ANIMAL MODEL DEVELOPMENT OF GASTROINTESTINAL-ACUTE RADIATION SYNDROME (GI-ARS) IN MINIPIGS: APPROACHES TO MODEL DEVELOPMENT, AND HARMONIZATION

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Minipig GI-ARS Model Development Overview

- BARDA Mission
- Acute Radiation Injury
- BARDA Minipig Collaborators
- Harmonized GI-ARS Minipig Model
- Natural History Lethality Response
- Biomarkers
- Conclusions
- Future Directions
BARDA’s Mission

Support the advanced development and procurement of medical countermeasures for CBRN threats, pandemic influenza, and emerging infectious diseases

O’Neill Building, Washington, DC
Acute Radiation Injury

Cellular Damage through Many Pathways:
- DNA Damage
- ROS pathway
- Inflammatory Response
- Stem Cell Loss
- Endothelial Damage
- Glutathione metabolism
- Bacterial Translocation
- Coagulopathy

Blood: (Hematopoietic)
- Decrease in blood count
- Pancytopenia (Neutropenia, Thrombocytopenia)
- Severe bone marrow damage

Intestines: (Gastrointestinal)
- Mild damage
- Moderate damage
- Severe damage

Lungs: (Pulmonary)
- Pneumonitis, fibrosis

Cell death & Differing Cell turnover rates

Leads to Manifestation in Organ systems
BARDA Minipig Collaborators

- Soligenix, Inc. - Contractor for MCM development
- BARDA Task Orders in Nonclinical Studies Network
  - Lovelace Biomedical and Environmental Research Institute (LBERI)
  - SRI International (with CiTox LAB)
- Inter-Agency Agreement with Armed Forces Radiological Research Institute (AFRRI)
- With BARDA, these institutions make up a consortium to develop the minipig GI-ARS model
GI-ARS Minipig Model

- Relevance to human physiology already established
- High levels of radiation are needed to cause structural damage to crypts and villi - GI cell turnover is rapid
- Early studies showed BM shielding and protection of heart and lungs were required for long term survival
- Chronic “wasting” observed in early studies required linkage of mortality to functional GI damage
- Similar harmonization was used to establish the natural history and biomarkers in the H-ARS model
Harmonized Parameters

- Co60 and LINAC sources (0.5-0.8 Gy per min)
- Weight 9-16 Kg
- Göttingen 5-7 Mo (Sinclair 3-4 Mo)
- 45-Day duration with minimal supportive care
- Radiation doses 12, 14, and 16 Gy to the GI
- Hemi-body shielding (~50% BM; head, forelimbs and thorax)
- Harmonization of veterinary care and euthanasia criteria
Natural History for GI-ARS using Göttingen Minipigs

- Mortality at D-45 and scheduled sacrifice for Histology assessments.
- Radiation dose-response curve: \( \leq 12\text{Gy} \) has minimal impact.
- Hematopoietic salvage: decrease of platelets and neutrophils kept to \( \leq 1\) log, even at 16Gy
- Effective antibiotics: negative blood cultures at both unscheduled or scheduled euthanasia
- Primary cause of mortality: BW loss, hypothermia, respiratory distress, renal failure.
Weight Changes and Lethality

- **At 8 and 12 Gy:**
  - 0% mortality
  - BW similar to non-IR controls
  - Some GI damage seen histologically

- **At 14 Gy:**
  - 45 day survival rate ~80%
  - Chronic body weight loss
  - Significant GI damage seen histologically

- **At 16 Gy:**
  - Significant mortality (50-100%)
  - Mortality after Day 25 associated with a “wasting” disease
Hematopoietic Markers

- Neutrophils and Platelets: minimal nadir with recovery by Day 20.
- Lymphocytes showed more significant suppression
Histology Markers

- Crypt counts: drop on Day 5, recover by day 15
- Cell proliferation: greatest Day 5-9 and returns to baseline
- Necrosis and regeneration of kidney collecting tubules was most severe injury in animals that survived to Day 30
ARS Clinical Markers

- Urea, Creatinine, Citrulline
- C-Reactive Protein
- No significant changes in absorption of labeled nutrients
  - D-Glucose, L-Tyrosine, and Octanoic acid
- Metabolomic changes observed (analyses still underway)
Conclusions

- Göttingen minipig model demonstrates reproducible, dose-dependent effects for GI-ARS.
- Partial body shielding for hematopoietic support and protection of heart and lungs were required to assess recovery of GI structure and function.
- Harmonized parameters provided a robust model suitable for evaluation of potential MCMs.
- Renal damage was a significant late stage injury.
- Respiratory distress was a significant finding, especially with shielding of the lungs.
Future Directions

- GI showed recovery but mortality appeared more closely associated with vascular injury and other organ failures, even within the shielded area.

- Extensive data mining of numerous BARDA ARS studies is underway.

- Similar underlying etiologies supports moving away from organ-centric ARS sub-syndromes (Lung, GI, CNS etc.)

- New model and MCM efforts will focus more on a systems biology approach (Radiation induced vascular injury and coagulopathies).
Disclaimer

These are the views of the author and are not specifically representative of BARDA, or the U.S. Department of Health and Human Services.

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Thank You