (photon/low LET) studies were compared with results collected from radiation accident victims and radiation therapy patients, which revealed very good similarities. Reported on development of IL-18 and IL-18 binding protein (IL-18BP) as dual biomarkers for assessment of radiation dose, severity and lethality in mice after TBI. Reported microRNA-30, as a radiation biomarker, inhibits antiapoptotic factor Mcl-1 and induces apoptosis in mouse and human hematopoietic cells after radiation exposure. Identified two hematology and leukemia markers during leukemogenesis that were differentially expressed at early and late phases of transformation. Determined that epigenetic changes, i.e., histone acetylation markers, could discriminate between differences in dose rate at low doses (<10 cGy).			
FY 2017 Plans: Perform partial-body radiation exposure study to characterize organ specific injury biomarkers using abdomen exposures of mice. Initiate studies to evaluate radiation-induced chromosomal damage in murine radiation model. Develop multivariate discriminate model using several endpoints measured in premature chromosome condensation assay to assess radiation dose. Establish partial-body radiation model using mice involving exposure of abdomen with AFRRI's small animal irradiator to support studies identifying and validating organ (i.e., small intestine, kidney) injury biomarkers. Initiate use of commercially available automated dicentric scoring software to generate dose-response for dicentric yields in irradiated lymphocytes. Participate in annual performance evaluations to demonstrate accuracy in dose assessment by cytogenetics. Evaluate correlations between levels of radiation biomarkers (IL-18, IL-18BP and miR-34) and survival rate in individual mice 1 to 40 days after radiation. Evaluate effects and mechanisms of proinflammatory cytokine IL-18 and IL-18BP in radiation-induced cell damage and apoptosis pathways. Develop circulating miRNA profile in serum from mice exposed to different doses of gamma-radiation mouse serum using miRNA microarray and quantitative reverse transcription (RT)-real-time-polymerase chain reaction (PCR). Study signal pathways regulated by miRNAs in response to different radiation doses. Continue with further analysis of natural history of diagnostic usefulness of urine IL-18 with remaining samples using archived nonhuman primate samples. Apply IL-18 biomarker in combination with blood biomarkers in multivariate regression analysis approach for estimating degree of radiation injury/exposure. Continue evaluating new predictive radiation-responsive biomarkers in animal models for prediction of ARS severity and outcome. Continue studies to evaluate new radiation-responsive biomarkers in animal models for early-phase and organ-specific damage. Continue correlating other early-phase and organ-specific damage biomarkers with results of necropsies performed on NHPs in studies with limited and full supportive care (i.e., G-CSF or Neupogen® [filgrastim], antibiotics, blood transfusions, etc.) to determine radiation dose-dependent damage to different organs/tissues. Continue comparing results/data from NHP dose-			

Exhibit R-2A, RDT&E Project Justification: FY 2018 Defense Health Agency		Date: May 2017
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 2016	FY 2017	FY 2018
response TBI (photon/low LET) studies with data collected from radiation accident victims and radiation therapy patients. Continue evaluating new predicative radiation-responsive biomarkers in animal models for a prediction of the ARS severity and outcome. Evaluate additional hematology and leukemia markers during leukemogenesis that are differentially expressed at early and late phases of transformation. Identify additional epigenetic changes that discriminate between differences in dose rate at low doses (<10 cGy). ***FY 2018 Plans:*** Establish suite of biodosimetry analysis software tools and standard operating procedures to support analysis of chromosomal aberrations used in radiation dose assessment. Establish dose-response for dicentric yields in irradiated lymphocytes using automated dicentric scoring software utility. Perform dose response study measuring dicentric chromosomal aberrations after exposure to mixed neutron and photon radiation. Identify radiation-responsive targets (i.e., miRNA, proteomic) specific to radiation sensitive organ systems in mouse partial-body exposure model. Participate in annual performance evaluations to demonstrate accuracy in dose assessment by cytogenetics; implement processes to enhance throughput capability for processing and scoring of chromosomal aberrations. Establish partial-body animal radiation models (mouse) using low-LET/photon exposure with AFRRI small-animal irradiator (for mice) to assess organ-specific radiation injury biomarkers evaluated earlier in low-LET TBI studies. Establish partial-body animal radiation models (mouse and NHP) using low-LET/photon exposure with AFRRI small-animal irradiator (for mice) and LINAC (for NHPs) to assess organ-specific radiation injury biomarkers evaluated earlier in low-LET TBI studies. Establish mouse TBI model for combined hematological and proteomic biodosimetry approach following mixed-field (neutrons and photons, high-LET) in addition to one already established and evaluated for a pure photon (60Co gamma-rays, low-LET) exposure. Develop IL-18 and IL-12 as dual radiation biomarkers in non-human primate urine for assessment of radiation doses, severity and lethality after TBI. Develop miRNA profile in urine of gamma-irradiated NHPs using miRNA microarray and quantitative RT-PCR. Compare miRNA profiles in gamma-irradiated mouse serum and NHP urine and identify sensitive and accurate radiation biomarkers. Evaluate effects of low and moderate doses of gamma-radiation on hematopoietic and immune system of mice (in vivo) and human cells (in vitro). Evaluate mechanisms of radiation-induced lymphocyte damage. Evaluate additional hematology and leukemia markers during leukemogenesis that are differentially expressed at early and late phases of transformation. Identify additional epigenetic changes that discriminate between differences in dose rate at low doses (<10 cGy).			
Accomplishments/Planned Programs Subtotals	0.231	0.254	0.272

C. Other Program Funding Summary ($ in Millions)

N/A

Remarks

D. Acquisition Strategy

N/A

Exhibit R-2A, RDT&E Project Justification: FY 2018 Defense Health Agency		Date: May 2017
Appropriation/Budget Activity 0130 / 2	**R-1 Program Element (Number/Name)** PE 0602787DHA / *Medical Technology (AFRRI)*	**Project (Number/Name)** 241A / *Biodosimetry (USUHS)*

E. Performance Metrics

By FY 2016
- Demonstrate accuracy in dose assessment by cytogenetics chromosomal aberration assay in blind exercise.
- Report on efforts to provide algorithms to convert radiation-responsive biomarkers data to radiation dose and injury.
- Complete analysis of archived AFRRI NHP urine samples (1-30 days post-irradiation) for variations in NHP urine metabolite levels, amylase and C-reactive protein, and IL-18 associated with different radiation doses (0 Gy, 1 Gy, 3.5 Gy, 5.0 Gy, 6.5 Gy and 8.5 Gy (in collaboration with NIH using tandem mass spectroscopy, WRAIR).
- Continue analyses of blood samples from mouse and NHP TBI models to identify novel tissue- and organ-specific biomarkers.
- Continue correlating other early-phase and organ-specific damage biomarkers with results of necropsies performed on NHPs in studies with limited and full supportive care (i.e., G-CSF or Neupogen® [filgrastim], antibiotics, blood transfusions, etc.) to determine radiation dose-dependent damage to different organs/tissues.
- Complete analyses of blood serum chemistry collected in NHP dose-response studies with limited and full supportive care (i.e., G-CSF or Neupogen® [filgrastim], antibiotics, blood transfusions, etc.) to evaluate radiation damage to specific organs.
- Provide proof-of-concept dose-response data to transition combined proteomic and hematological concept for further development of diagnostic devices (i.e., hand-held, field deployable) in support of FDA approval.

By FY 2017
- Perform initial analysis of multiple parameter biodosimetry assessment using murine partial-body exposure model.
- Establish use of automated metaphase finder to enhance throughput for processing samples and automated scoring of dicentrics.
- Evaluate correlations between levels of radiation biomarkers (IL-18, IL-18BP and miR-34) and survival rates in individual mice 1 to 40 days after radiation.
- Report on further analysis of IL-18 and develop algorithm using IL-18 as significant variable for use in combination with archived complete blood count and serum chemistry data (from same NHP dataset) for estimating radiation injury.
- Develop biomarkers which can identify “treatment-point” in individual mice after radiation injury.
- Identify the network of miRNAs and their targeted mRNAs in radiation-induced apoptotic signal pathways.
- Continue evaluating new early-phase and organ-specific damage radiation-responsive biomarkers in animal models.
- Continue comparing and correlating hematology, blood serum chemistry, protein biomarkers and necropsy results in NHP dose-response study to evaluate radiation damage to specific organs.
- Continue comparing results/data from NHP dose-response TBI (photon/low LET) studies with data collected from radiation accident victims and radiation therapy patients.
- Continue refining combination of radiation biomarkers in blood with best balance of discrimination, sensitivity and specificity.
- Continue evaluating the predictive radiation-responsive biomarkers in animal models for prediction of ARS severity and outcome.
- Measure specific methylation and histone changes using RT-PCR in low dose and high dose exposed murine spleen samples.

By FY2018
- Characterize partial-body animal radiation models (murine) using animals involving low-LET exposure with AFRRI small-animal irradiator (for mice) to identify organ-specific radiation injury biomarkers evaluated earlier in low-LET TBI studies.
- Initiate studies to characterize cytogenetic chromosomal aberration yields following exposure to neutron and photon mixed field sources.

Exhibit R-2A, RDT&E Project Justification: FY 2018 Defense Health Agency		Date: May 2017
Appropriation/Budget Activity 0130 / 2	**R-1 Program Element (Number/Name)** PE 0602787DHA / *Medical Technology (AFRRI)*	**Project (Number/Name)** 241A / *Biodosimetry (USUHS)*

- Perform mass-casualty exercise to test throughput capability in dose assessment by cytogenetics.
- Continue scoring dicentric aberrations following exposure to neutron and photon mixed field exposures.
- Establish partial-body animal radiation models (mouse and NHP) using low-LET photon exposure with AFRRI small-animal irradiator (for mice) and LINAC (for NHPs) to identify organ-specific radiation injury biomarkers evaluated earlier in low-LET TBI studies.
- Establish mouse TBI model for combined hematological and proteomic biodosimetry following 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.
- Develop miRNA profile for urine of gamma-irradiated NHPs urine using miRNA microarray and quantitative RT-PCR.
- Evaluate IL-18 and IL-12 as dual radiation biomarkers in NHP urine.
- Evaluate effects of low-moderate doses of gamma-radiation on hematopoietic and immune cell injury.
- Develop miRNA profile and identify sensitive and accurate biomarkers in mouse and human hematopoietic and immune cells after low-moderate doses radiation exposure.
- Evaluate effects of low-moderate doses of radiation on induced proinflammatory factor activation in mouse thymus, BM and spleen cells and human CD34+ cells.
- Ascertain mechanisms by which low-moderate doses of radiation induce stress responses in mouse and human immune and hematopoietic cells, and lymphocyte depletion.
- Initiate murine leukemia model to concomitantly predict leukemia development based on epigenetic markers identified in FY16 and FY17.

Exhibit R-2A, RDT&E Project Justification: FY 2018 Defense Health Agency			Date: May 2017
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 2016	FY 2017	FY 2018 Base	FY 2018 OCO	FY 2018 Total	FY 2019	FY 2020	FY 2021	FY 2022	Cost To Complete	Total Cost
241B: *Internal Contamination (USUHS)*	0.730	0.121	0.133	0.143	-	0.143	0.146	0.149	0.152	0.155	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 2016	FY 2017	FY 2018
Title: Internal Contamination (USUHS)	0.121	0.133	0.143

Description: 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.

FY 2016 Accomplishments:
Began synthesis of molecularly imprinted polymers using non-radioactive templates to assess potential of using these non-hazardous surrogates to prepare compounds for decorporation of high-specific activity radionuclides. Completed assessment of surrogate-templated molecularly imprinted polymers with respect to binding specificity and initiated cytotoxicity assessments.

FY 2017 Plans:
Continue assessment of surrogate-templated molecularly imprinted polymers with respect to binding specificity. Initiate cytotoxicity assessments of newly synthesized molecularly imprinted polymers.

FY 2018 Plans:
Continue cytotoxicity testing of surrogate-templated molecularly imprinted polymers; begin assessment of extracorporeal decorporation ability in laboratory rat model. Design feasibility study to assess potential of chemically-modified dendrimeric structures as radionuclide decorporation agents. Design feasibility study to assess potential of chemically-modified dendrimeric structures as radionuclide decorporation agents. Continue assessment of dendrimeric structures as potential radionuclide

Exhibit R-2A, RDT&E Project Justification: FY 2018 Defense Health Agency		Date: May 2017
Appropriation/Budget Activity 0130 / 2	**R-1 Program Element (Number/Name)** PE 0602787DHA / *Medical Technology (AFRRI)*	**Project (Number/Name)** 241B / *Internal Contamination (USUHS)*

B. Accomplishments/Planned Programs ($ in Millions)	FY 2016	FY 2017	FY 2018
decorporation agents as regards specificity, binding strength and cytotoxicity. Initiate a study to determine if non-toxic plant-based metal chelators can be effectively used as radionuclide decorporation agents.			
Accomplishments/Planned Programs Subtotals	0.121	0.133	0.143

C. Other Program Funding Summary ($ in Millions)

N/A

Remarks

D. Acquisition Strategy

N/A

E. Performance Metrics

By FY 2017
- Complete molecularly imprinted polymer binding specificity studies; initiate cytotoxicity assessments.

By FY2018
- Complete cytotoxicity and extracorporeal decorporation assessments of surrogate-templated molecularly imprinted polymers.

By FY2019
- Initiate study into feasibility of chemically-modified dendrimeric structures as radionuclide decorporation agents.

By FY2020
- Complete feasibility study on the use of chemically-modified dendrimeric structures as radionuclide decorporation agents and determine if continued investigation is warranted.

By FY2021
- Initiate investigation into the applicability of non-toxic plant-based chelators as radionuclide decorporation agents using in vitro model systems.

Exhibit R-2A, RDT&E Project Justification: FY 2018 Defense Health Agency			Date: May 2017
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 2016	FY 2017	FY 2018 Base	FY 2018 OCO	FY 2018 Total	FY 2019	FY 2020	FY 2021	FY 2022	Cost To Complete	Total Cost
241C: *Radiation Countermeasures (USUHS)*	4.745	0.779	0.855	0.916	-	0.916	0.933	0.951	0.970	0.989	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 2016	FY 2017	FY 2018
Title: Radiation Countermeasures (USUHS)	0.779	0.855	0.916

Description: 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.

FY 2016 Accomplishments:

Sustained studies evaluating radiation-responsive biomarkers in animal models for early-phase and organ-specific bioindicators. Provided necessary proof-of-concept dose-response data to transition combined proteomic and hematological concept for further development of diagnostic devices (i.e., hand-held, field deployable). Reported on hematology and blood serum chemistry data collected in NHP radiation study with limited- and full-supportive care (G-CSF, antibiotics, blood transfusions, etc.) to evaluate radiation damage to specific organs. Identified additional hematology and leukemia markers during leukemogenesis that are differentially expressed at early and late phases of transformation including miRNAs. Using two models of neutron energy spectra, measured a differential pattern in miRNA biomarkers between neutron radiation expected at close distance to epicenter and at longer distances from epicenter. Identified additional epigenetic changes that discriminate between differences in dose rate at low

Exhibit R-2A, RDT&E Project Justification: FY 2018 Defense Health Agency		Date: May 2017
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 2016	FY 2017	FY 2018
doses (<10 cGy) and determined that acetylation was more significantly affected and may be a useful bio-indicator. Continued efforts to establish robust cytogenetic biodosimetry capability; initiated studies to characterize length ratio (ratio of longest to smallest chromosome) using premature chromosome condensation assay in irradiated lymphocytes. Evaluated diagnostic utility of urinary radiation biomarkers using radiation doses (0 Gy, 1 Gy, 3.5 Gy, 5.0 Gy, 6.5 Gy and 8.5 Gy) in nonhuman primate model between 1-30 days post-irradiation; Completed analysis of urinary amylase and CRP where results were not correlated with radiation dose; Measured changes in urine IL-18 expression up to 5 days post-irradiation, showing diagnostic usefulness for distinguishing radiation exposure. Evaluated 5 of total 18 proposed new radiation-responsive protein biomarkers in mouse and nonhuman primate (NHP) total-body irradiation (TBI) models for early-phase and organ-specific damage. Plasma Citrullinated proteins were evaluated as a potential new biomarker of the epithelial radiation-induced small bowel damage in animal models using commercially available antibodies and assays developed at AFRRI by Dr. Ossetrova (Ossetrova NI. “Immunoassays for Citrullinated Proteins”, PCT/US2009/061660, filed on October 22, 2009, claiming priority to U.S. Provisional Application No. 61/107,446, filed on October 22, 2008. US Patent Number 9,063,148 issued on 6/23/2015. Citrullinated proteins were evaluated as a new predicative radiation-responsive biomarkers in animal models for a prediction of the acute radiation sickness (ARS) outcome. Completed the analyses of hematology and blood serum chemistry data collected in the NHP dose-response study with limited and full supportive care (i.e., G-CSF or Neupogen® [filgrastim], antibiotics, blood transfusions, etc.) to evaluate radiation damage to specific organs. Completed the analyses of results of necropsies performed on NHPs in studies with limited and full supportive care (i.e., G-CSF or Neupogen® [filgrastim], antibiotics, blood transfusions, etc.) to determine the radiation dose-dependent damage to different organs/tissues and correlate those results with levels of already evaluated tissue/organ-specific protein biomarkers. Some results/data from the NHP dose-response TBI (photon/low LET) studies were compared with results collected from radiation accident victims and radiation therapy patients and revealed the very good similarities. Reported on development of IL-18 and IL-18 binding protein (IL-18BP) as dual biomarkers for assessment of radiation dose, severity and lethality in mice after TBI. Reported microRNA-30, as a radiation biomarker, inhibits antiapoptotic factor Mcl-1 and induces apoptosis in mouse and human hematopoietic cells after radiation exposure. Identified two hematology and leukemia markers during leukemogenesis that were differentially expressed at early and late phases of transformation. Determined that epigenetic changes, i.e., histone acetylation markers, could discriminate between differences in dose rate at low doses (<10 cGy). Identified additional hematology and leukemia markers during leukemogenesis that are differentially expressed at early and late phases of transformation including miRNAs. Using two models of neutron energy spectra, measured a differential pattern in miRNA biomarkers between neutron radiation expected at close distance to epicenter and at longer distances from epicenter. Identified additional epigenetic changes that discriminate between differences in dose rate at low doses (<10 cGy) and determined that acetylation was more significantly affected and may be a useful bio-indicator.			
FY 2017 Plans: Screen five new drugs in mouse model for their radiation countermeasure potential (prophylactic). Continue to evaluate micro-RNA profiles in mouse serum after both radiation alone and combination with wound trauma with treatment with countermeasures.			

Exhibit R-2A, RDT&E Project Justification: FY 2018 Defense Health Agency		Date: May 2017
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 2016	FY 2017	FY 2018
Complete analysis of gene array data from irradiated human marrow endothelial cells and hematopoietic progenitor cells. Identify dynamic changes in circulatory blood cell counts, bone marrow cellularity and ileum structure morphology after radiation-wound combined injury with or without ghrelin. Evaluate mTOR-AKT signaling and MAPK signaling in bone marrow cells and ileum after exposure to gamma-radiation combined with hemorrhage. Assess modulation and correlation of cytokine profiles in serum and ileum after ghrelin therapy in order to find key cytokine(s) that is/are associated with ileal recovery after CI. Evaluate cytokine changes after gamma irradiation at various radiation dose rates. Verify identity and complex kinetics of MAPkinase pathway intermediates activated by virus in macrophages. Determine identity and kinetics of MAPkinase pathway intermediates by IR and combined exposure. Determine whether AKT pathway is activated by radiation and combined radiation virus exposure. Complete characterization of reporter cells as alternate interferon assay method for general use. Conduct experiments using dual reporter cells and pathway inhibitors to gain additional insight into differential gene promoter activation after combined radiation and virus exposure. Use macrophages with and without transgene reporters to gain insights into best timing of MAPK inhibitor control of radiation induced cytokine and chemokine production. Determine effects on IR and combined exposures on production of Type I interferon by macrophages. Complete development of oxidation-sensitive drug delivery system tuned to degrade at rate corresponding to level of oxidants present within microenvironment of cell. Complete development of multi-photon-responsive nanocarrier designed to respond to UV light, near infrared (NIR) light and IR. Identify histone modifications associated with radiation exposure and determine whether dose, dose rate, or radiation quality affect different modifications. Using bioinformatics, identify gene signaling pathway (s) most associated with low dose radiation delayed effects. Establish cell model system and low dose exposure linked to specific low dose cancer biomarkers in epigenome that can be targeted for countermeasure development. Examine these chemical modifications/biomarkers as they change depending on the dose, dose rate, or type of radiation. Fully evaluate the ability of on demand release nanoparticles and radiation induced release nanoparticles to modulate gene activation of multiple gene reporter cells. Evaluate the nanoparticle release of MAPKase inhibitors to modulate radiation and combined injury induction of cytokine and chemokines. Evaluate the nanoparticle deliver of small molecule modulators on ex vivo macrophages specifically murine bone marrow derived and human macrophages exposed to radiation. Develop collaborative efforts with DoD and HHS Institutes (USACEHR and NCATs) to establish a drug screening approach in the Intramural Screening Program. Determine optimum dose and schedule for PrC-210 to achieve optimum radioprotective survival efficacy. Determine the effect of PrC-210 on accelerating recovery from radiation-induced peripheral blood cytopenia and bone marrow damage. Determine optimum schedule of subcutaneous administration (prophylactic) of TPOm and BBT-059 at optimum dose to achieve optimum radioprotective survival efficacy. Determine dose-reduction factor of TPOm and BBT-059 with optimum dose and time. Demonstrate the effect of BBT-059 in protecting bone marrow progenitor cells from radiation damage. Evaluate the effect of TPOm on endothelial dysfunction markers (Thrombomodulin, ICAM-1, Endothelin-1, E-Selectin, MMP-9, sVCAM-1 and PAI-1) in mouse serum. Evaluate the effect of TPOm in inducing cytokines/chemokines using a 23-plex cytokine luminex assay. Evaluate the radiation-induced long non-coding RNAs (lncRNAs) in mouse spleen and study the effect of CDX-301. Study the down-stream proteins of ERK, MAP2K, and Smad2/3 pathway using western blot in mouse spleen and jejunum and test the effect of CDX-301. Screen three new drugs (acquired through NIAID NCEA) in mouse model for their radiation countermeasure potential			

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B. Accomplishments/Planned Programs ($ in Millions)	FY 2016	FY 2017	FY 2018
(prophylactic). Continue to perform ghrelin mechanism on survival improvement after combined injury. Continue to evaluate radiation effects in minipigs. Continue to evaluate in vitro mesenchymal stem cell responses to radiation through network of AKT-MAPK cross talk and mTOR-Wnt interaction. ***FY 2018 Plans:*** Continue murine leukemia model to concomitantly predict leukemia development based on epigenetic markers identified in FY16 and FY17 at low and high doses. Continue lifespan study to continue evaluation of dual benefit radiation mitigation of both acute and delayed effects. Test new candidates under Intramural screening program (ISP) in collaboration with NCATs. Screen five new drugs (acquired through NIAID NCEA) in mouse model for their radiation countermeasure potential (prophylactic). Study mechanism of action of promising drugs using primary and transformed cell lines. Develop BBT-059 in mouse model administered shortly after radiation. Test promising countermeasure candidates in irradiated gut and/or lung mouse model. Understand long term effects of acute radiation exposure in in surviving mice. Will evaluate effects of ghrelin treatment in survival of minipigs or NHP after irradiation. Will continue to evaluate effects of combined drugs on H-ARS and GI-ARS in irradiated and combined injured mice. Will gather sufficient data to provide insight of radiation sensitivity variations among species. Will extend mechanistic elucidation to lungs. Determine whether modulation of the radiation-virus induced inflammatory response is best inhibited by use of broad MAPkinase inhibitors or ones selective for specific targeted pathway intermediates. Determine details of the MAPK and IRF pathway signaling pathways in human ex vivo macrophages and the response during combined exposure to ionizing radiation and FLUA. Determine the effects of additional anti-oxidants and other response modifiers of radiation, infectious disease inflammatory stimulation and combined injury which result in activation of the stable transcription factor reporters. Extend currently characterized gene-promoter reporter cells to understand the gene activation of radiation exposure combined with LPS (bacterial) exposure. Determine the level and kinetic changes of oxygen free radical species in reporter gene cells in response to different qualities and rates of ionizing radiation. Conduct pilot study of ionizing radiation effect on cell lines having unique oxidative and virus resistance profiles. Continue murine leukemia model to concomitantly predict leukemia development based on epigenetic markers identified in FY16 and FY17 at low and high doses. Continue lifespan study to continue evaluation of dual benefit radiation mitigation of both acute and delayed effects. Test new candidates under Intramural screening program (ISP) in collaboration with NCATs. Screen five new drugs (acquired through NIAID NCEA) in mouse model for their radiation countermeasure potential (prophylactic). Study mechanism of action of promising drugs using primary and transformed cell lines. Develop BBT-059 in mouse model administered shortly after radiation. Test promising countermeasure candidates in irradiated gut and/or lung mouse model. Understand long term effects of acute radiation exposure in in surviving mice. Will evaluate effects of ghrelin treatment in survival of minipigs or NHP after irradiation. Will continue to evaluate effects of combined drugs on H-ARS and GI-ARS in irradiated and combined injured mice. Will gather sufficient data to provide insight of radiation sensitivity variations among species. Will extend mechanistic elucidation to lungs. Determine whether modulation of the radiation-virus induced inflammatory response is best inhibited by use of broad MAPkinase inhibitors or ones selective for specific targeted pathway intermediates. Determine details of the MAPK and IRF pathway signaling pathways in human ex vivo macrophages and			

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B. Accomplishments/Planned Programs ($ in Millions)	FY 2016	FY 2017	FY 2018
the response during combined exposure to ionizing radiation and FLUA. Determine the effects of additional anti-oxidants and other response modifiers of radiation, infectious disease inflammatory stimulation and combined injury which result in activation of the stable transcription factor reporters. Extend currently characterized gene-promoter reporter cells to understand the gene activation of radiation exposure combined with LPS (bacterial) exposure. Determine the level and kinetic changes of oxygen free radical species in reporter gene cells in response to different qualities and rates of ionizing radiation. Conduct pilot study of ionizing radiation effect on cell lines having unique oxidative and virus resistance profiles. Develop new candidates in mouse model under Intramural screening program in collaboration with NCATs. Screen five new drugs (acquired through NIAID NCEA) in mouse model for their radiation countermeasure potential (prophylactic). Test promising countermeasure candidates in irradiated gut and/or lung mouse model. Study mechanism of action of promising drugs using primary and transformed cell lines. Elucidate the signal transduction pathways for promising drugs. Understand long term effects of acute radiation exposure in surviving mice. Will determine the lead combined drugs on mitigating H-ARS and GI-ARS in mice. Will elucidate molecularly the lead combined drugs on mitigating H-ARS in mice. Determine details of the upstream MAPK and IRF pathway intermediates in human ex vivo macrophages and the response during combined exposure to ionizing radiation and FLUA. Determine the identity and kinetics cytokine and chemokine production by combine exposure to LPS (bacterial) exposure. Determine the effects of combined ionizing radiation and LPS exposures on activation and kinetics for NFkB and MAPK in macrophages. Use currently characterized gene-promoter reporter cells to understand differences in gene activation by different qualities of radiation exposure notably gamma versus neutron and mixed-field exposures. Pilot studies on using cell reporter assays as high throughput systems (HTS) to identify off target effects of radiation countermeasure(s) during radiation and combined injury exposures. Develop new candidates in mouse model under Intramural screening program in collaboration with NCATs. Screen five new drugs (acquired through NIAID NCEA) in mouse model for their radiation countermeasure potential (prophylactic). Test promising countermeasure candidates in irradiated gut and/or lung mouse model. Test promising countermeasure candidates in mixed field radiation. Understand the mechanism of action of promising candidates using primary and transformed cell lines. Will determine the lead combined drugs on mitigating H-ARS and GI-ARS in minipigs or NHP. Will continue to elucidate molecularly the lead combined drugs on mitigating GI-ARS in mice. Determine the effects of combined ionizing radiation and LPS exposures on activation of NFkB and MAPK in in human ex vivo macrophages. Determine if upstream events activating transcription factors in reporter gene cells differ for different qualities and dose rates of ionizing radiation. Develop new candidates in mouse model under Intramural screening program in collaboration with NCATs. Screen five new drugs (acquired through NIAID NCEA) in mouse model for their radiation countermeasure potential (prophylactic). Test promising countermeasure candidates in irradiated gut and/or lung mouse model. Test promising countermeasure candidates in mixed field radiation. Understand the mechanism of action of promising candidates using primary and transformed cell lines. Will elucidate molecularly the lead combined drugs on mitigating H-ARS in minipigs or NHP. Will elucidate molecularly the lead combined drugs on mitigating GI-ARS in minipigs or NHP. Determine combinations of response NFkB and MAPK response modifiers for control of LPS and radiation induced cytokines and chemokines. Determine NFkB and MAPK activation and cytokine and chemokine production during sequential combined radiation-virus-LPS exposures.			

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B. Accomplishments/Planned Programs ($ in Millions)	FY 2016	FY 2017	FY 2018
Determine the panel of gene reporter cells and methodologies to use this system for identification of on and off target effects of radiation countermeasures.			
Accomplishments/Planned Programs Subtotals	0.779	0.855	0.916

C. Other Program Funding Summary ($ in Millions)

N/A

Remarks

D. Acquisition Strategy

N/A

E. Performance Metrics

By FY 2016

- Complete evaluation of micro-RNA profile in mouse serum after radiation alone and combination with wound trauma.
- Complete evaluation of molecular mechanisms involved in radiation, wounding, hemorrhage, and/or combined injury.
- Complete publication of combined injury model with radiation followed by hemorrhage.
- Complete identification and kinetics of MAPKinase signaling pathway molecules which are activated by IR-virus combined injury.
- Complete evaluation of gene activation reporter cells as new and novel Type I interferon assay.
- Complete assessment of current nanoparticle constructs ability to modulate macrophage inflammatory responses to radiation.
- Measure miRNAs differentially expressed after low dose radiation exposure and low dose rates.
- Conduct experiments using gamma, x-ray, alpha, and neutron sources and measure histone modifications in early, mid, and late neoplastic clones.
- Assess non-targeted radiation effects in co-cultured cells that transform to malignant cells following high LET radiation, assess magnitude following low LET radiation.
- Conduct low dose x-ray radiation fractionated exposures, compare to a single high dose exposure, and determine whether multiple exposures of low dose radiation induced different malignancy rates than single higher total dose.

By FY 2017

- Identify novel countermeasures from drug screening.
- Continue to identify dynamic changes in circulatory blood cell counts, bone marrow cellularity and ileum structure morphology after radiation-wound combined injury.
- Complete evaluation of mTOR-AKT signaling and MAPK signaling in ileum and ileal morphology after exposure to gamma-radiation combined with hemorrhage.
- Complete assessment of modulation and correlation of cytokine profiles in serum and ileum after ghrelin therapy in order to find key cytokine(s) associated with ileal recovery after CI.
- Begin to measure cytokines, CRP, C3, IgM, PGE2, and Flt-3 ligand in serum of minipigs after Co-60 irradiation.

- Begin to measure cytokines, CRP, C3, IgM, PGE2, and Flt-3 ligand in serum of mice after Co-60 irradiation at various dose rates. Preliminary data show that high radiation dose at very low dose rate fails to alter cytokine concentrations.
- Complete assessment of timing and duration of effects of MAPK pathway inhibitors on inflammatory macrophages exposed to radiation.
- Complete assessment of ex vivo human macrophage response to IR, viral infection, and combined injury.
- Complete assessment of transcription factor reporter cells to test biological response modulators of gene activation induced by IR, microbial agonists, and combined exposures.
- Complete development of oxidation-sensitive drug delivery system tuned to degrade at rate corresponding to level of oxidants present within microenvironment of cell.
- Complete development of multi-photon-responsive nanocarrier designed to respond to UV light, near infrared (NIR) light, and IR.
- Complete assessment of nanoparticle constructs' ability to modulate macrophage inflammatory responses to combined radiation-microbial agonist exposures.
- Identify and measure early epigenomic steps in post-radiation process caused by low dose gamma radiation and low dose rates to stem cell populations.
- Identify specific histone modifications associated with low LET radiation (gamma or x-ray) compared to high LET radiation (alpha or neutron) at multiple dose rates and low doses.
- Identify specific DNA modifications associated with low LET radiation (gamma or x-ray) compared to high LET radiation (alpha or neutron) at multiple dose rates and low doses.
- Measure effects of low doses (<100 cGy) at different dose rates (34 µGy to 10 cGy/min) on neural stem (NSC) cell potential, DNA damage, histone acetylation/ methylation, and DNA methylation. Compare radiation qualities (x-ray/LINAC, gamma, alpha particle, and neutrons).
- Measure effects of low doses (<100 cGy) at different dose rates (34 µGy to 10 cGy/min) on mesenchymal stem cell (MSC) potential, DNA damage, histone acetylation/ methylation, and DNA methylation.
- Measure effects of low doses of gamma (<100 cGy) at different dose rates (34 µGy to 10 cGy/min) on MSC in vivo, evaluating DNA damage, histone acetylation/ methylation, and DNA methylation.
- Measure effects of low doses of alpha particles (<100 cGy) at different dose rates (34 µGy to 10 cGy/min) on MSC in vivo.

By FY 2018
- Test new potential drugs as radiation countermeasures.
- Continue to measure cytokines, CRP, C3, IgM, PGE2, and Flt-3 ligand in serum of minipigs after Co-60 irradiation.
- Continue to measure cytokines, CRP, C3, IgM, PGE2, and Flt-3 ligand in serum of mice after Co-60 irradiation at various dose rates.
- Continue to measure cytokines in spleen and bone marrow of mice after mixed field irradiation to study differential effects of genders and radiation dose rate.
- Correlate mTOR-AKT and MAPK signaling network and ATP production after in vitro radiation-burn combined injury.
- Evaluate mTOR-AKT signaling and MAPK signaling in ex vitro bone marrow mesenchymal cells and in vitro small intestine cells after exposure to gamma-radiation combined with burn trauma for determining survival signaling.
- Complete assessment of ex vivo human macrophage response to IR, viral infection and combined injury.
- Complete assessment of timing and duration of using MAPK pathway inhibitors to alter inflammatory macrophages exposed to radiation.
- Complete determination of effect of IR on cell signaling pathways that control production of Type I interferon.
- Establish novel cell model system to examine specific low dose cancer biomarkers in the epigenome that can be targeted for countermeasure development.
- Establish methylation and histone-regulated reporter plasmids, test for responsiveness to IR.

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- Initiate low dose and dose-rate studies to test reporter plasmid assays to determine potential use to identify new countermeasures based on specific epigenomic changes.
- Use bioinformatics to identify gene signaling pathway(s) most associated with low dose radiation-induced neoplasia in vitro.
- Complete DRF (dose reduction factor) of TPOm and BBT-059
- Study the effect of TPOm on radiation-induced endothelial dysfunction
- Study the downstream effect of CDX-301 on signaling targets of ERK, MAP2K, and Smad2/3
- Identify lncRNAs in spleen from mice treated with CDX-301
- Identify novel countermeasures from drug screening
- Complete identification of MAPkinase pathway intermediates by ionizing radiation and ionizing radiation-virus combined injury.
- Complete evaluation of gene activation reporter cells as new and novel Type I interferon assay.
- Complete assessment of transcription factor reporter cells to test biological response modulators of gene activation induced by ionizing radiation, microbial agonists and combined exposures.
- Complete assessment of current nanoparticle constructs ability to modulate macrophage inflammatory responses to radiation.

By FY 2018

- Initiate murine leukemia model and measure multiple epigenetic markers in serum and WBCs after exposure to low and high doses and a low versus high dose rate
- Initiate mouse lifespan study to induce ARS and provide countermeasure and then to continue countermeasure to assess development of delayed radiation effects including leukemia and thymic tumors
- Understand the molecular pathways involved in the radioprotection by TPOm and BBT-059
- Understand the molecular pathways involved in the radioprotection by BBT-059
- Understand the effect of PrC-210 on recovery of radiation-induced depletion of peripheral blood cells and bone marrow progenitor cells
- Test new potential drugs as radiation countermeasures
- Continue to identify dynamic changes in circulatory blood cell counts, bone marrow cellularity and ileum structure morphology after radiation-wound combined injury.
- Complete evaluation of mTOR-AKT signaling and MAPK signaling in ileum and ileal morphology after exposure to gamma-radiation combined with hemorrhage.
- Complete assessment of modulation and correlation of cytokine profiles in serum and ileum after ghrelin therapy in order to find key cytokine(s) associated with ileal recovery after CI.
- Begin to measure cytokines, CRP, C3, IgM, PGE2, and Flt-3 ligand in serum of minipigs after Co-60 irradiation.
- Begin to measure cytokines, CRP, C3, IgM, PGE2, and Flt-3 ligand in serum of mice after Co-60 irradiation at various dose rates. Preliminary data show that high radiation dose at very low dose rate fails to alter cytokine concentrations.
- Complete measurement of kinetics of MAPKinase signaling pathway molecules which are activated by ionizing radiation-virus combined injury.
- Complete kinetic profile for radiation modulation of Type I interferon production
- Complete development of an oxidation-sensitive drug delivery system that is tuned to degrade at a rate corresponding to the level of oxidants present within the microenvironment of the cell.
- Complete development a multi-photon-responsive nanocarrier designed to respond to UV light, near infrared (NIR) light and ionizing radiation (IR).

- Complete initial studies for using nanoparticules to modulate inflammatory responses to radiation exposure.

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- Complete assessment of nanoparticle constructs ability to modulate macrophage inflammatory responses to combined radiation-microbial agonist exposures.

By FY 2019

- Assess leukemia development concomitantly with measurement of multiple epigenetic markers in serum and WBCs using microarray technology
- Assess leukemia development in mice recovered from ARS but receiving late effects countermeasure; use necropsy to determine cause of death.
- Test promising candidates in mixed field
- Test promising candidates after exposure to gut using SARRP
- Identify new potential drugs as radiation countermeasures