Harmonization of BARDA’s Non-Clinical Models of Radiation Injury

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Systemic Damage Occurs Across Radiation Syndromes

**Blood:** (Hematopoietic)
- 0 Gy
- 2 Gy
- 4 Gy
- Decrease in blood count
- Pancytopenia (Neutropenia; Thrombocytopenia)
- Severe bone marrow damage
- Mild damage
- Moderate damage
- Severe damage

**Intestines:** (Gastrointestinal)
- 2 Gy
- 4 Gy
- 6 Gy
- 8 Gy
- 10 Gy
- 12 Gy
- Pneumonitis, fibrosis
- Hemostasis Dysregulation

**Traditional Animal Models**
- Total Body Irradiation (TBI)
- Partial Body Irradiation (PBI) (with bone marrow sparing)
- Targeted Irradiation ex. Whole-Thorax Lung Irradiation (WTLI)
Targeted Natural History for MCM Development

- Vascular Injury / Sepsis
- Coagulopathy / Fibrinolysis
- Inflammation
- Cell Death
- Ischemia

BLEEDING
CLOTTING
HYPOXIA
SEPSIS
INFLAMMATION
INFECTION
Lessons Learned From Animal Models
Analgesics - prophylactic

Antibiotics - prophylactic

6 MeV Linac

Radiation Dose Response Curve - NHP

Predicted Mortality Probability
With 95% Confidence Limits

LD$_{50} \sim 6.8$

With minimal supportive care
Animal Model Radiation Dose Response Curves

- **UIC**
  - LD$_{50}$ ~ 7.2

- **Gottingen**
  - LD$_{50}$ ~ 2.5

- **UM-SOM**
  - LD$_{50}$ ~ 7.4

- **SNBL/ Altasciences**
  - LD$_{50}$ ~ 2.1

- **LBERI**
  - LD$_{50}$ ~ 2.5
Mortality in NHPs Occurs Primarily Between Days 13-20 Across TBI Radiation Doses

LD$_{50/60}$ ~ 6.8 Gy
n= 10 ♂/ group
Majority of Deaths: Days 13-20
Radiation Induced Mortality in Rabbits and Minipigs

**UIC**
- Days 9-13

**SNBL/Altasciences**
- Days 13-25

**UM-SOM**
- Days 9-14

**LBERI**
- Days 9-21

- Dose (Gy) | LD_{50/60} |
- 6.5       | LD_{50}    |
- 7.5       | LD_{50}    |
- 8.5       | LD_{50}    |
- 9.5       | LD_{50}    |
NHP Peripheral Neutrophil Decline Begins a Few Days Following Irradiation

- Neutrophils ($10^3/\mu$L)
- Time Post Irradiation (d)

- Nadir~ day 13
- Recovery~ day 20

- Radiation doses: 5.2 Gy, 5.7 Gy, 6.2 Gy, 6.7 Gy, 7.2 Gy, 7.7 Gy, 8.2 Gy
Neutrophil Decline in Rabbits and Minipigs Follows a Similar Trajectory to NHPs

**UIC**

- Neutrophil count over time for different doses of radiation.
  - Nadir ~ day 11

**SNBL/Altasciences**

- Neutrophil count over time for different doses of radiation.
  - Nadir ~ day 20

**UMSOM**

- Neutrophil count over time for different doses of radiation.

**LBERI**

- Neutrophil count over time for different doses of radiation.
After a Steep Drop Following Radiation, NHP Lymphopenia Continues Through Day 17
Rabbit and Minipig Lymphopenias Follow a Similar Time Course to NHPs

**UIC**

![Graph showing ALC (x10^3/μL) vs. Days Post Irradiation for UIC with different irradiation doses (7 Gy, 8 Gy, 10 Gy).]

**SNBL/Altasciences**

![Graph showing ALC (x10^3/μL) vs. Days post irradiation for SNBL/Altasciences with different irradiation doses (1.8 Gy, 2.1 Gy).]

**UM-SOM**

![Graph showing ALC (K/μL) Mean ± SEM vs. Study Day for UM-SOM with 7.0 Gy.]

**LBERI**

![Graph showing Lymphocytes (10^3/μL) vs. Days Post-Irradiation for LBERI with 7.0 Gy.]

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**Saving Lives. Protecting Americans.**
NHP Platelets Begin to Decline Between Days 4-7 in Response to Ionizing Radiation

Nadir~ day 14
Recovery~ day 25
Rabbits and Minipigs have a Similar Thrombocytopenic Response Following Irradiation

**UIC**

- Platelets (10^3/mL)
- Days Post Irradiation
- Nadir ~ day 9-10

**SNBL/Altasciences**

- Platelet counts over time
- Nadir ~ day 15

**UMSOM**

- 7.0 Gy

**LBERI**

- Sham
- 1.94 Gy
- 2.3 Gy
- 2.46 Gy
- 2.8 Gy
- 2.9 Gy

*Saving Lives. Protecting Americans.*
RBCs Decrease Following Irradiation of Rabbits and Minipigs

UIC

SNBL/Altasciences

UMSOM

LBERI

Control

1.8 Gy

2.1 Gy

7.0 Gy

RBC (10^6/μL)

Study Day

Days post Irradiation

Examples of Bleeding in Irradiated Rabbits and Minipigs

Male New Zealand Rabbit
RIC07, 7.50 Gy

Male Gottingen Minipig
ID690, D13, 2.50 Gy

RIC03, 8.50 Gy

ID690, D13, 2.50 Gy
Critical Parameters of Thromboelastometry (ROTEM or TEG)
Radiation Impairs Clot Formation in NZW Rabbits

7.0 Gy TBI

Clot Formation Time (sec)

Platelets (10^3/μL)

Study Day

Sham-d15, Day 5, Day 7, Day 10, etc.

0 500 1000 1500

0 10 100 1000

0 10 20 30 40 50

University of Maryland School of Medicine

Radiation Impairs Clot Formation in Sinclair Minipigs
Dysregulation of all Coagulation Factor Levels in the Irradiated Göttingen Minipig
Deposition of Fibrin in Livers of Irradiated Rabbits

Control animal, not irradiated
200x

10 Gy
Sacrifice on day 12
200x

University of Illinois at Chicago
Additional Assays to Characterize Natural History

Hematology Parameters
- Thromboelastometry
- Activated Partial Thrombin Time (aPTT)
- D-Dimer
- Fibrinogen
- Prothrombin
- Antithrombin
- Coagulation Factor Tests (Intrinsic and Extrinsic)
  - Protein C
  - Thrombin generation

Serum Chemistry
- Alanine Transaminase (ALT; U/L), Alkaline Phosphatase (U/L), Aspartate Transaminase (AST; U/L), Total Bilirubin (mg/dL)
- Creatinine (mg/dL)
- Blood glucose
- Hemoglobin (g/dL), Hematocrit (Hct), Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC)
- Protein
- Protein C, Protein S, Protein Z

Coagulation Tests
- Protein C
- Thrombin generation

Vascular Injury / Sepsis
- Kidney
- Liver
- Skin / Coagulation E, F, G
- Brain

Histology
- H and E
- Carstairs' stain (fibrin and platelets)
- anti-fibrin antibody

Ischemia

Coagulopathy / Fibrinolysis

Cell Death

Inflammation

Necropsy and Histology
- Heart
- Lungs
- Intestines
- Thymus
- Spleen
- Kidneys
- Skin
- Liver
- Brain

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How to Contact BARDA

medicalcountermeasures.gov
Portal to BARDA: Register to request a TechWatch meeting!

www.fbo.gov/ (FedBizOpps)
Official announcements and info for all government contract solicitations

https://www.phe.gov/about/
BARDA/Pages/default.aspx
Program description, information, news, announcements

www.drive.hhs.gov
DRIVE questions

https://www.usajobs.gov/
Join the team!