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**Exhibit R-2, RDT&E Budget Item Justification:** PB 2015 Defense Health Program **Date:** March 2014

<b>Appropriation/Budget Activity</b> 0130: Defense Health Program I BA 2: RDT&E	<b>R-1 Program Element (Number/Name)</b> PE 0603002HP I Medical Advanced Technology (AFRRI)
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COST (\$ in Millions)	Prior Years	FY 2013	FY 2014	FY 2015 Base	FY 2015 OCO #	FY 2015 Total	FY 2016	FY 2017	FY 2018	FY 2019	Cost To Complete	Total Cost
Total Program Element	0.739	0.250	0.295	0.279	-	0.279	0.305	0.310	0.332	0.287	Continuing	Continuing
242A: Biodosimetry (USUHS)	0.444	0.150	0.177	0.167	-	0.167	0.183	0.186	0.199	0.172	Continuing	Continuing
242B: Radiation Countermeasures (USUHS)	0.295	0.100	0.118	0.112	-	0.112	0.122	0.124	0.133	0.115	Continuing	Continuing

# The FY 2015 OCO Request will be submitted at a later date.

**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.

<b>B. Program Change Summary (\$ in Millions)</b>	<b>FY 2013</b>	<b>FY 2014</b>	<b>FY 2015 Base</b>	<b>FY 2015 OCO</b>	<b>FY 2015 Total</b>
Previous President's Budget	0.298	0.304	0.310	-	0.310
Current President's Budget	0.250	0.295	0.279	-	0.279
Total Adjustments	-0.048	-0.009	-0.031	-	-0.031
• Congressional General Reductions	-	-			
• Congressional Directed Reductions	-0.168	-			
• Congressional Rescissions	-	-			
• Congressional Adds	-	-			
• Congressional Directed Transfers	-	-			
• Reprogrammings	0.124	-			
• SBIR/STTR Transfer	-0.004	-0.009			
• Reductions related to Departmental Efficiencies - Project 242A	-	-	-0.019	-	-0.019
• Reductions related to Departmental Efficiencies - Project 242B	-	-	-0.012	-	-0.012

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<b>Change Summary Explanation</b> FY 2013: Realignment from Defense Health Program, Research, Development, Test and Evaluation (DHP RDT&E), PE 0603002-Advanced Technology (AFRRI) (-\$0.004 million) to DHP RDT&E PE 0605502-Small Business Innovation Research (SBIR) Program (+\$0.004 million).  FY 2013: General Congressional Reductions to DHP RDT&E, PE 0603002-Advanced Technology (AFRRI) (-\$0.000 million).  FY 2013: Congressional Directed Reductions (Sequestration) to DHP RDT&E, PE 0603002-Advanced Technology (AFRRI) (-\$0.168 million).  FY 2013: Below Threshold Reprogramming (BTR) from DHP RDT&E PE, 0604110-Medical Products Support and Advanced Concept Development (-\$0.124 million) to DHP RDT&E PE, 0603002-Advanced Technology (AFRRI) (+\$0.124 million).  FY 2014: Realignment from Defense Health Program, Research, Development, Test and Evaluation (DHP RDT&E), PE 0603002-Advanced Technology (AFRRI) (-\$0.009 million) to DHP RDT&E PE 0605502-Small Business Innovation Research (SBIR) Program (+\$0.009 million).  FY 2015: Reduces non-combat injury research funding in order to focus and continue the pace of progress in critical and high priority research areas for DHP RDT&E, PE 0603002-Advanced Technology (AFRRI) (-\$0.031 million).		

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Exhibit R-2A, RDT&E Project Justification: PB 2015 Defense Health Program										Date: March 2014		
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 2013	FY 2014	FY 2015 Base	FY 2015 OCO #	FY 2015 Total	FY 2016	FY 2017	FY 2018	FY 2019	Cost To Complete	Total Cost
242A: Biodosimetry (USUHS)	0.444	0.150	0.177	0.167	-	0.167	0.183	0.186	0.199	0.172	Continuing	Continuing

# The FY 2015 OCO Request will be submitted at a later date.

## 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)

	<b>FY 2013</b>	<b>FY 2014</b>	<b>FY 2015</b>
<b>Title:</b> Biodosimetry (USUHS)	0.150	0.177	0.167
<b>FY 2013 Accomplishments:</b> <ul style="list-style-type: none"> <li>-Continued evaluation of radiation-responsive biomarkers panel using higher order animals and human models.</li> <li>-Initiated studies to evaluate the validity of minipigs as biodosimetric model for dose response assessment using blood count and clinical chemistry parameters.</li> <li>-Characterized dose response and repair kinetics of <math>\gamma</math>-HA2X cytogenetic biomarker in the minipig radiation model.</li> <li>-Identified several promising new radiation biomarkers using non-human primate radiation model. Confirmed that a subset of the biomarkers responds to radiation in the relevant dose (0-8.5 Gy) and time (6 h – 7 d) range following total-body irradiation (60Co – gamma rays).</li> <li>-Completed establishment of an ARS severity scoring system using NHP radiation model.</li> <li>-Added plasma biomarkers to NHP ARS severity scoring system to provide enhanced prognostic diagnostics of radiation injury.</li> <li>-Developed a dose prediction algorithm based on the combination of hematology and proteomic biomarkers in a NHP radiation model.</li> <li>-Modeled late phase (&gt;7 days) radiation injury parameters based from predictive CBC and blood chemistry parameters; multivariate based algorithm developed for injury prediction based on results obtained 7 to 25 days after irradiation.</li> <li>-Identified urinary biomarkers that provide promise for radiation dose assessment.</li> <li>-Modeled archived NHP urine metabolite data for determining predictive biomarkers for estimating radiation doses between 1-8.5 Gy.</li> <li>-Created a cytogenetic image database to facilitate development of machine learning methods to automate analysis of chromosome aberrations.</li> <li>-Established a bioinformatics platform for identifying established radiation gene signatures by data-base searching.</li> </ul>			

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<b>B. Accomplishments/Planned Programs (\$ in Millions)</b>		<b>FY 2013</b>	<b>FY 2014</b>
<ul style="list-style-type: none"> <li>-Developed a Monte Carlo based radiation casualty simulation to evaluate sample processing bottlenecks within a high-throughput automated scoring system.</li> <li>-Sustained 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) in triage biodosimetry applications and obtain necessary FDA approval.</li> <li>-Filed joint (AFRRI/MSD) provisional patent application entitled: "Biodosimetry Panels and Methods" based in part on new biomarkers discovered in nonhuman primate and human studies.</li> </ul> <p><b>FY 2014 Plans:</b></p> <ul style="list-style-type: none"> <li>-Continue the evaluation and validation of discovered new radiation-responsive biomarkers in higher order animals and human models for biodosimetric diagnostic applications.</li> <li>-Determine the feasibility of developing an early phase (&lt;7 days) radiation dose assessment model and algorithm using predictive biomarkers from AFRRI archived mini-pig hematology and serum chemistry data for estimating a 1.6-2 Gy radiation dose.</li> <li>-Establish the baseline levels of body weights, body widths, body temperatures, hematology, blood chemistry, proteomic biomarker parameters, and ARS severity scores in the nonhuman primate total body irradiation model prior to irradiation.</li> <li>-Perform a pilot study using samples from the NHP total-body irradiation model, to permit testing of the measurement of novel organ specific biomarkers in isolated peripheral blood using commercially available antibodies.</li> <li>-Begin the full dose-response algorithm dose assessment study in NHP total-body irradiation model.</li> <li>-Begin the evaluation of the effects of treatment (G-CSF, IV fluids, antibiotics, blood transfusion, etc.) on the candidate biomarkers in NHP total-body irradiation model.</li> <li>-Determine the feasibility of developing an early phase (&lt;7 days) radiation dose assessment model and algorithm for estimating radiation doses between 1-8.5 Gy using archived NHP urine metabolite data.</li> <li>-Develop and validate a radiation dose algorithm using NHP hematology and plasma proteomic biomarker results using independent ("blinded") samples.</li> <li>-Establish LIMS (Laboratory Information Management Systems) modules and controls for remote access. Test, validate and release the developed BETA version of the automated chromosome aberration scoring system to end user using a virtual protocol network.</li> <li>-Develop 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.</li> <li>-Develop and establish ultra-high-throughput miRNA based triage models.</li> <li>-Contribute in the preparation of the 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 biomarkers results using minipigs and nonhuman primate model system.</li> </ul>			

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<b>B. Accomplishments/Planned Programs (\$ in Millions)</b>		<b>FY 2013</b>	<b>FY 2014</b>	<b>FY 2015</b>
-Continue 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. -Begin to develop the protocol on evaluated and newly developed protein biomarkers for use in human radiation accident cases.  <b>FY 2015 Plans:</b> -Contribute to the further evaluation of discovered new radiation-responsive biomarkers in higher order animal and human models for diagnostic biodosimetry applications. -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). -Perform biodosimetry GLP studies in NHP total-body irradiation models to establish the algorithm for radiation dose assessment and dose-dependent discrimination of animal groups using combined hematological and proteomic profiles. -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 studies results. -Begin to develop the protocol for evaluating newly discovered protein biomarkers for use in human radiation accident cases.				
<b>Accomplishments/Planned Programs Subtotals</b>		0.150	0.177	0.167
<b>C. Other Program Funding Summary (\$ in Millions)</b>				
N/A				
<b>Remarks</b>				
<b>D. Acquisition Strategy</b>				
N/A				
<b>E. Performance Metrics</b>				
By FY 2013				
-Expand the panel of radiation-responsive protein biomarkers using higher-order animal and human models. -Continue the further evaluation of discovered new radiation-responsive biomarkers for ARS sub-syndromes in animal models. -Demonstrate accurate radiological detection from biological samples into quartiles of doses 0-1 Gy, 1-3 Gy, 3-6 Gy, 6-10 Gy, and greater than 10 Gy. -Create the ARS category score system based on multiple biodosimetric endpoints (i.e., peripheral blood cell counts and radiation-responsive protein expression profile). -Evaluate the subset of radiation biomarkers affected by full supportive care and cytokine (G-CSF) treatment in pilot study using NHP TBI model.				

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<p>-Provide a preliminary report on the development of an algorithm for estimating radiation dose in minipigs and NHPs using either early and/or late phase' time-point data.</p> <p>-Initiated efforts to characterize levels of radiation biomarkers using a large cohort of healthy human adults to establish a multivariate biomarker baseline.</p> <p>By FY 2014</p> <p>-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.</p> <p>-Investigate the influence of potential confounding effects (i.e., gender, age, radiation quality) on the proteomic biomarker based algorithm for dose assessment.</p> <p>-Evaluate new radiation-responsive biomarkers for ARS sub-syndromes in non-human primate total-body irradiation model. Demonstrate accurate radiological detection from biological samples into quartiles of doses 0-1 Gy, 1-3 Gy, 3-6 Gy, and 6-9 Gy.</p> <p>-Evaluate the two algorithms by comparing their differences, such as in the biomarkers selected, the derived beta (weighting) coefficients, amount of co-linearity between the independent variables, data collection time-points and the dose estimation efficiency percentage as indicated by multiple-R values.</p> <p>-Begin to develop the protocol on evaluated and newly developed protein biomarkers for use in human radiation accident cases.</p> <p>-Establish and evaluate hardware and automated machinery architecture within CLASP for its implementation, throughput and efficiency after inclusion of new multi-parametric approaches with end user reporting.</p> <p>-Integration of new imaging and analyses methods within CLASP to develop Boolean operations based on machine learning for automated close to human prediction, using Artificial Intelligence.</p> <p>-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.</p> <p>-Integrate and cross-link the existing CLASP platform to incorporate pathway and genomic data from established search engines to provide a better user annotation.</p> <p>By FY 2015</p> <p>-Exercise protocols for evaluation of newly developed proteomic biomarkers for use in radiation accident cases.</p> <p>-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 the necessary FDA approval. Prepare preliminary report for FDA on combined utility of hematological and protein biomarkers for biodosimetry applications in two FDA-required animal models.</p>		

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Appropriation/Budget Activity 0130 / 2					R-1 Program Element (Number/Name) PE 0603002HP / Medical Advanced Technology (AFRRI)				Project (Number/Name) 242B / Radiation Countermeasures (USUHS)			
COST (\$ in Millions)	Prior Years	FY 2013	FY 2014	FY 2015 Base	FY 2015 OCO #	FY 2015 Total	FY 2016	FY 2017	FY 2018	FY 2019	Cost To Complete	Total Cost
242B: Radiation Countermeasures (USUHS)	0.295	0.100	0.118	0.112	-	0.112	0.122	0.124	0.133	0.115	Continuing	Continuing
# The FY 2015 OCO Request will be submitted at a later date.												
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 2013	FY 2014	FY 2015
Title: Radiation Countermeasures (USUHS)										0.100	0.118	0.112
FY 2013 Accomplishments:												
-Initiated studies to evaluate the effects of genistein administered before irradiation in combination with G-CSF administered postirradiation.												
-Initiated study to determine role of estrogen receptor on genistein-induced radioprotection.												
-Studied radioprotective efficacy of GT3 in NHP – used three different radiation doses and two different drug doses.												
-Investigated effect of GT3 on translocation of gut bacteria to various organs of NHPs receiving high doses of gamma-radiation.												
-Evaluated effect of TS-mobilized progenitors on radiation-induced apoptosis.												
-Investigated efficacy of TS-mobilized progenitors on cell proliferation and bacterial translocation in irradiated mice.												
-Investigated efficacy of TS-mobilized progenitors in combined injury model (radiation exposure and wound).												
-Demonstrated phenylbutyrate was ineffective as a radiation countermeasure when administered sc, 4 or 24 h after pure gamma-rays (9.2 Gy) or mixed neutron/gamma fields (5.71 Gy).												
FY 2014 Plans:												
-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).												

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<b>B. Accomplishments/Planned Programs (\$ in Millions)</b>		<b>FY 2013</b>	<b>FY 2014</b>
-Compare efficacy of CDX-301 as a radiation countermeasure when administered after pure gamma-rays or mixed neutron/gamma fields.  <b>FY 2015 Plans:</b> -Evaluate radioprotective effects of genistein as a function of radiation dose rate. -Study GT3 biomarkers for efficacy in nonhuman primates.			
<b>Accomplishments/Planned Programs Subtotals</b>		0.100	0.118
<b>C. Other Program Funding Summary (\$ in Millions)</b>			
N/A			
<b>Remarks</b>			
<b>D. Acquisition Strategy</b>			
N/A			
<b>E. Performance Metrics</b>			
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).			