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Exhibit R-2, RDT&E Budget Item Justification: PB 2016 Defense Health Program **Date:** February 2015

Appropriation/Budget Activity					R-1 Program Element (Number/Name)							
0130: <i>Defense Health Program I BA 2: RDT&E</i>					PE 0603002HP <i>I Medical Advanced Technology (AFRRI)</i>							
COST (\$ in Millions)	Prior Years	FY 2014	FY 2015	FY 2016 Base	FY 2016 OCO	FY 2016 Total	FY 2017	FY 2018	FY 2019	FY 2020	Cost To Complete	Total Cost
Total Program Element	0.989	0.284	0.310	0.305	-	0.305	0.310	0.332	0.338	0.345	Continuing	Continuing
030A: <i>CSI - Congressional Special Interests</i>	0.000	-	0.031	-	-	-	-	-	-	-	Continuing	Continuing
242A: <i>Biodosimetry (USUHS)</i>	0.594	0.171	0.167	0.183	-	0.183	0.186	0.199	0.202	0.206	Continuing	Continuing
242B: <i>Radiation Countermeasures (USUHS)</i>	0.395	0.113	0.112	0.122	-	0.122	0.124	0.133	0.136	0.139	Continuing	Continuing

A. Mission Description and Budget Item Justification

For the Uniformed Services University of the Health Sciences/ Armed Forces Radiobiology Research Institute (USUHS/AFRRI), this program supports applied research for advanced development of biomedical strategies to prevent, treat and assess health consequences from exposure to ionizing radiation. It capitalizes on findings under PE 0602787HP, Medical Technology, and from industry and academia to advance novel medical countermeasures into and through pre-clinical studies toward newly licensed products. Program objectives focus on mitigating the health consequences from exposures to ionizing radiation(alone or in combination with other injuries) that represent the highest probable threat to US forces in current tactical, humanitarian and counterterrorism mission environments. Findings from basic and developmental research are integrated into focused advanced technology development studies to produce the following: (1) protective and therapeutic strategies; (2) novel biological markers and delivery platforms for rapid, field-based individual medical assessment; and (3) experimental data needed to build accurate models for predicting casualties from complex injuries involving radiation and other battlefield insults. The AFRRI, because of its multidisciplinary staff and exceptional laboratory and radiation facilities, is uniquely positioned to execute the program as prescribed by its mission.

<u>B. Program Change Summary (\$ in Millions)</u>	<u>FY 2014</u>	<u>FY 2015</u>	<u>FY 2016 Base</u>	<u>FY 2016 OCO</u>	<u>FY 2016 Total</u>
Previous President's Budget	0.304	0.279	0.305	-	0.305
Current President's Budget	0.284	0.310	0.305	-	0.305
Total Adjustments	-0.020	0.031	-	-	-
• Congressional General Reductions	-	-			
• Congressional Directed Reductions	-	-			
• Congressional Rescissions	-	-			
• Congressional Adds	-	0.031			
• Congressional Directed Transfers	-	-			
• Reprogrammings	-	-			
• SBIR/STTR Transfer	-0.020	-			

Congressional Add Details (\$ in Millions, and Includes General Reductions)

Project: 030A: *CSI - Congressional Special Interests*

Congressional Add: 473A – *Program Increase: Restore Core Research Funding Reduction (USUHS)*

FY 2014	FY 2015
-	0.031

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Exhibit R-2, RDT&E Budget Item Justification: PB 2016 Defense Health Program		Date: February 2015	
Appropriation/Budget Activity 0130: <i>Defense Health Program I BA 2: RDT&E</i>		R-1 Program Element (Number/Name) PE 0603002HP <i>I Medical Advanced Technology (AFRRI)</i>	
<u>Congressional Add Details (\$ in Millions, and Includes General Reductions)</u>		FY 2014	FY 2015
Congressional Add Subtotals for Project: 030A		-	0.031
Congressional Add Totals for all Projects		-	0.031
<u>Change Summary Explanation</u>			
FY 2014: Realignment from Defense Health Program, Research, Development, Test and Evaluation (DHP RDT&E), PE 0603002-Advanced Technology (AFRRI) (-\$0.020 million) to DHP RDT&E PE 0605502-Small Business Innovation Research (SBIR) Program (+\$0.020 million).			
FY 2015: Congressional Special Interest (CSI) Additions to DHP RDT&E, PE 0603002-Advanced Technology (AFRRI) (+\$0.031 million).			
FY 2016: No Change.			

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Exhibit R-2A, RDT&E Project Justification: PB 2016 Defense Health Program										Date: February 2015		
Appropriation/Budget Activity 0130 / 2					R-1 Program Element (Number/Name) PE 0603002HP / <i>Medical Advanced Technology (AFRRI)</i>				Project (Number/Name) 030A / <i>CSI - Congressional Special Interests</i>			
COST (\$ in Millions)	Prior Years	FY 2014	FY 2015	FY 2016 Base	FY 2016 OCO	FY 2016 Total	FY 2017	FY 2018	FY 2019	FY 2020	Cost To Complete	Total Cost
030A: <i>CSI - Congressional Special Interests</i>	-	-	0.031	-	-	-	-	-	-	-	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) 0603002 - Medical Advanced Technology (AFRRI). Because of the CSI annual structure, out-year funding is not programmed.

B. Accomplishments/Planned Programs (\$ in Millions)	FY 2014	FY 2015
<i>Congressional Add:</i> 473A – Program Increase: Restore Core Research Funding Reduction (USUHS)	-	0.031
<i>FY 2014 Accomplishments:</i> No funding programmed. This is an FY 2015 DHP Congressional Special Interest (CSI) spending item.		
<i>FY 2015 Plans:</i> The FY15 DHP Congressional Special Interest (CSI) funding is directed toward core research initiatives in Program Element (PE) 0603002 - Medical Advanced Technology (AFRRI). Because of the CSI annual structure, out-year funding is not programmed.		
Congressional Adds Subtotals	-	0.031

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

Remarks

D. Acquisition Strategy
 N/A

E. Performance Metrics
 N/A

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Appropriation/Budget Activity 0130 / 2					R-1 Program Element (Number/Name) PE 0603002HP / Medical Advanced Technology (AFRRI)				Project (Number/Name) 242A / Biodosimetry (USUHS)			
COST (\$ in Millions)	Prior Years	FY 2014	FY 2015	FY 2016 Base	FY 2016 OCO	FY 2016 Total	FY 2017	FY 2018	FY 2019	FY 2020	Cost To Complete	Total Cost
242A: Biodosimetry (USUHS)	0.594	0.171	0.167	0.183	-	0.183	0.186	0.199	0.202	0.206	Continuing	Continuing

A. Mission Description and Budget Item Justification

Biodosimetry (USUHS): For the Uniformed Services University of the Health Sciences (USUHS), this program supports applied research for advanced development of biomedical and biophysical strategies to assess health consequences from exposure to ionizing radiation. It capitalizes on findings under PE 0602787HP, Medical Technology, and from industry and academia to advance novel biological markers and delivery platforms for rapid, field-based individual dose assessment and experimental data needed to build accurate models for predicting casualties from complex injuries involving radiation and other battlefield insults.

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

	FY 2014	FY 2015	FY 2016
Title: Biodosimetry (USUHS)	0.171	0.167	0.183
FY 2014 Accomplishments: -Continued the evaluation and validation of new radiation-responsive biomarkers in higher order animal (NHP) and human models for biodosimetric diagnostic applications. -Sustained efforts to establish a quality control and assurance plan for measurement of dose by cytogenetic chromosome aberration assay. -Optimized an interphase cytogenetic assay for high-dose and partial-body dose assessment. -Participated in two cytogenetic biodosimetry exercises that demonstrated the ability to successfully ship from military operations in CONUS and the laboratory's accuracy for dose assessment of unknown samples in an inter-laboratory comparison study. -Determined the feasibility of developing an early phase (<7 days) radiation dose assessment model and algorithm using predictive biomarkers from AFRRI archived minipig hematology and serum chemistry data for estimating a 1.6-2 Gy radiation dose. -Established baseline levels of body weight, body width, body temperature, hematology, blood chemistry, proteomic biomarkers, and ARS severity scores in the nonhuman primate total body irradiation model prior to irradiation. -Reported on study using samples from the NHP total-body dose-response irradiation model, to permit testing of the measurement of organ specific biomarkers in isolated peripheral blood using commercially available antibodies. -A full dose-response algorithm dose assessment (6 h – 7 d) was developed for combinations of selected protein and hematological biomarkers in the NHP total-body irradiation model. -Determined the feasibility of developing an early phase (<7 days) radiation dose assessment model and algorithm for estimating radiation doses between 1-8.5 Gy using archived NHP urine metabolite data. -Developed and validated a radiation dose algorithm using NHP hematology and plasma proteomic biomarker results using independent ("blinded") samples.			

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Appropriation/Budget Activity 0130 / 2		R-1 Program Element (Number/Name) PE 0603002HP / <i>Medical Advanced Technology (AFRRI)</i>		Project (Number/Name) 242A / <i>Biodosimetry (USUHS)</i>	
B. Accomplishments/Planned Programs (\$ in Millions)			FY 2014	FY 2015	FY 2016
-Establish LIMS (Laboratory Information Management Systems) modules and controls for remote access. Tested, validated and released the developed BETA version of the automated chromosome aberration scoring system to end user using a virtual protocol network. -Developed specificity and sensitivity models as well as multi-parametric approaches for internal automated self-validation of data before end-user reporting for the automated chromosome aberration analysis system. -Developed and established ultra-high-throughput miRNA based triage models. -Contributed to the preparation of a summary report for FDA use on the diagnostic utility of combined hematological and proteomic approach for triage biodosimetry applications based on the combination of hematological and proteomic biomarker results using the minipigs and nonhuman primate model systems. -Continued to provide 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) for necessary FDA approval. -Began to develop the protocol on evaluated and newly developed protein biomarkers for use in human radiation accident cases. FY 2015 Plans: -Contribute to the further evaluation of discovered new radiation-responsive biomarkers in higher order animal and human models for diagnostic biodosimetry applications. -Begin a pilot study using samples from the mouse and NHP total-body irradiation models to permit testing of the measurement of novel tissue- and organ-specific biomarkers in peripheral blood using commercially available antibodies and assays developed at AFRRI. -Begin to analyze blood chemistry data collected in the NHP dose-response study with limited supportive care and in the high-dose study with full supportive care (G-CSF, antibiotics, blood transfusions, etc.) to evaluate radiation damage to specific organs. -Begin to analyze results of necropsies performed on NHPs (limited and full supportive care) to determine radiation dose-dependent damage to different organs/tissues and correlate those results with levels of tissue/organ-specific protein biomarkers. -Complete NHP-specific ARS category score system based on multiple biodosimetric endpoints (i.e., clinical signs, peripheral blood cell counts, and radiation-responsive protein expression profile). -Sustain efforts to provide 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) and obtain necessary FDA approval. -Complete report for FDA on combined utility of hematological and protein biomarkers for biodosimetry applications in two FDA required animal models. -Continue preparation of report for FDA on combined utility of hematological and protein biomarkers for biodosimetry applications using GLP study results. -Begin to develop the protocol for evaluating newly discovered protein biomarkers for use in human radiation accident cases. FY 2016 Plans: -Report a dose response algorithm using amylase activity 1 day after exposure.					

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B. Accomplishments/Planned Programs (\$ in Millions)		FY 2014	FY 2015
-Extend dose response radiation calibration curves to include low doses (10 cGy) and low-dose rates (10 cGy/min) for the lymphocyte metaphase spread dicentric assay. -Initiate efforts to adopt centromeric straining using the interphase chromosome aberration assay to permit scoring of dicentric aberrations			
Accomplishments/Planned Programs Subtotals		0.171	0.167
C. Other Program Funding Summary (\$ in Millions)			
N/A			
Remarks			
D. Acquisition Strategy			
N/A			
E. Performance Metrics			
By FY 2014			
-Evaluate proof of concept of two NHP radiation injury algorithms for estimating METREPOL Response Category (RC) 3, by comparing their differences, such as in the blood-based biomarkers selected, the derived beta (weighted-interaction) coefficients, amount of co-linearity between the independent variables, data collection time-points and the RC estimation efficiency percentages as indicated by multiple-R values. -Begin to develop the protocol on evaluated and newly developed protein biomarkers for use in human radiation accident cases. -Establish and evaluate hardware and automated machinery architecture within CLASP for its implementation, throughput and efficiency after inclusion of new multiparametric approaches with end user reporting. -Integration of new imaging and analysis methods within CLASP to develop Boolean operations based on machine learning for automated close to human prediction, using Artificial Intelligence. -Establish and develop filter-assays for quick distinction of Very Low Priority (VLP) cohorts to develop an effective triage dose model for miRNA based gene expression profiles. -Integrate and cross-link the existing CLASP platform to incorporate pathway and genomic data from established search engines to provide a better user annotation.			
By FY 2015			
-Perform a pilot study using samples from the mouse and NHP total-body irradiation models to permit testing of the measurement of novel tissue- and organ-specific biomarkers in peripheral blood using commercially available antibodies and assays developed at AFRRI. -Complete analysis of blood chemistry data collected in the NHP dose-response study with limited supportive care and in the high-dose study with full supportive care (G-CSF, antibiotics, blood transfusions, etc.) to evaluate radiation damage to specific organs.			

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-Complete analysis of results of necropsies performed on NHPs (limited and full supportive care) to determine radiation dose-dependent damage to different organs/ tissues and correlate those results with levels of tissue/organ-specific protein biomarkers. -Begin to evaluate the identified tissue- and organ-specific biomarkers in partial-body irradiation models. -Exercise protocols for evaluation of newly developed proteomic biomarkers for use in radiation accident cases. -Provide 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) to obtain the necessary FDA approval. -Report on natural history of ARS in NHP using total body irradiation radiation dose response model. -Establish a gamma-ray dose response calibration curve for high-dose and partial-body cytogenetic assay. By FY2016 -Initiate efforts to expand AFRRI's dose assessment tools to include plasma protein biomarkers. -Provide an updated report on AFRRI's radiation calibration curves expanded to include low dose (10 cGy) and low-dose rates (10 cGy/min) for the metaphase spread dicentric chromosome aberration assay. -Demonstrate the utility of a multiple parameter biodosimetry diagnostic system.		

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COST (\$ in Millions)	Prior Years	FY 2014	FY 2015	FY 2016 Base	FY 2016 OCO	FY 2016 Total	FY 2017	FY 2018	FY 2019	FY 2020	Cost To Complete	Total Cost
242B: Radiation Countermeasures (USUHS)	0.395	0.113	0.112	0.122	-	0.122	0.124	0.133	0.136	0.139	Continuing	Continuing
A. Mission Description and Budget Item Justification												
Radiation Countermeasures (USUHS): For the Uniformed Services University of the Health Sciences (USUHS), this program supports applied research for advanced development of biomedical strategies to prevent, treat and assess health consequences from exposure to ionizing radiation. It capitalizes on findings under PE 0602787HP, Medical Technology, and from industry and academia to advance novel medical countermeasures into and through pre-clinical studies toward newly licensed products. Program objectives focus on mitigating the health consequences from exposures to ionizing radiation alone or in combination with other injuries, in the context of probable threats to US forces in current tactical, humanitarian and counterterrorism mission environments. Findings from basic and developmental research are integrated into highly focused advanced technology development studies yielding protective and therapeutic strategies.												
B. Accomplishments/Planned Programs (\$ in Millions)										FY 2014	FY 2015	FY 2016
Title: Radiation Countermeasures (USUHS)										0.113	0.112	0.122
FY 2014 Accomplishments: -Complete study examining effects of genistein in combination with G-CSF as a radiation countermeasure regimen. -Complete study evaluating effects of the role of the estrogen receptor on genistein-induced radioprotection. -Complete PK/PD analysis of NHP study samples for GT3. -Complete pilot NHP study for GT3 and analyze various biomarkers. -Investigate the radiomitigation potential of TS-mobilized progenitors in large animals (minipig or NHP). -Compare efficacy of CDX-301 as a radiation countermeasure when administered after pure gamma-rays or mixed neutron/gamma fields. -Complete study evaluating bone marrow endothelial cells as a radiation mitigator.												
FY 2015 Plans: -Evaluate radioprotective effects of genistein as a function of radiation dose rate. -Study GT3 biomarkers for efficacy in nonhuman primates.												
FY 2016 Plans: -Assess the effects of reduced doses of the radiation protector genistein in combination with other radioprotectors to increase both the therapeutic index and radioprotective efficacy. -Study radioprotective efficacy of two drug combination acting through two different mechanisms of action such as gamma-tocotrienol (GT3) and amifostine.												

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B. Accomplishments/Planned Programs (\$ in Millions)		FY 2014	FY 2015
-Study radioprotective efficacy of Ex-RAD in different strains of mice.			
Accomplishments/Planned Programs Subtotals		0.113	0.112
C. Other Program Funding Summary (\$ in Millions) N/A			
Remarks			
D. Acquisition Strategy N/A			
E. Performance Metrics			
By FY 2014			
-Complete study evaluating radioprotective effects when genistein is combined with a leucocyte growth factor.			
-Complete study evaluating effects of the role of the estrogen receptor on genistein-induced radioprotection.			
-Study the radioprotective efficacy of GT3 in at least six nonhuman primates.			
-Survival, hematopoietic measures, and cytokine measurements in mice administered CDX-301 after pure gamma rays or mixed neutron/gamma fields.			
By FY 2015			
-Evaluate radioprotective effect of genistein as a function of radiation dose rate.			
-Study efficacy biomarkers for GT3 efficacy in NHP.			
-Study efficacy of TS-mobilized progenitors in large animals (mini pig or NHP).			
By FY 2016			
-Assess the effects of reduced doses of the radiation protector genistein in combination with other radioprotectors to increase both the therapeutic index and radioprotective efficacy.			
-Evaluate effects of GT3 and amifostine combination.			