



DEVELOPMENT OF MODELS OF ACUTE RADIATION SYNDROME IN GÖTTINGEN MINIPIGS

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Minipig H-ARS Model Development Overview

- BARDA Minipig Collaborators
- Harmonization Efforts
- Natural History for h-ARS
- Multi-Institutional Lethality Curves
- Hematopoietic and Other Biomarkers
- MCM Efficacy Testing in the Minipig Model
- Conclusions



BARDA Minipig Collaborators

- BARDA Nonclinical Studies Network established IDIQ Contracts for Animal Model Development
 - Three Minipig Task Orders were awarded in Apr-May 2012
 - Interagency Agreement signed with Armed Forces Radiological Research Institute (AFRRI) in Jan 2013
- With BARDA, these institutions make up a Minipig Consortium to develop minipig ARS models.

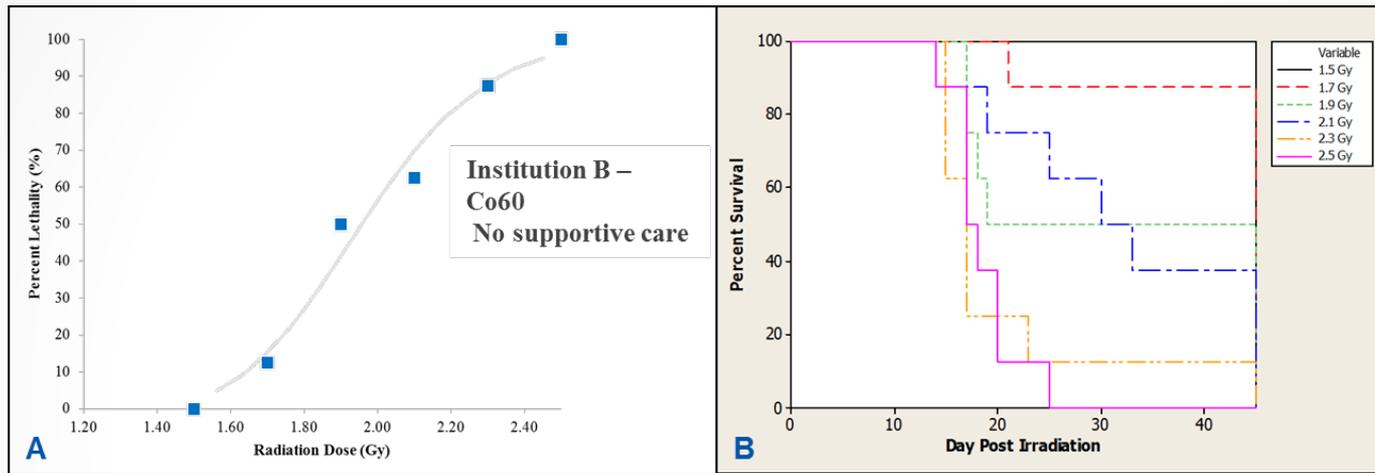


Harmonization Efforts

- Documentation of all parameters was critical.
- BARDA required harmonization of key parameters (sex, age, size, housing, enrichment and veterinary care, euthanasia criteria).
- Harmonized parameters were used to establish the natural history and biomarkers for the minipig H-ARS model.
- H-ARS Biomarkers were assessed for consistency across institutions. Non-H-ARS markers distributed for breadth of coverage.

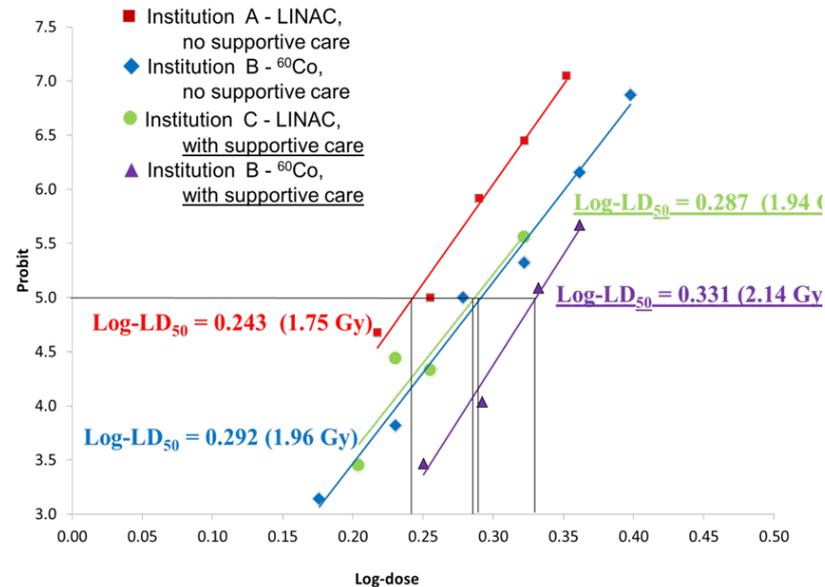


Natural History for H-ARS using Göttingen Minipigs



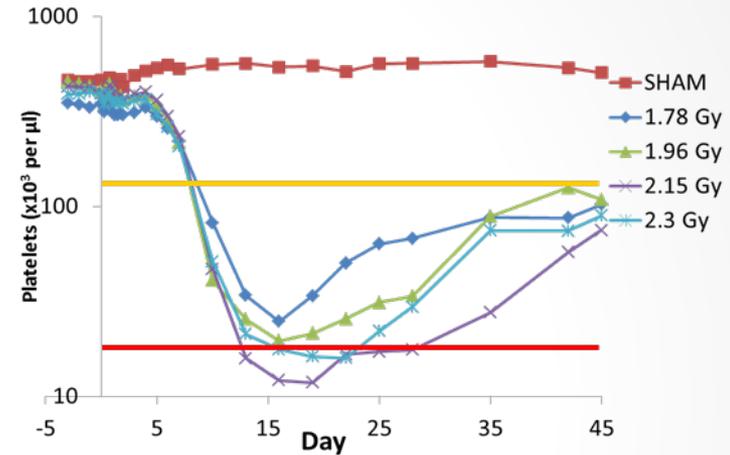
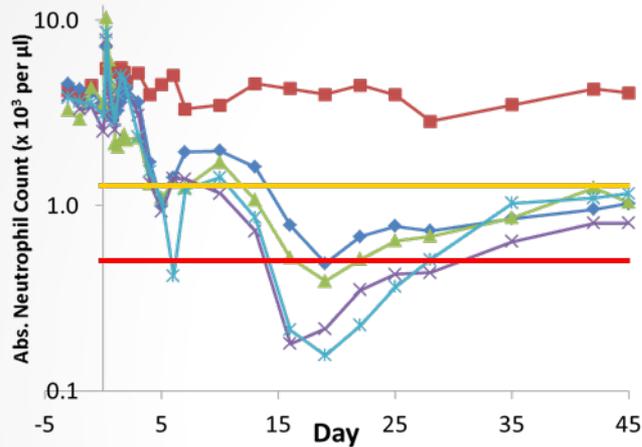
- Radiation dose-response curve (A) for the model is predictive with an LD50/45 comparable to canine but lower than murine and NHP ARS animal models.
- Kaplan Meier plot (B) shows similar time frame of mortality H-ARS as other murine, canine, and NHP models.
- Some deaths post 30 days support the 45 day duration of minipig studies.

Multi-Institutional Plot of Lethality Curves



- Parallel probit plots demonstrate general overall predictability and reproducibility of the model.
- A Dose Modification Factor (DMF) of about 1.1 observed between radiation sources and supportive care paradigms (CONOPs relevant prophylactic antibiotics and fluids).

Hematopoietic Markers



- Neutrophils and platelets are significantly impacted with dose-dependent nadir around day 15, similar to other H-ARS models.
- Similar data out to 45 days was reported across all institutions with incomplete recovery to Day 45.

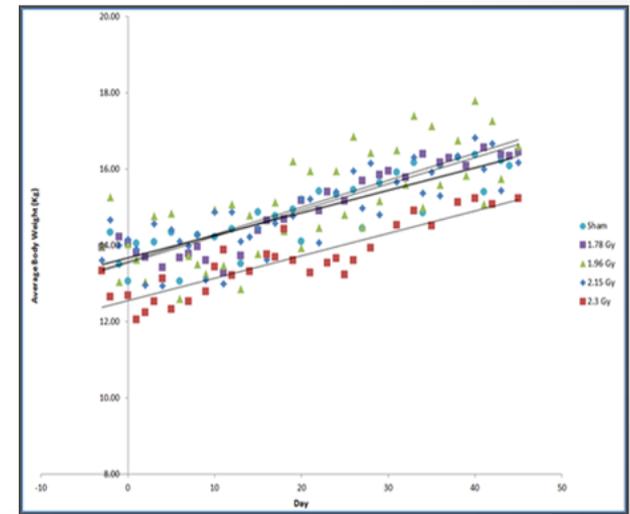
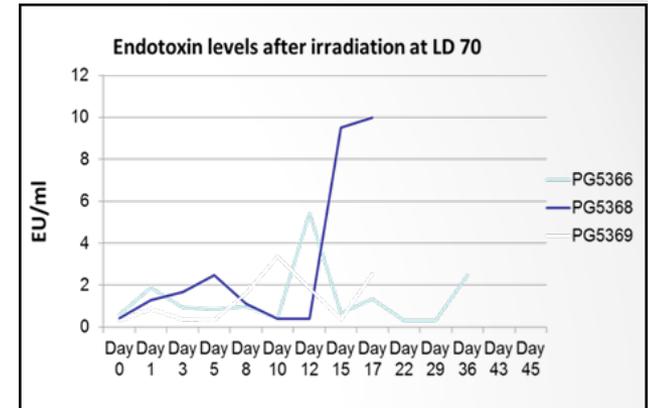
Biomarker Targets

- High priority biomarkers were tested in multiple labs, to assess reproducibility.
- Institutions also performed a unique set of individual biomarkers, often based on lab expertise, to broaden coverage

Biomarker	Institution			
	A	B	C	D
CBC	X	X	X	X
Bone Marrow	X	X	X	
Clin Chem	X	X		
C-Reactive Protein (CRP)	X	X	X	X
Cytokines	X	IL-6	multiplex	IL-6
FLT-3 Ligand	X	X		X
Endotoxin	X	X	X	
Citrulline	X		X	
D-dimer		X		X
SAA (Serum Amyloid A)		X		X
Adhesion markers				X
Coagulation markers				X

ARS Clinical Markers

- Endotoxin – Low endotoxin levels observed, suggesting effectiveness of prophylactic antibiotics in this model.
- Body weight – Animals presented a steady weight gain for the duration of the studies.



ARS Clinical Markers

- Pathology – Moribund animals and survivors to terminal necropsy showed internal hemorrhage and injuries similar with other ARS models.
- Doses of 2.5-3 Gy were 100% lethal at 30 days, and showed significant lung collapse, effusion and cardiac injury.
- Evaluation of ARS sub-syndromes involving higher radiation exposures would require shielding of sensitive organ.



MCM Efficacy Testing in the Harmonized Minipig Model

- Testing of MCM Efficacy / Testing of the Model
- Blinded study performed at AFRRI under “GLP”
- Bilateral irradiation @ LD50, minimal supportive care
- Statistically powered to 0.7 for 30% change at $\alpha = 0.05$ using an N=24/group
- 60 day study, longer term hematopoietic recovery data.



ARS Minipig Model Conclusions

- Gottingen minipig model demonstrates reproducible, predictable dose-dependent effects for H-ARS.
- Harmonized parameters provide a robust model suitable for qualification through the US FDA Program and evaluation of potential MCMs.
- Natural history and biomarkers are evaluated by survivors and non-survivors through Day 45.
- Partial body shielding for hematopoietic support and protecting specific organs is required for other ARS sub-syndromes involving radiation levels >3 Gy.



Thank You

