Prediction of Total Body and Partial Body Exposures to Radiation Using Plasma Proteomic Expression Profiles

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Project Aims

- Need for biomarkers of radiation exposure to quantify unknown dose to enhance medical management of radiation exposures from potential future IND, RED, RDD events.

Biodosimetry ≠ Bioassay

- ***Biodosimetry*** uses physiological biomarkers of the bodies response to ionizing radiation exposure to estimate received dose

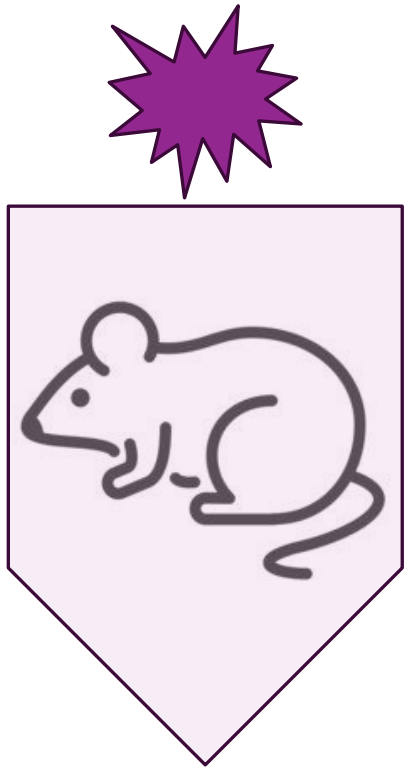
- ***Bioassay*** quantifies the amount of uptake/excretion of isotope to estimate received dose

"Any procedure used to determine the nature, activity, location or retention of radionuclides in the body by direct (in vivo) measurement or by in vitro analysis of material excreted or otherwise removed from the body" *IAEA

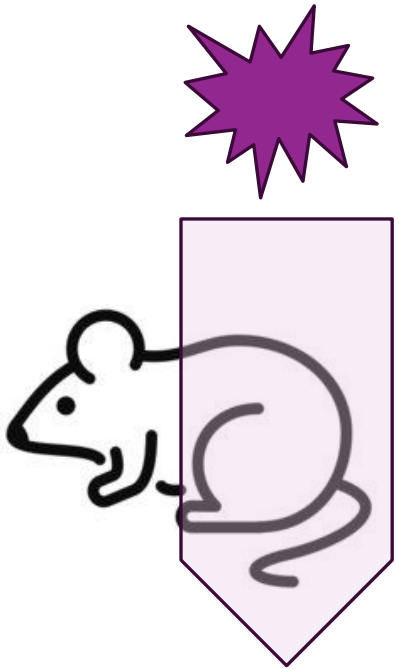
Biodosimetry “dose” vs. “damage”

- Development of biomarker algorithms for “dose” prediction
- Accepted that we are approximating radiation “dose”
- Biodosimetry “dose” is a surrogate for “damage” or injury severity
- Designed to guide medical management decisions

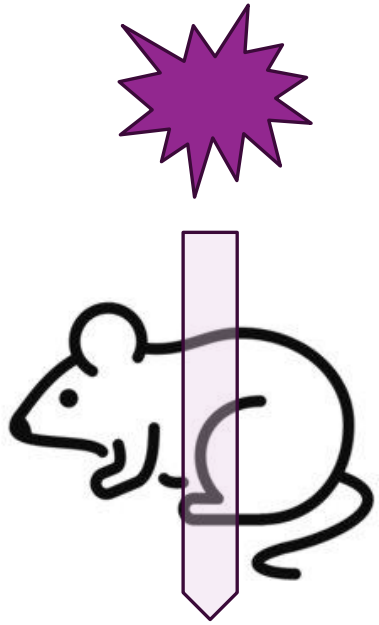
Radiation Exposure Paradigms



Total Body Irradiation



Partial Body Exposure



Organ Specific
Partial Body Exposure

Need for both Total-body and Partial-body Biomarker Characterization

- Biodosimetry purposes: Mass casualty medical management/ Field Triage
  Uniform vs. Heterogeneous radiation exposures

- Acute Radiation Syndrome (ARS):
  Hematopoietic syndrome H-ARS
  Gastrointestinal syndrome GI-ARS
  Cardiovascular CV-ARS
  Central Nervous System syndrome CNS- ARS

- Medical Management of multi-organ injury (MOI):
  Overlap/interaction between ARS sub-syndromes

Project Aims

- Evaluate prospective protein biomarkers for radiation exposure
- Target Timeframe: Biomarker upregulation of expression between 24 hours and 1week post-exposure
- Detection: should be accessible in the blood and detectable using a commercially available proteomics platform.

Previous Studies

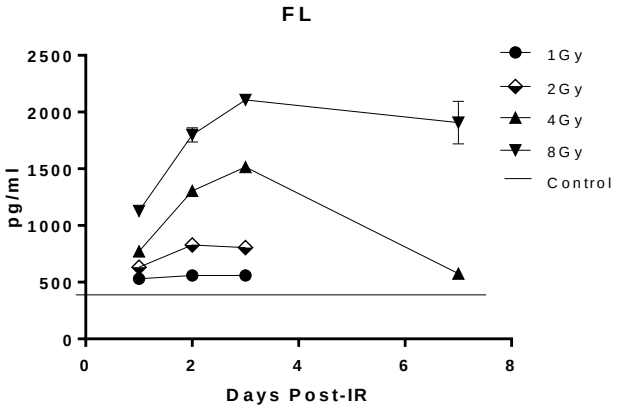
- Biodosimetry dose prediction algorithms for total body radiation exposures using a proteomic approach
- Strength of a multivariate approach for higher prediction accuracy*
- Prediction accuracy across time points/ fresh test samples/ across animal model strains

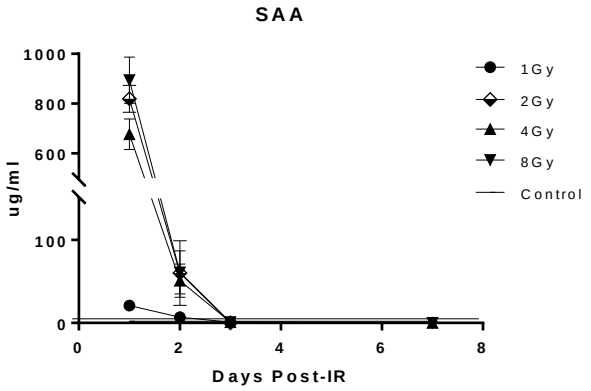
*Comparison of Proteomic Biodosimetry Biomarkers Across Five Different Murine Strains. **Sproull M**, Shankavaram U, Camphausen K. Radiat Res. 2019 Dec;192(6):640-648. doi: 10.1667/RR15442.1. Epub 2019 Oct 16.PMID: 31618122

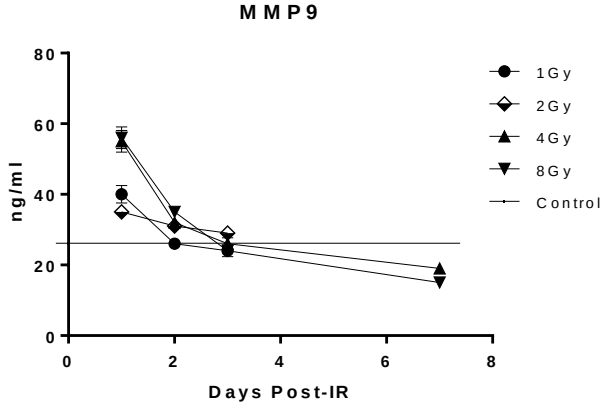
*Multivariate Analysis of Radiation Responsive Proteins to Predict Radiation Exposure in Total-Body Irradiation and Partial-Body Irradiation Models. **Sproull M**, Kramp T, Tandle A, Shankavaram U, Camphausen K. Radiat Res. 2017 Feb;187(2):251-258. doi: 10.1667/RR14558.1. Epub 2017 Jan 24.PMID: 28118115

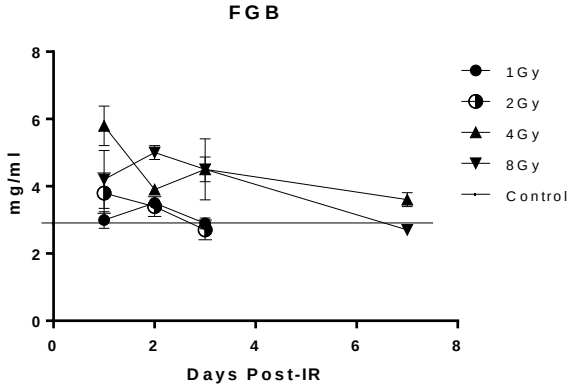
Radiation Biomarkers : TBI

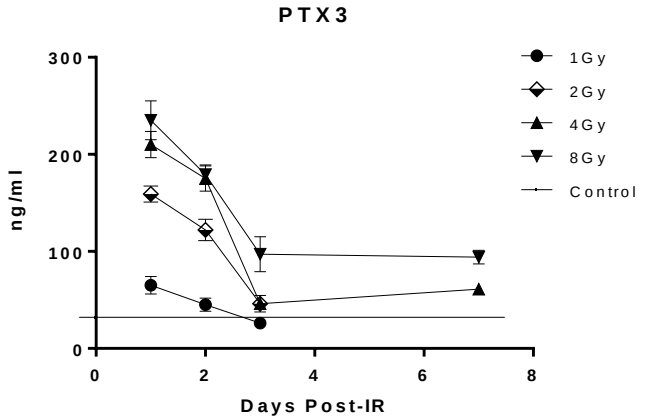
Singleplex ELISA







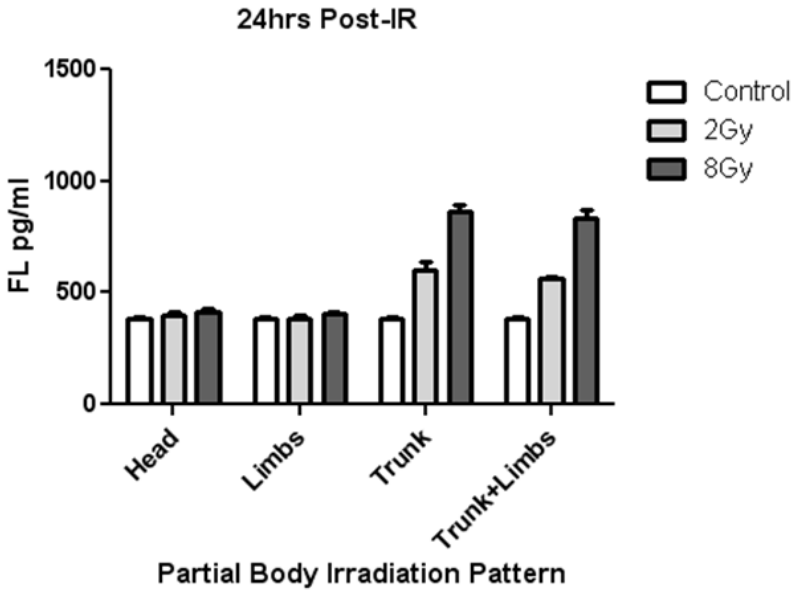


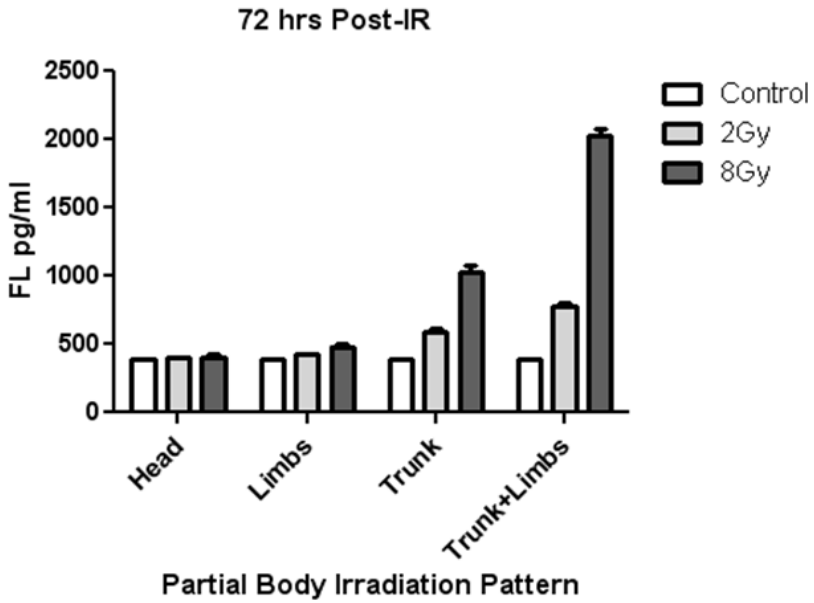


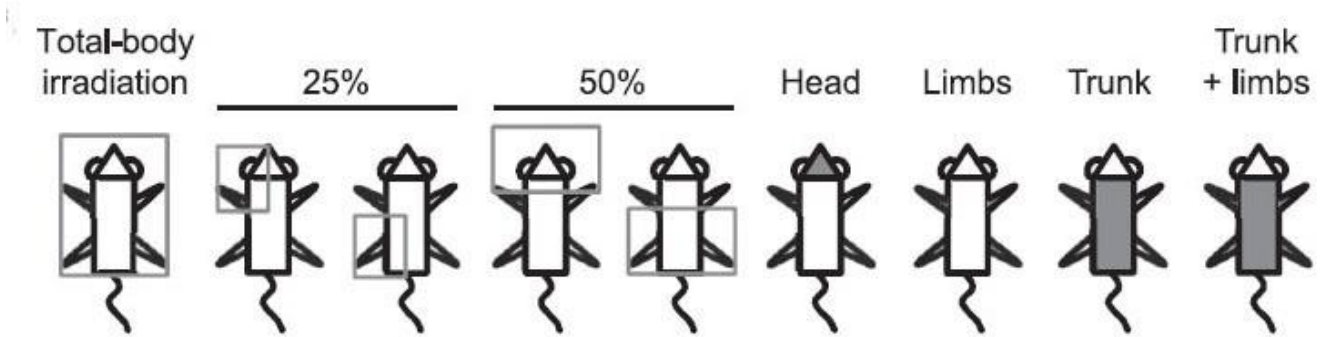
*Sproull M, Kramp T, Tandle A, Shankavaram U, Camphausen K. Serum Amyloid A as a Biomarker for Radiation Exposure. Radiat Res. 2015;184(1):14-23.
*Sproull M, Avondoglio D, Kramp T, Shankavaram U, Camphausen K. Correlation of plasma FL expression with bone marrow irradiation dose. PLoS One. 2013;8(3):e58558.

Partial Body FL Expression

Singleplex ELISA

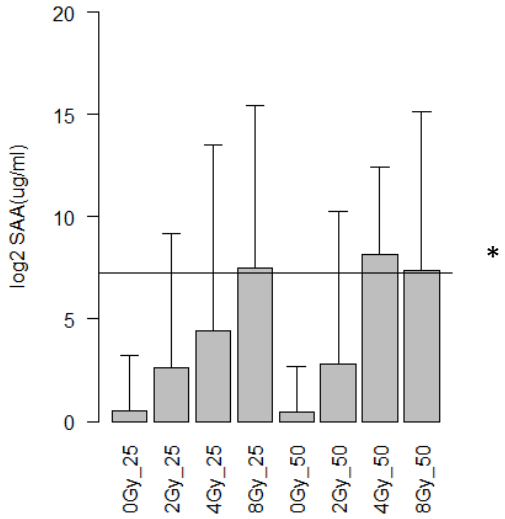


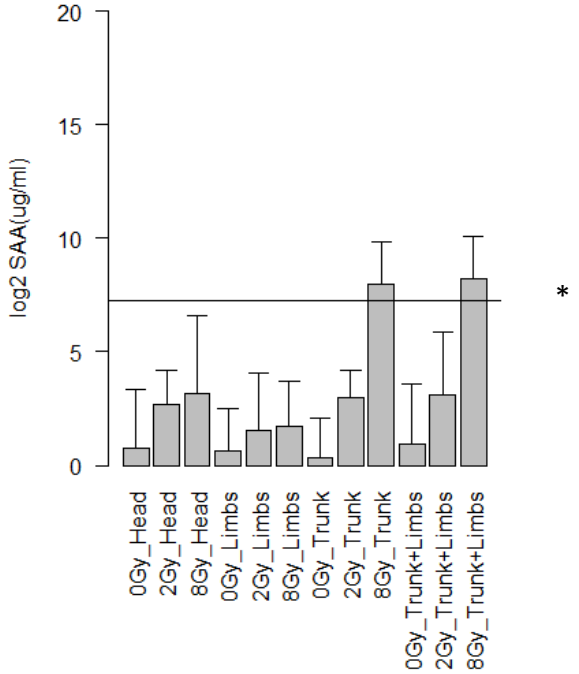


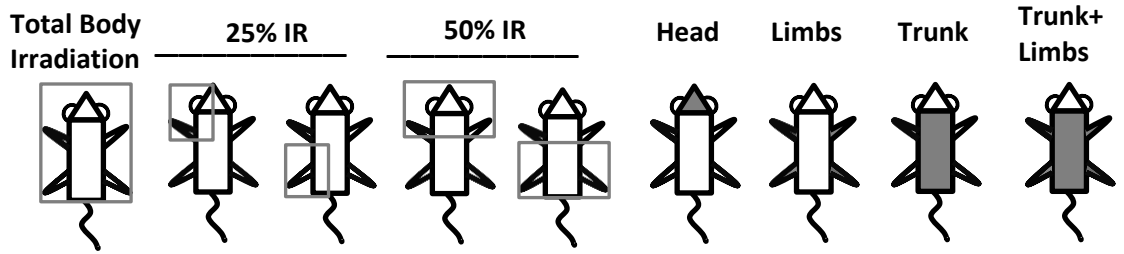


Partial Body SAA Expression

Singleplex ELISA





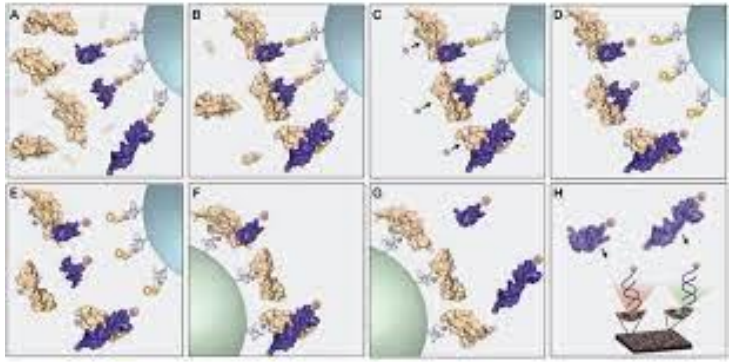


Proteomic Screening for Novel Biomarker Discovery:

- Leverage a multivariate approach
- Technologies more adaptable to the needs of mass casualty diagnostic screening
- Biodosimetry application for heterogeneous radiation exposures

Proteomic Screening for Novel Biomarker Discovery:

SomaLogic

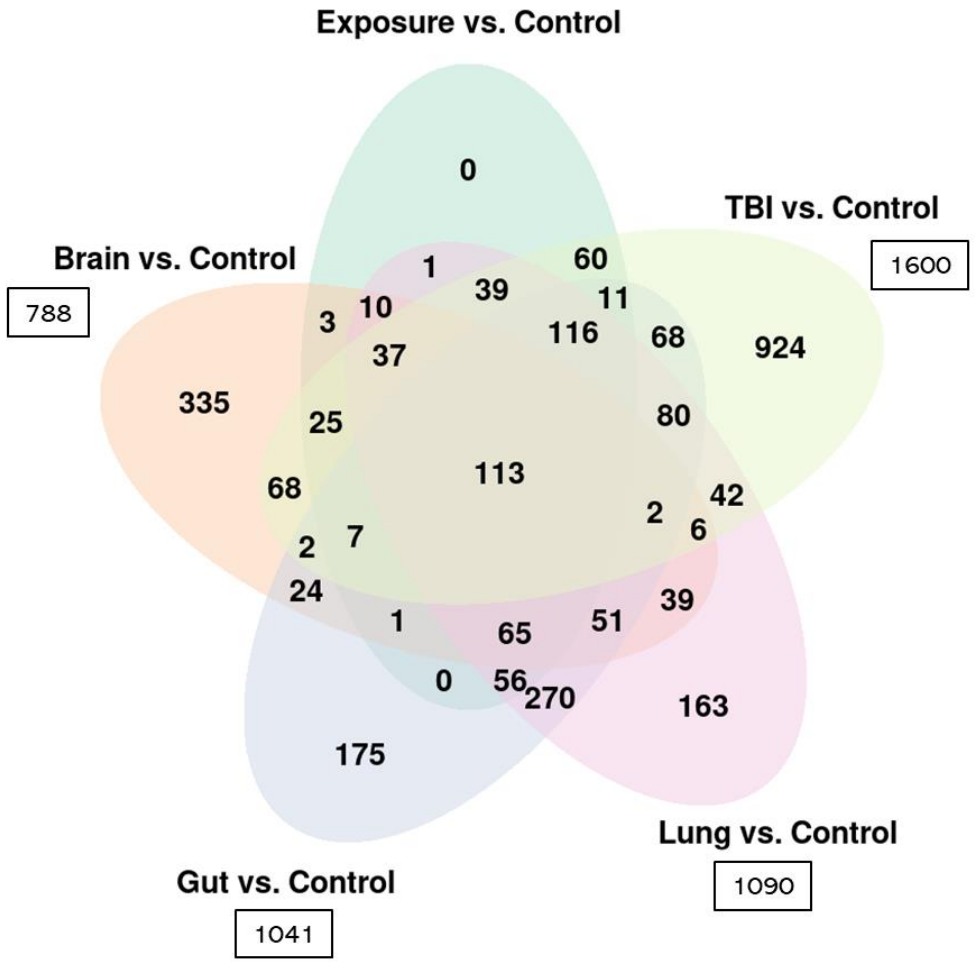


- Aptamer based multiplex proteomic screening platform
- SOMAscan HTS Assay 7K : simultaneously screens ~7000 protein targets
- Needs only small volume of sample (150 ul)
- Validated for both Human, NHP and murine samples

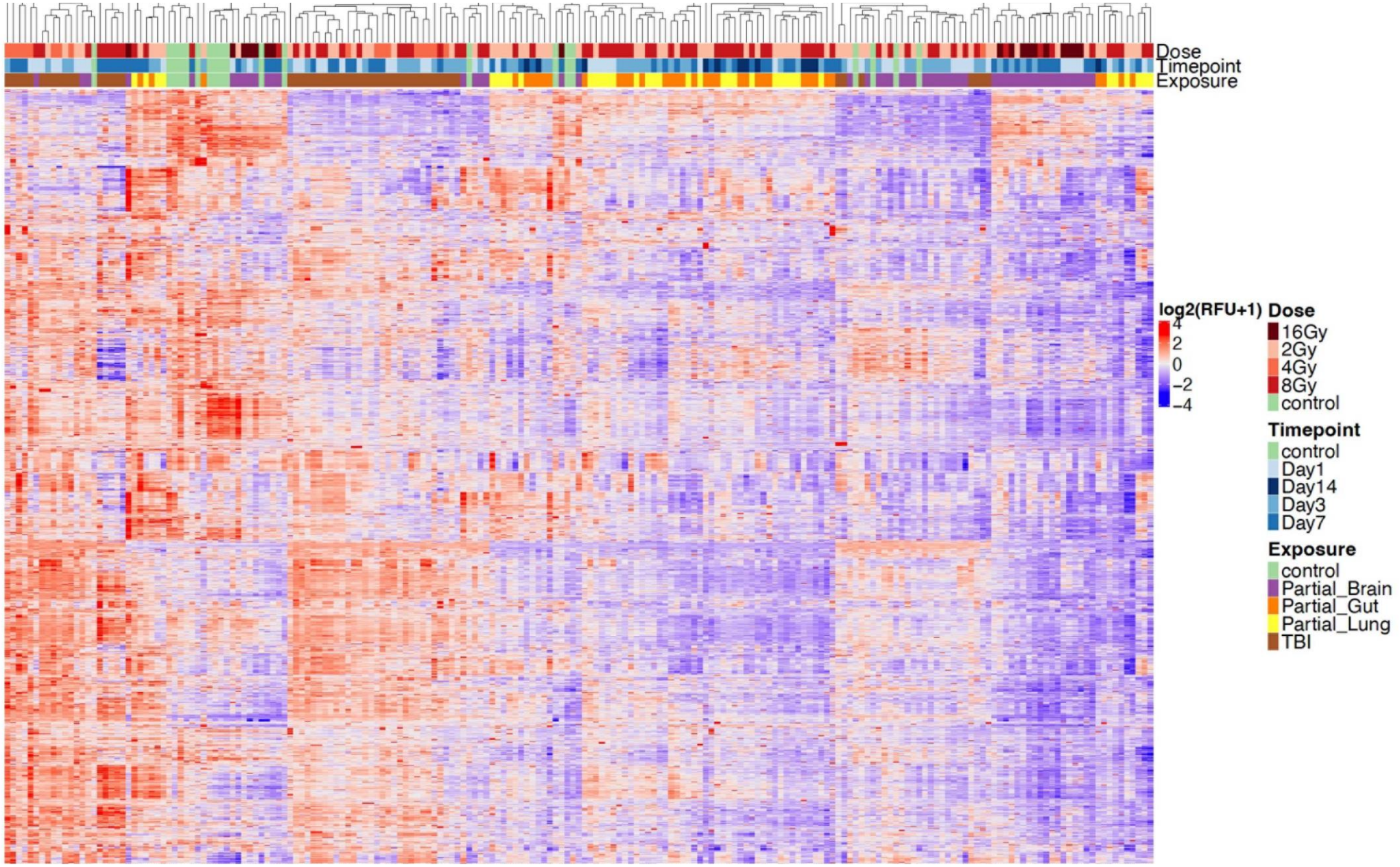
Proteomic Screening for Novel Biomarker Discovery: Design

- Partial body irradiation modeling: Organ specific exposures
    - Irradiation to only the Lung
    - Irradiation to only the Gut
    - Irradiation to only the Brain
- Model/algorithm building with field deployment applicability
- Relevance to medical management of radiation injury

Radiation Exposure Paradigms



Expression Profile of Significantly Altered Proteins



Algorithm Building for Models of Radiation Exposure

Prediction Models for Radiation Exposure

Model 1

Treatment Group	Proteomic panel
Control	CYSRT1
Exposure	COL10A1

Model 2

Treatment Group	Proteomic panel
Control	CYSRT1
TBI	NRP2
Partials	APLP1
	EDIL3
	B3GNT8
	IGH
	NSL1
	NAALADL1
	BTG2

Model 3

Treatment Group	Proteomic panel
Control	CYSRT1
Brain	IGH

Model 4

Treatment Group	Proteomic panel
Control	GNPTG
Gut	RBP4

Model 5

Treatment Group	Proteomic panel
Control	GNPTG
Lung	GOLM2

Model 6

Treatment Group	Proteomic panel
Control	CYSRT1
Brain	GKN1
Gut	APLP1
Lung	PSTPIP1
TBI	ACOT12
	CNN2
	EDIL3
	IL5
	RUNX3
	MADCAM1
	EYA2
	NTRK3
	SURF1
	B3GNT8
	NSL1
	GMPS
	IGH
	ADPRH
	OASL

Model 7

Treatment Group	Proteomic panel
Control	GKN1
Brain	CYSRT1
Gut/Lung	APLP1
TBI	PSTPIP1
	ANGPT2
	EDIL3
	GSN
	HS3ST5
	IL5
	ADPRH
	IGH
	NTRK3
	EPHB2
	B3GNT8
	MADCAM1
	NUBP1
	MGAT1
	NSL1
	OASL

Radiation Exposure Prediction Algorithms

Prediction Matrix Model Summary

Model 1

Training Data Set

	Control	Exposure
Control	14	0
Exposure	0	120
Overall Accuracy	**100**	

Test Data Set

	Control	Exposure
Control	3	3
Exposure	2	57
Overall Accuracy	**92.3**	

Model 2

Training Data Set

	Control	Partial	TBI
Control	14	0	0
Partial	0	84	0
TBI	0	0	36
Overall Accuracy	**100**		

Test Data Set

	Control	Partial	TBI
Control	3	3	0
Partial	2	39	0
TBI	0	0	18
Overall Accuracy	**92.3**		

Radiation Exposure Prediction Algorithms

Model 3

Training Data Set

	Control	Brain
Control	14	0
Brain	0	36
Overall Accuracy	**100**	

Test Data Set

	Control	Brain
Control	3	3
Brain	2	15
Overall Accuracy	**78.3**	

Model 4

Training Data Set

	Control	Gut
Control	14	0
Gut	0	24
Overall Accuracy	**100**	

Test Data Set

	Control	Gut
Control	4	2
Gut	0	12
Overall Accuracy	**88.9**	

Model 5

Training Data Set

	Control	Lung
Control	14	0
Lung	0	24
Overall Accuracy	**100**	

Test Data Set

	Control	Lung
Control	5	1
Lung	0	12
Overall Accuracy	**94.4**	

Radiation Exposure Prediction Algorithms

Model 6

Training Data Set

	Control	Brain	Gut	Lung	TBI
Control	14	0	0	0	0
Brain	0	36	0	0	0
Gut	0	0	24	0	0
Lung	0	0	0	24	0
TBI	0	0	0	0	36

Overall Accuracy **100**

Test Data Set

	Control	Brain	Gut	Lung	TBI
Control	3	3	0	0	0
Brain	2	15	0	0	0
Gut	0	0	8	4	0
Lung	0	0	2	10	0
TBI	0	0	0	0	18

Overall Accuracy **83.1**

Model 7

Training Data Set

	Control	Brain	Gut/Lung	TBI
Control	14	0	0	0
Brain	0	36	0	0
Gut/Lung	0	0	48	2
TBI	0	0	0	36

Overall Accuracy **100**

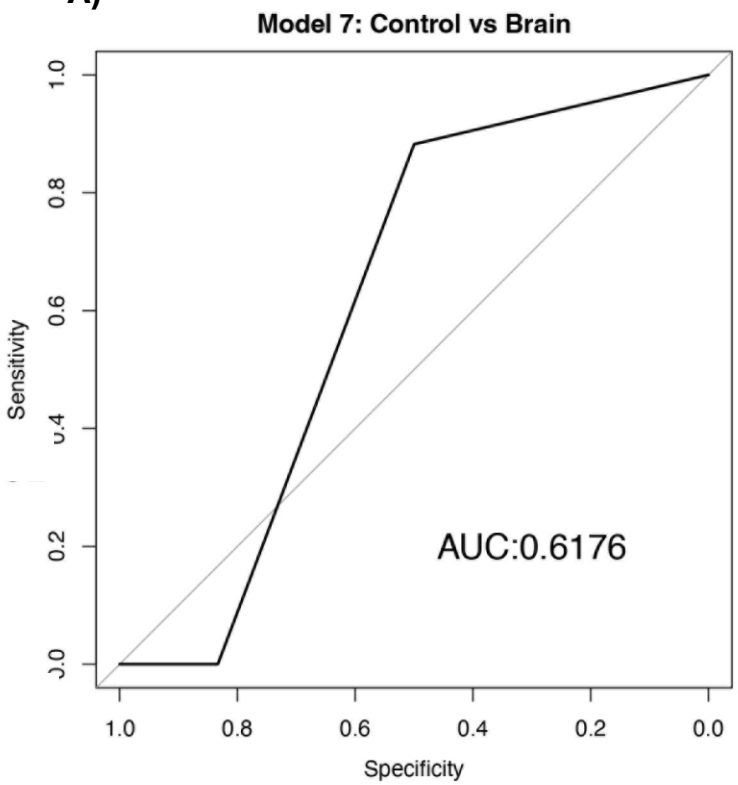
Test Data Set

	Control	Brain	Gut/Lung	TBI
Control	3	2	1	0
Brain	2	15	0	0
Gut/Lung	0	0	24	0
TBI	0	0	0	18

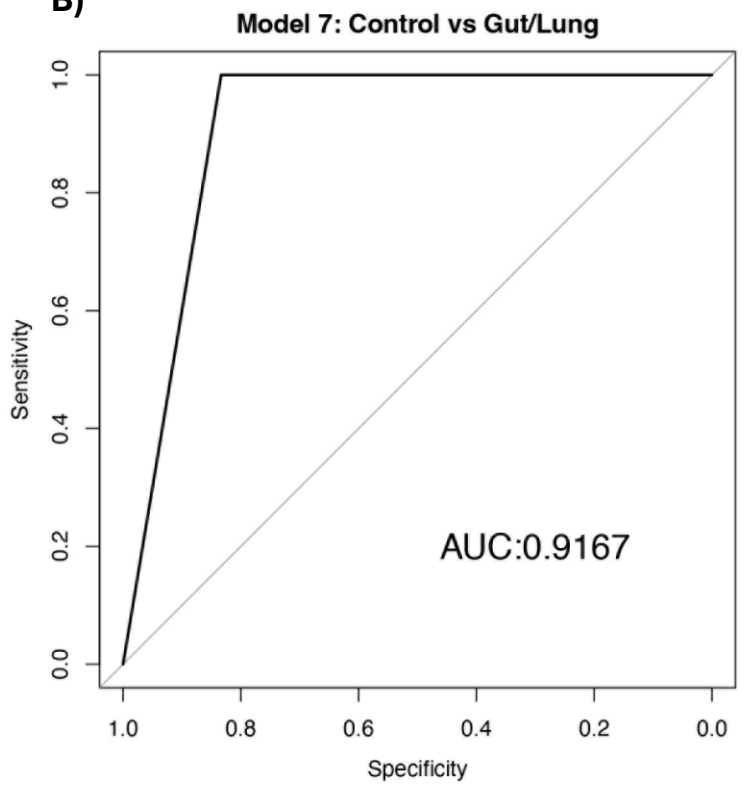
Overall Accuracy **92.3**

Model 7

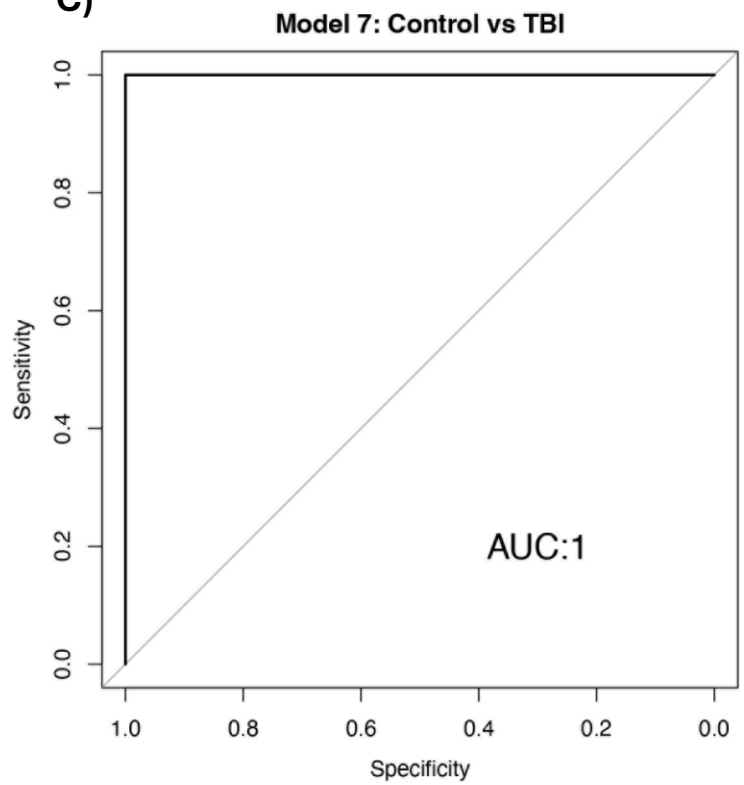
A)


Model 7: Control vs Brain
Sensitivity
Specificity
1.0
0.8
0.6
0.4
0.2
0.0
AUC:0.6176

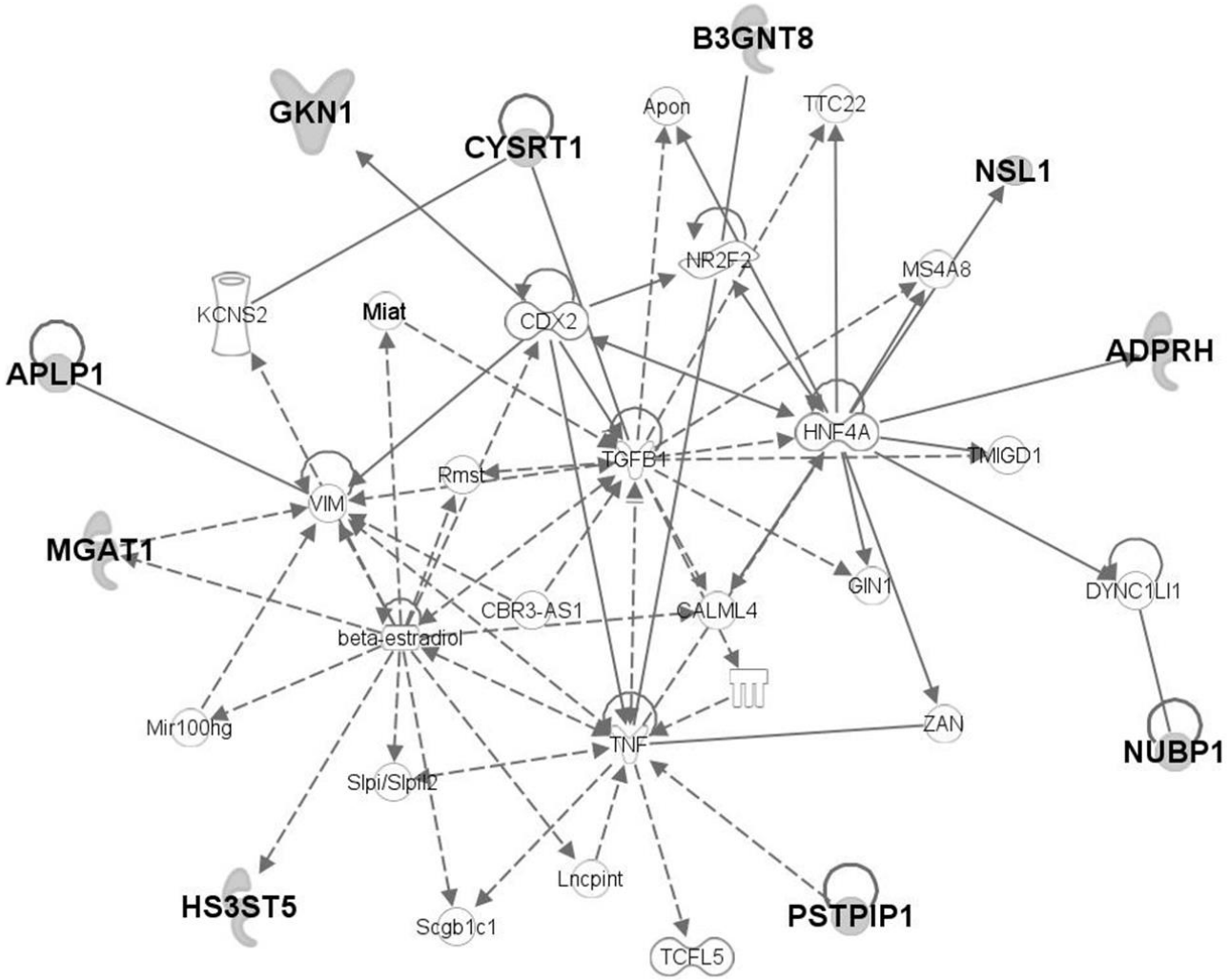
B)


Model 7: Control vs Gut/Lung
Sensitivity
Specificity
1.0
0.8
0.6
0.4
0.2
0.0
AUC:0.9167

C)


Model 7: Control vs TBI
Sensitivity
Specificity
1.0
0.8
0.6
0.4
0.2
0.0
AUC:1

Model 7 Algorithm Proteins: Pathway Analysis



Model 7 Algorithm Proteins: Pathway Analysis

Ingenuity Pathway Analysis

Top Diseases and BioFunctions:

Diseases and Disorders

	p value range	# Molecules
Organismal Injury and Abnormalities	4.99E-02 - 6.11E-05	19
Infectious Diseases	3.78E-02 - 7.91E-05	7
Hypersensitivity Response	4.39E-02 - 2.69E-04	2
Cancer	4.99E-02 - 5.89E-04	19
Dermatological Diseases and Conditions	4.39E-02 - 5.89E-04	6

Molecular and Cellular Functions

	p value range	# Molecules
Cell Signaling	2.33E-02 - 6.97E-06	8
Cell Morphology	4.84E-02 - 2.18E-05	7
Cellular Assembly and Organization	4.99E-02 - 3.21E-05	10
Cell-to-Cell Signaling and Interaction	4.99E-02 - 3.63E-05	11
Cellular Movement	4.77E-02 - 3.63E-05	8

Physiological System Development and Function

	p value range	# Molecules
Cardiovascular System Development and Function	4.46E-02 - 2.18E-05	8
Organ Development	4.92E-02 - 2.18E-05	8
Organ Morphology	4.54E-02 - 2.18E-05	6
Skeletal and Muscular System Development and Function	4.99E-02 - 2.18E-05	7
Nervious System Development and Function	4.99E-02 - 3.21E-05	7

Summary:

- Demonstrated identification of novel proteomic signatures for prediction of TBI and organ specific partial body radiation exposure with good predictive accuracy
- Highlight the need for partial body/heterogeneous exposure models -> best model for future radiation exposure scenarios
- Challenges of prediction of partial body exposures due to inherent biological limitations of radiation injury
- Potential utility of developing organ specific biomarkers to identify acute partial body exposures

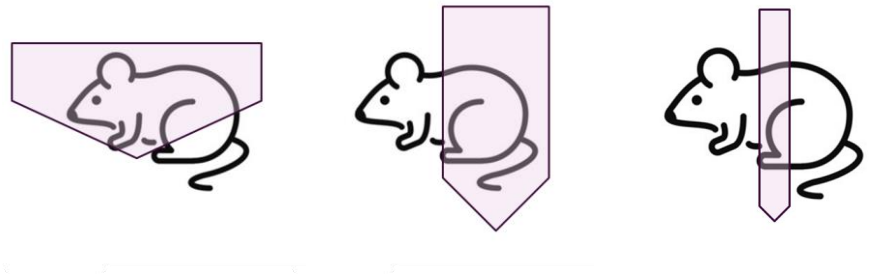
Needs: Radiation Measurements and Standards

- Nomenclature standardization within the MCM research community
- Very diverse meanings within “Partial body” radiation exposure animal models:

  Partial body: TBI with 2.5% bone marrow sparring

  Partial body: Gross % body fractions

  Partial body: Organ specific exposure



- Need for normalization of terms

Acknowledgements

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- Yu Fan PhD, Qingrong Chen PhD, Daoud Meerzaman PhD / Computational Genomics and Bioinformatics Branch, Center for Biomedical Informatics & Information Technology, NCI/NIH

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