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

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Radiological and Nuclear Countermeasures Branch
CBRN Division

BARDA Industry Day
October 30, 2018

Systemic Damage Occurs Across Radiation Syndromes

0 Gy

2 Gy

4 Gy

He

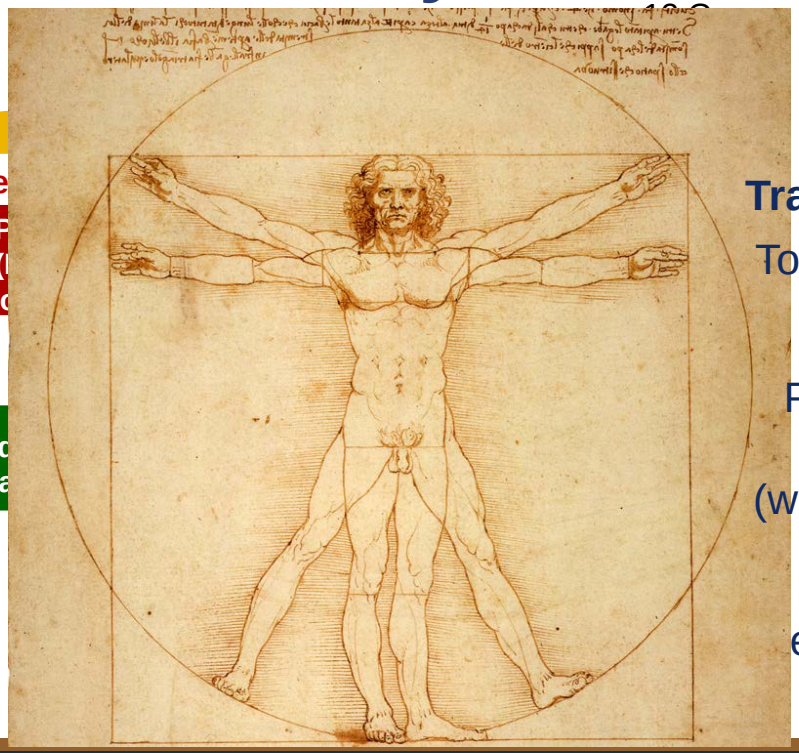
Blood:
(Hematopoietic)

Decrease in blood count

P
(
Thro

Intestines:
(Gastrointestinal)

Milc
dama



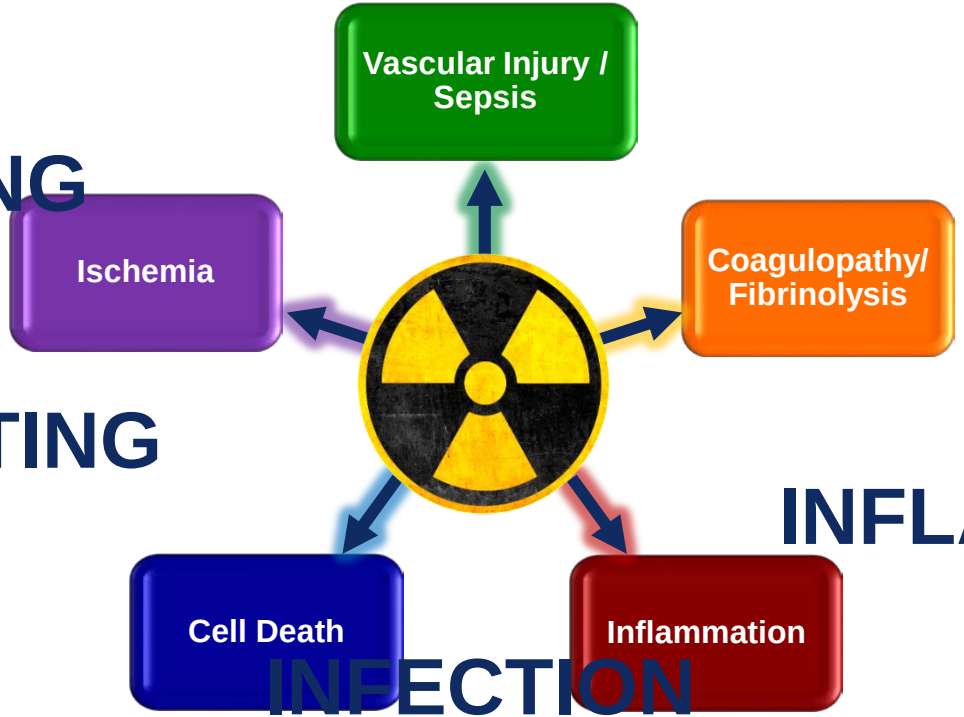
Traditional Animal Models

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



BLEEDING

HYPOXIA

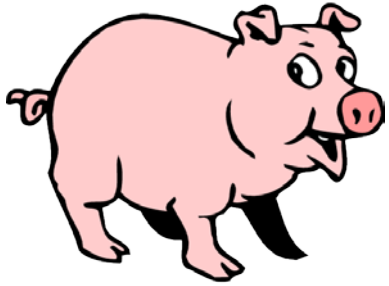
SEPSIS

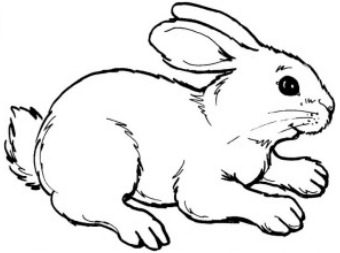
CLOTTING

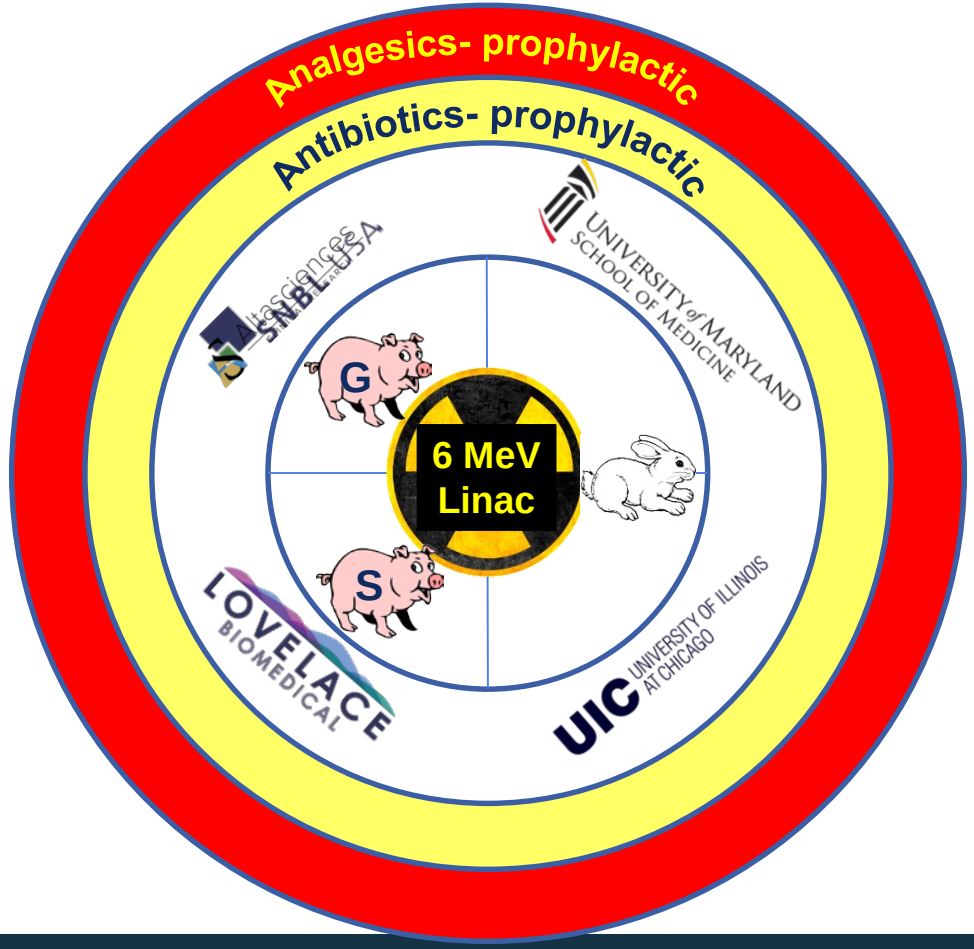
INFLAMMATION

INFECTION

Lessons Learned From Animal Models

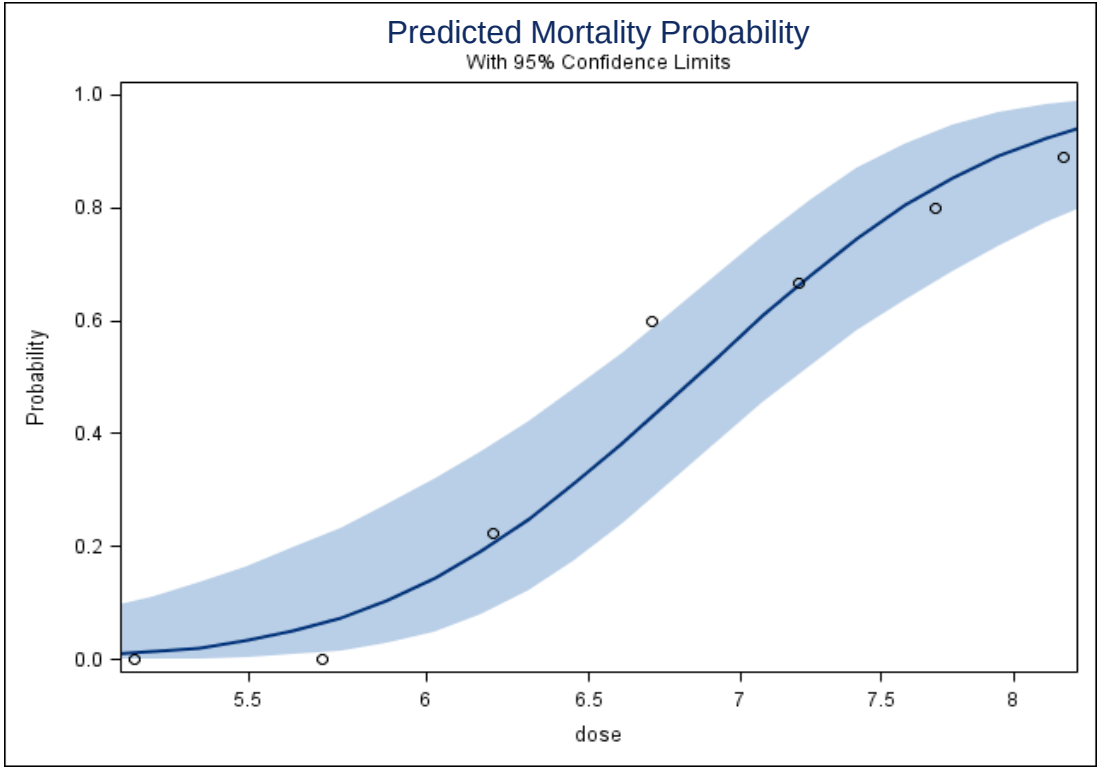






LOVELACE
BIOMEDICAL

Radiation Dose Response Curve- NHP



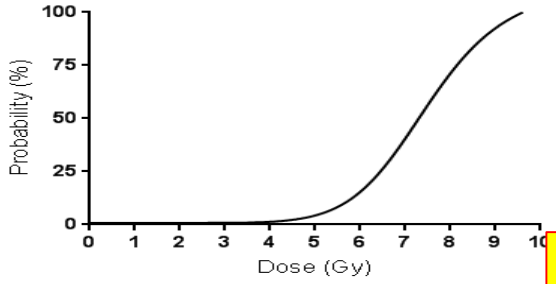
LD_{50}~ 6.8

With minimal supportive care

LOVELACE BIOMEDICAL

Animal Model Radiation Dose Response Curves

UIC

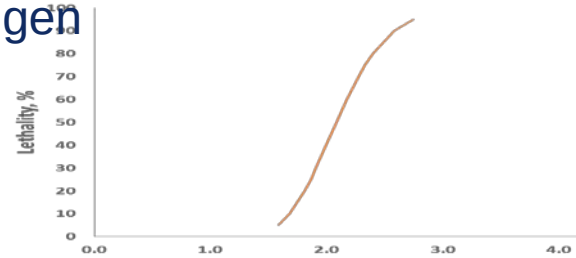


LD_{50}~ 7.2

SNBL/ Altasciences

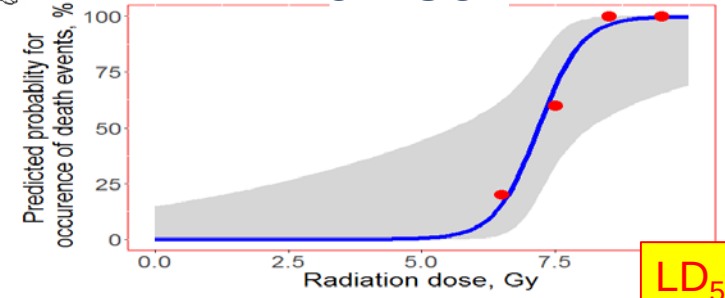
G

Göttingen



LD_{50}~ 2.1

UM-SOM

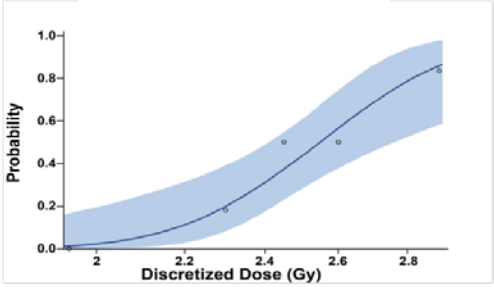


LD_{50}~ 7.4

LBERI

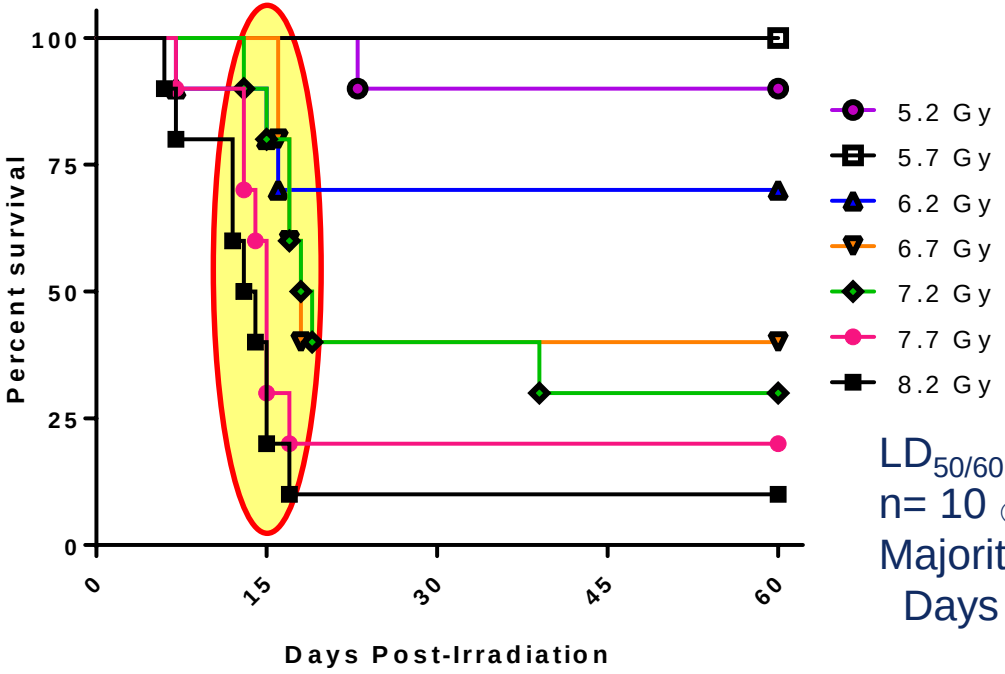
S

Sinclair



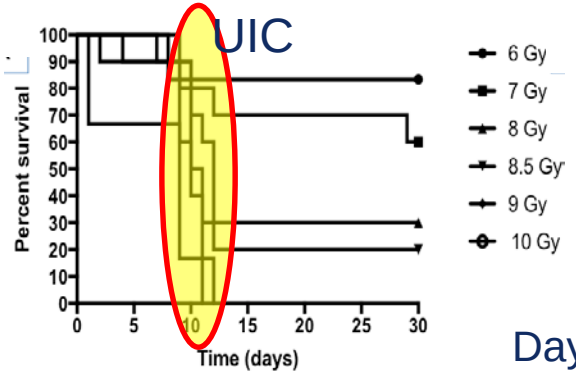
LD_{50}~ 2.5

Mortality in NHPs Occurs Primarily Between Days 13-20 Across TBI Radiation Doses

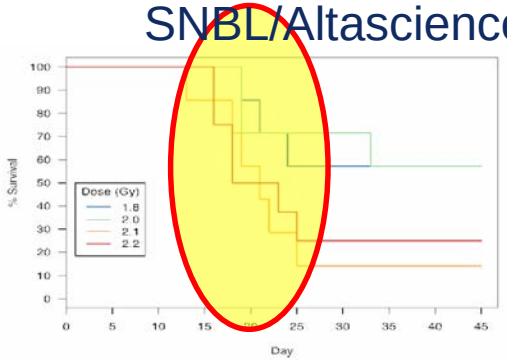


$LD_{50/60}$~ 6.8 Gy
n= 10 ♂/ group
Majority of Deaths:
Days 13-20

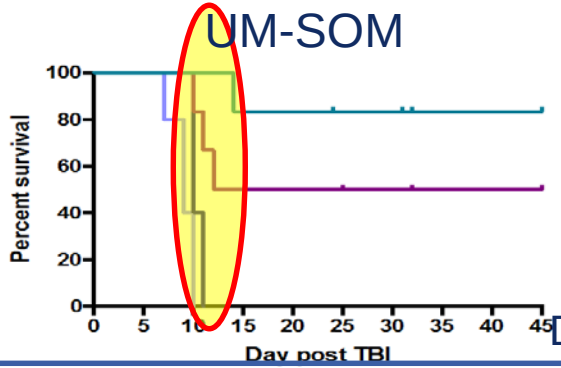
Radiation Induced Mortality in Rabbits and Minipigs



Days 9-13

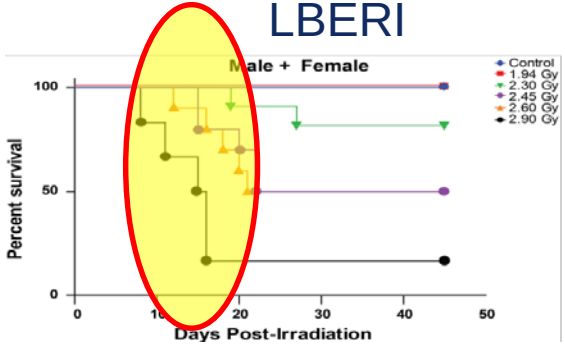


Days 13-25



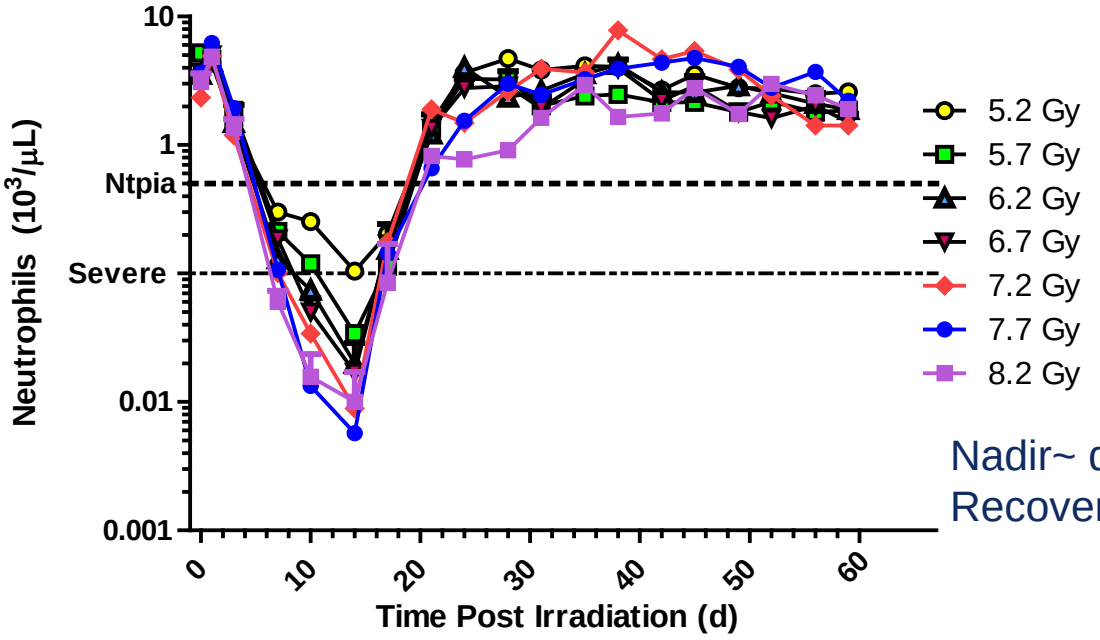
Dose (Gy)	$LD_{x/45}$
6.5	LD_{20}
7.5	LD_{60}
8.5	LD_{100}
9.5	LD_{100}

Days 9-14



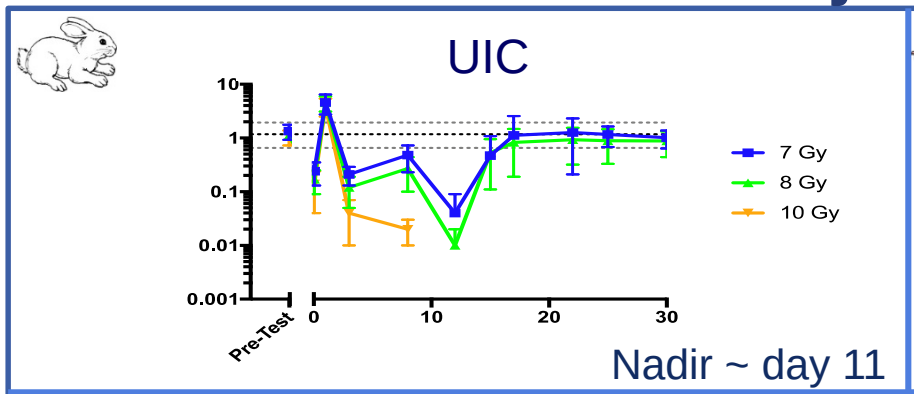
Days 9-21

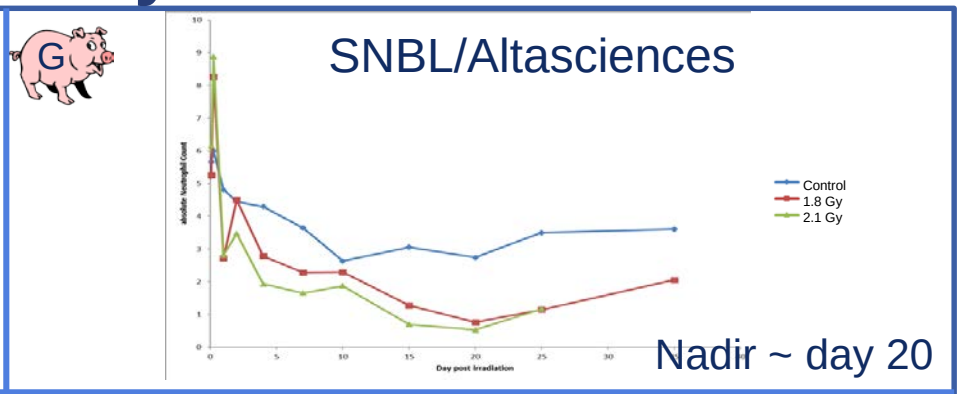
NHP Peripheral Neutrophil Decline Begins a Few Days Following Irradiation

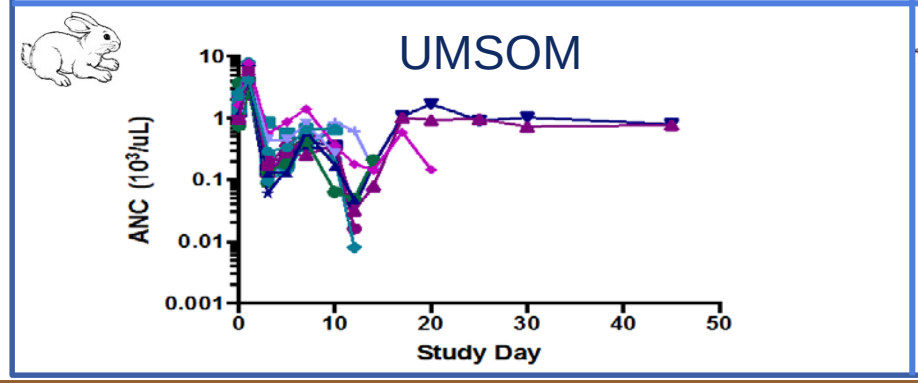


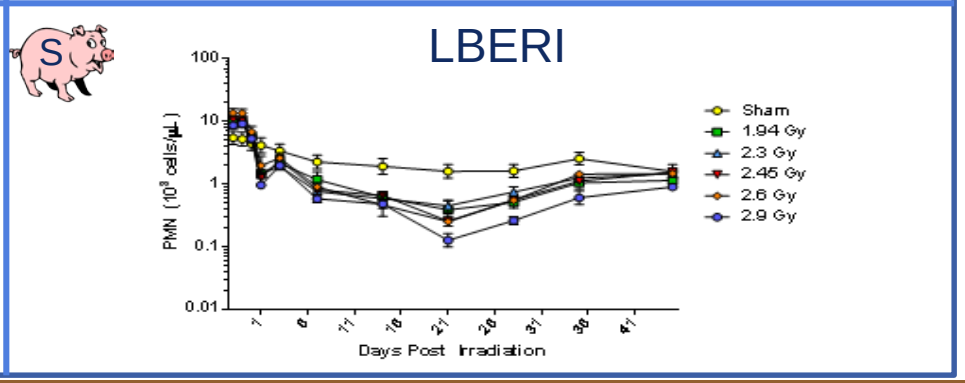
Nadir~ day 13
Recovery~day 20

Neutrophil Decline in Rabbits and Minipigs Follows a Similar Trajectory to NHPs

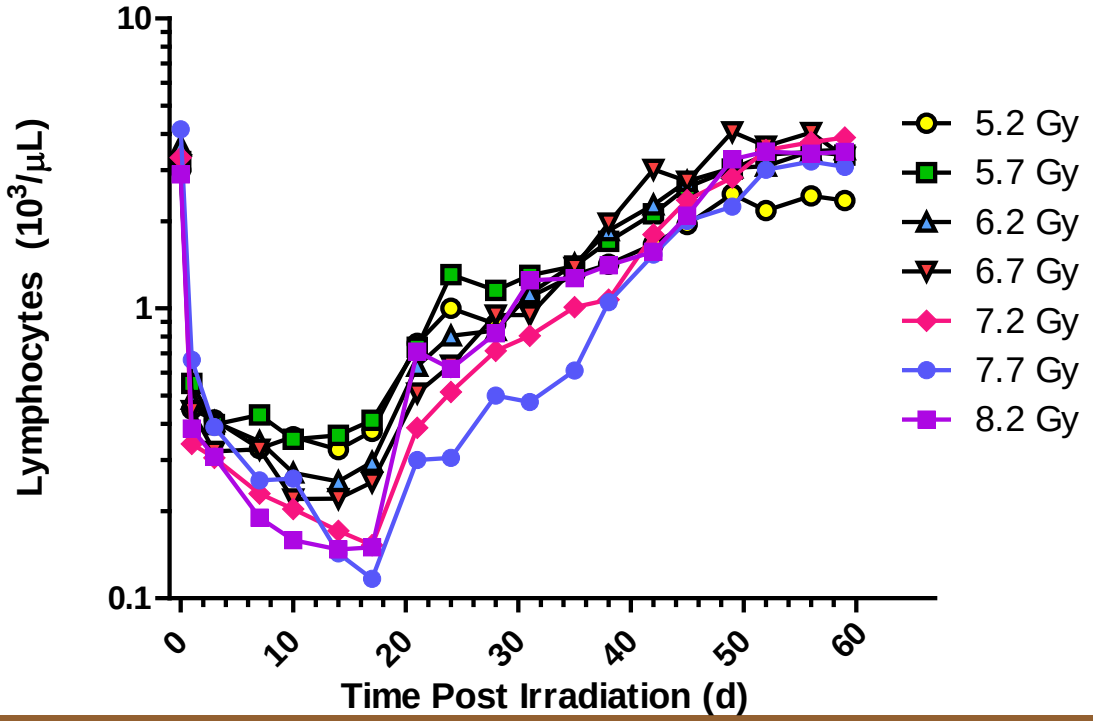






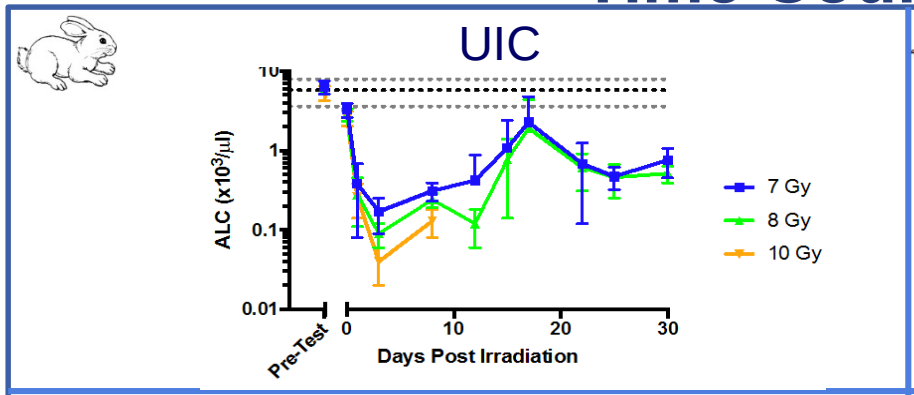


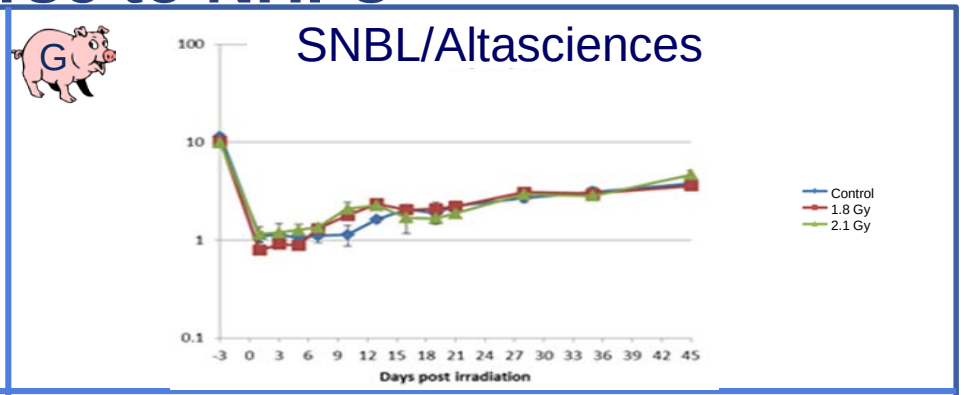
After a Steep Drop Following Radiation, NHP Lymphopenia Continues Through Day 17

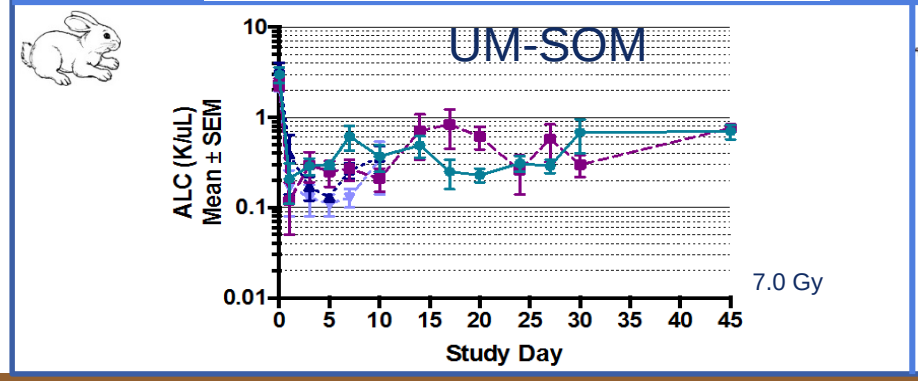


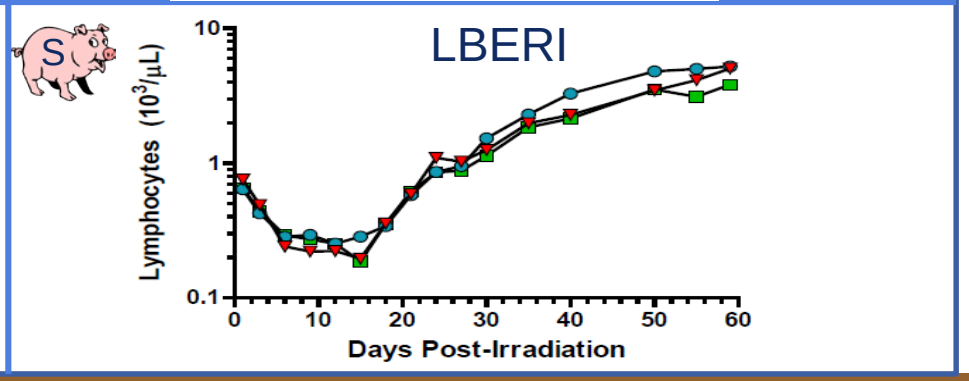
Nadir~ days 14-17

Rabbit and Minipig Lymphopenias Follow a Similar Time Course to NHPs

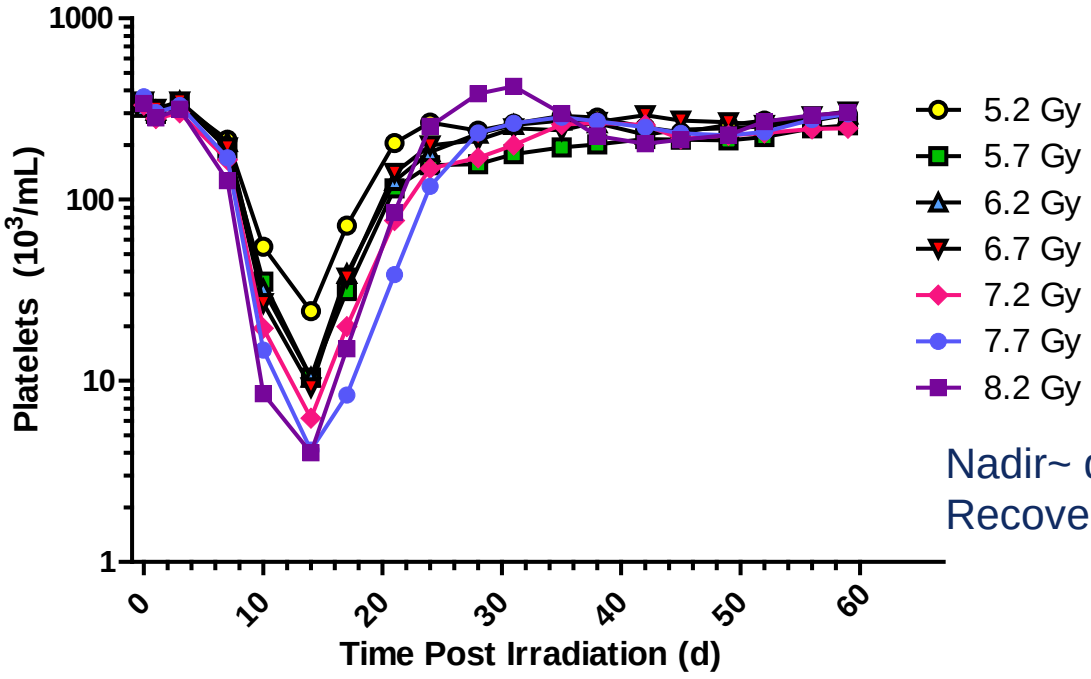






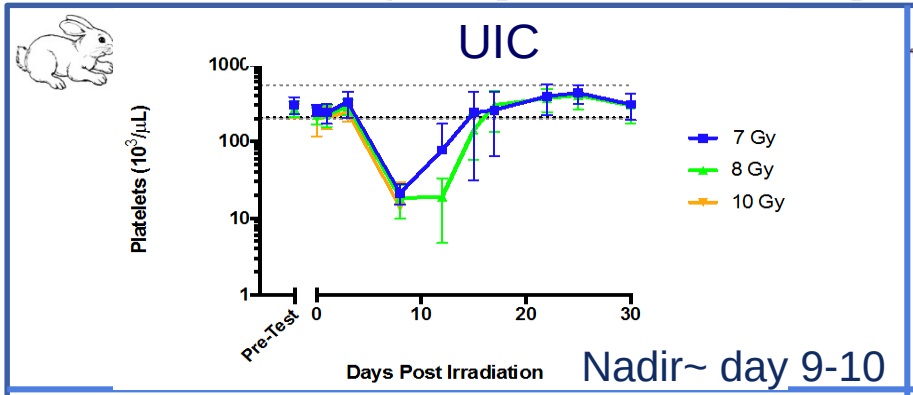


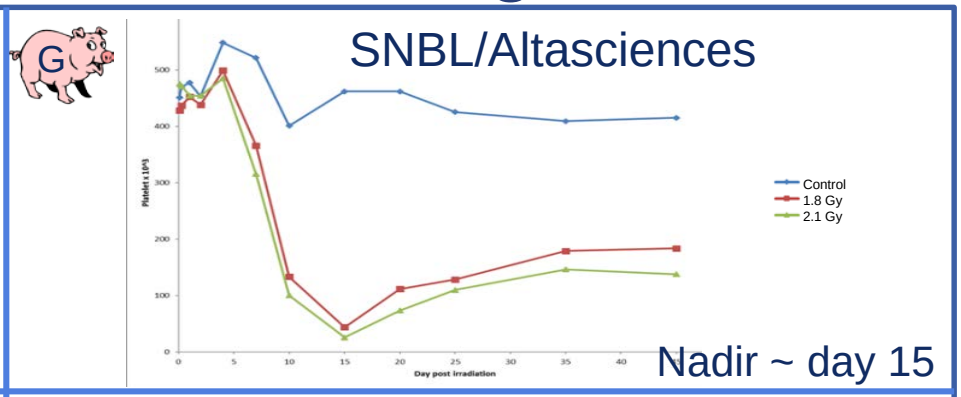
NHP Platelets Begin to Decline Between Days 4-7 in Response to Ionizing Radiation

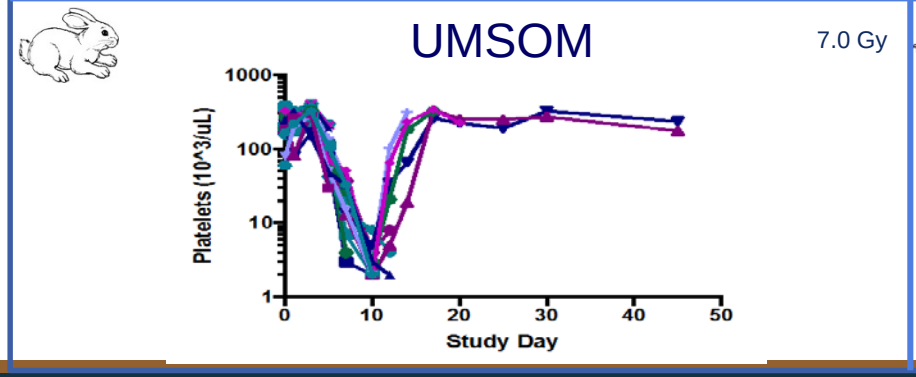


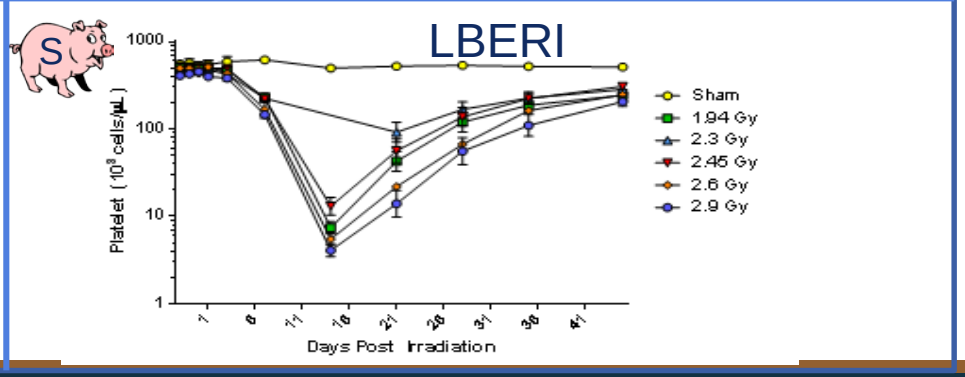
Nadir~ day 14
Recovery~ day 25

Rabbits and Minipigs have a Similar Thrombocytopenic Response Following Irradiation

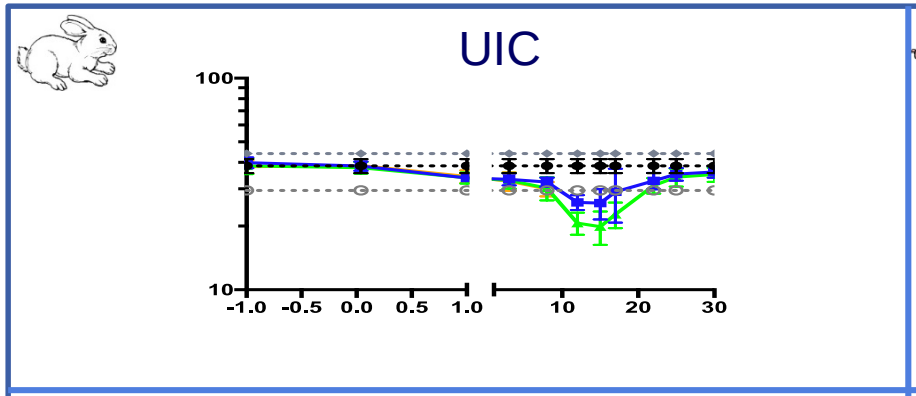


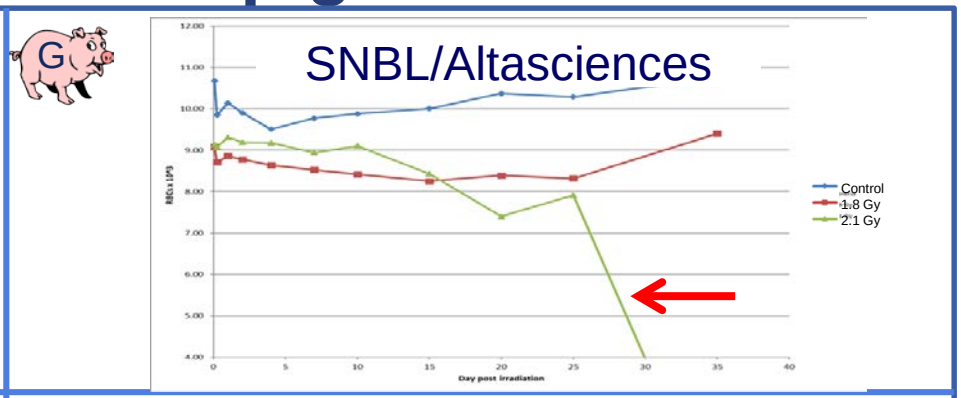


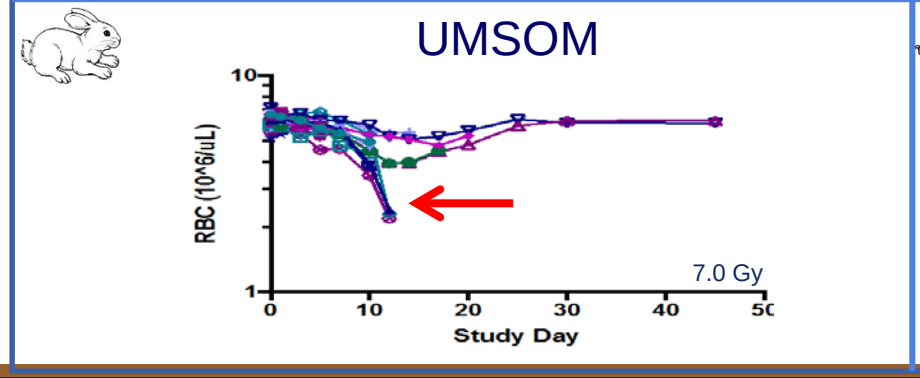


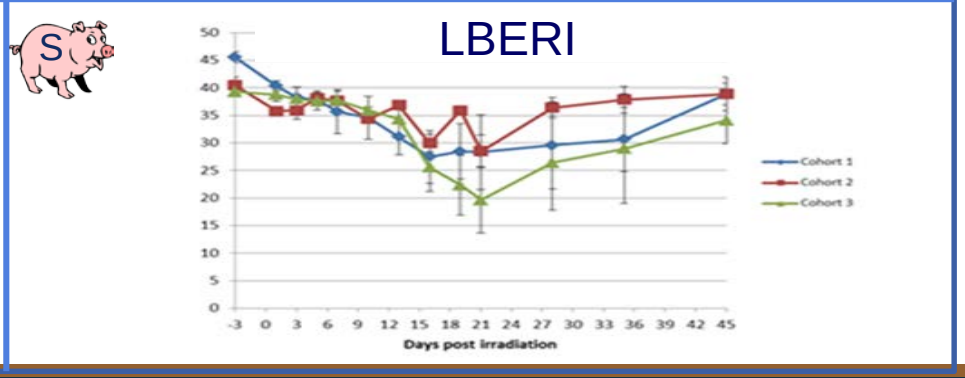


RBCs Decrease Following Irradiation of Rabbits and Minipigs





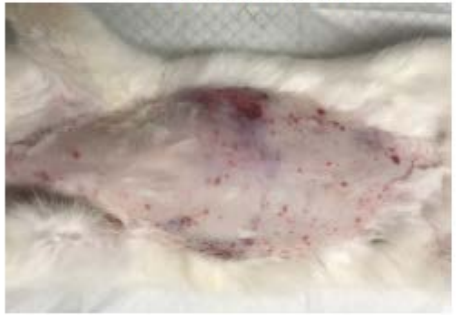




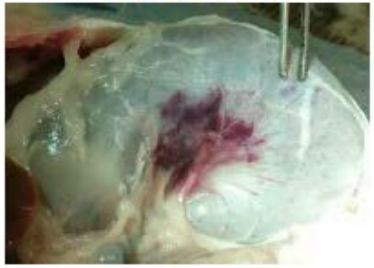
Examples of Bleeding in Irradiated Rabbits and Minipigs

Male New Zealand Rabbit

RIC07, 7.50 Gy



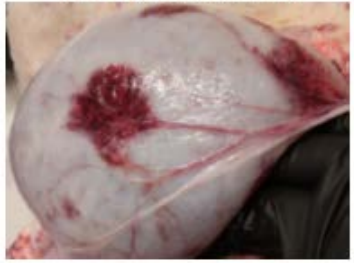
RIC03, 8.50 Gy



Male Gottingen Minipig

ID690, D13, 2.50 Gy

ID690, D13, 2.50 Gy



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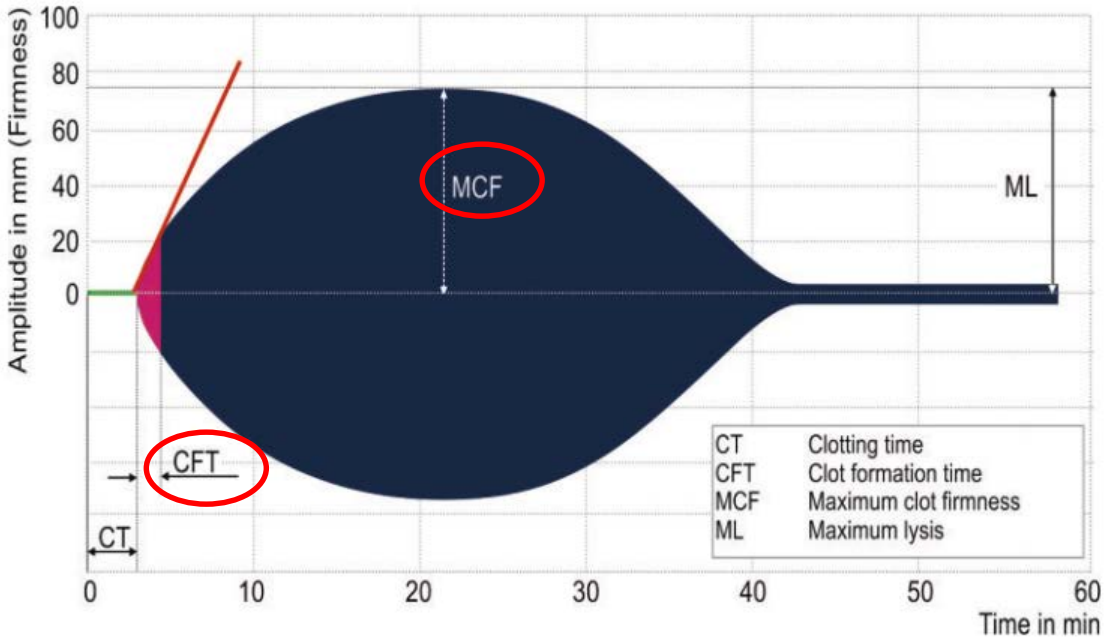
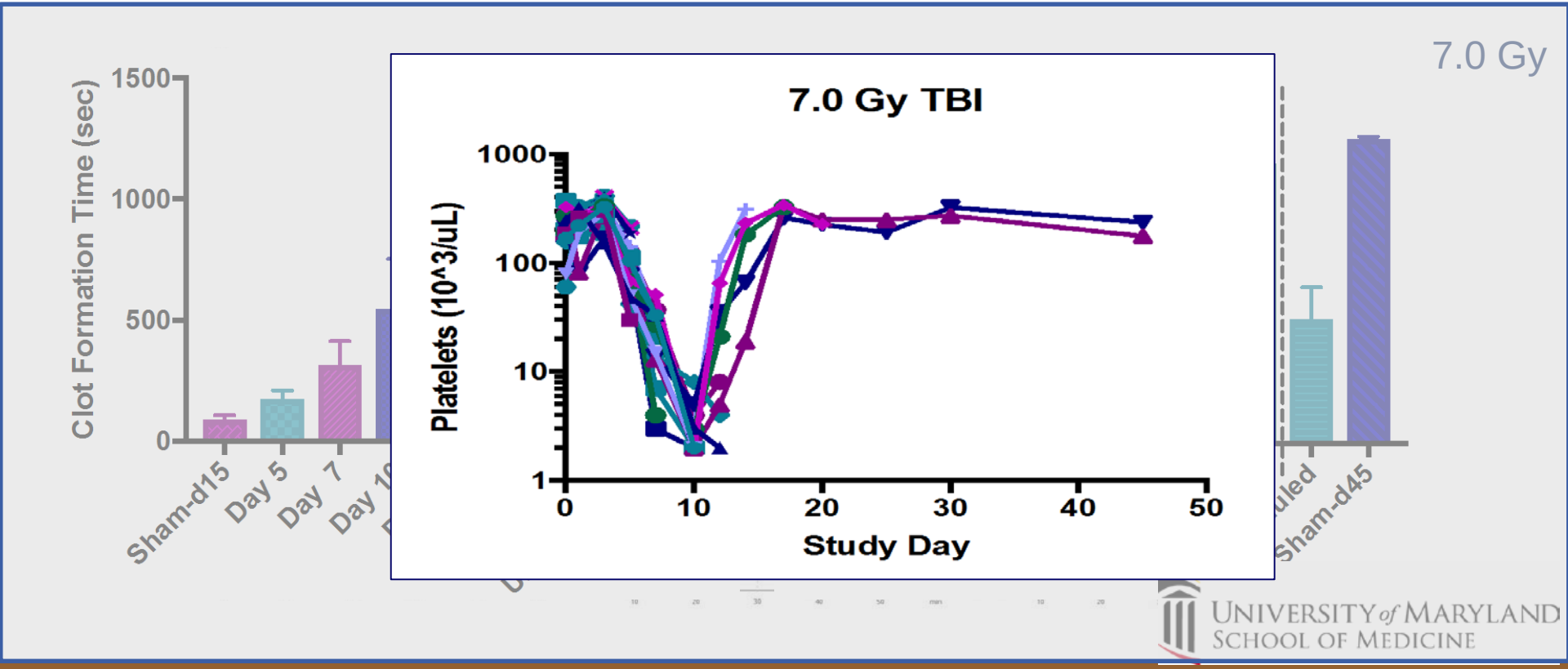
Critical Parameters of Thromboelastometry (ROTEM or TEG)



Radiation Impairs Clot Formation in NZW Rabbits



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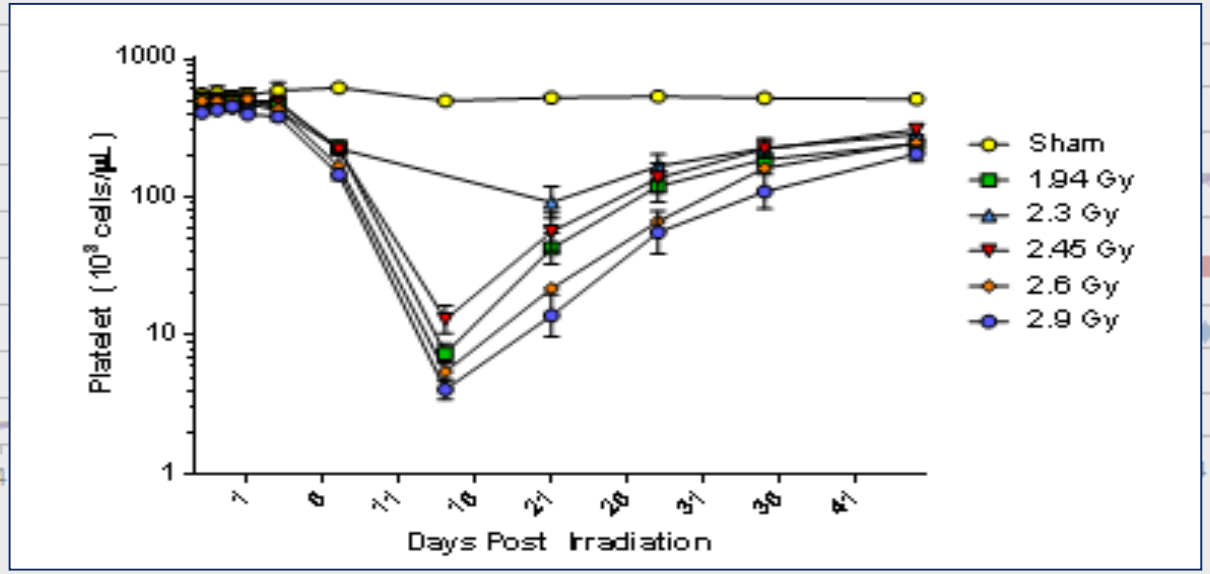
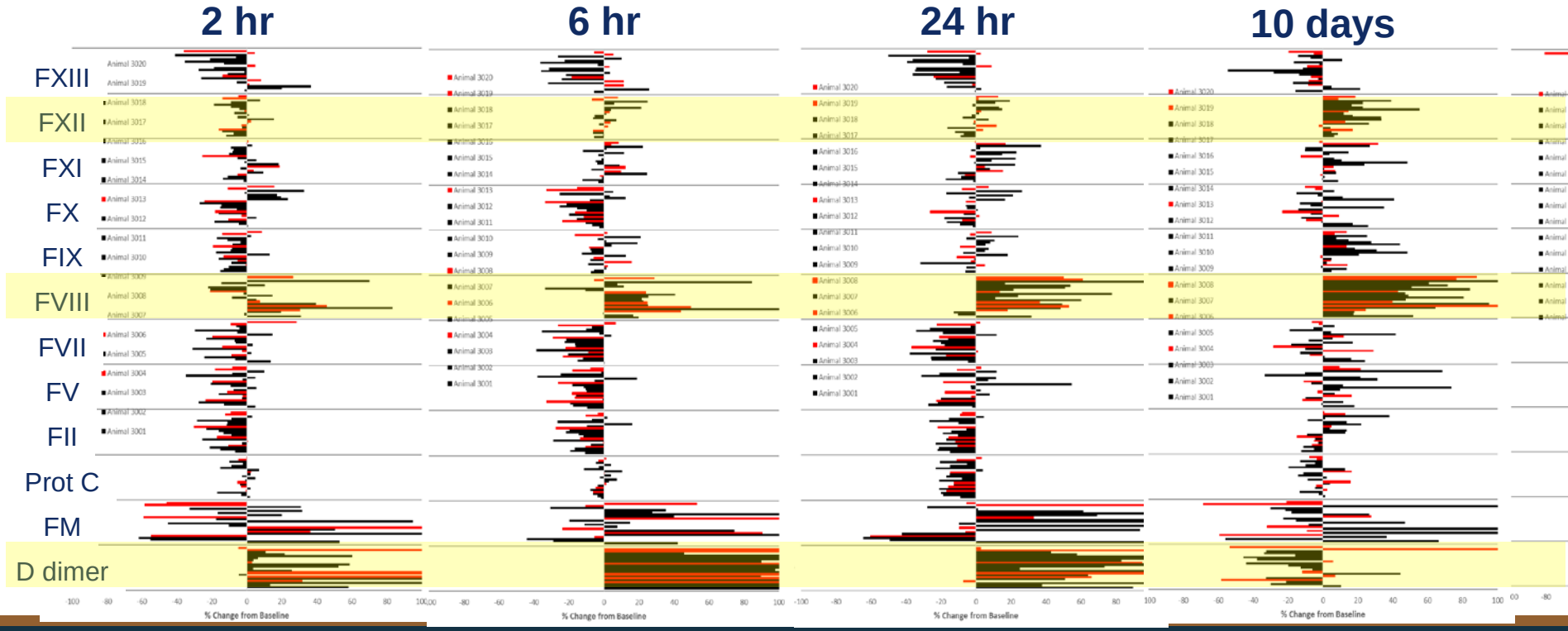
Radiation Impairs Clot Formation in Sinclair Minipigs



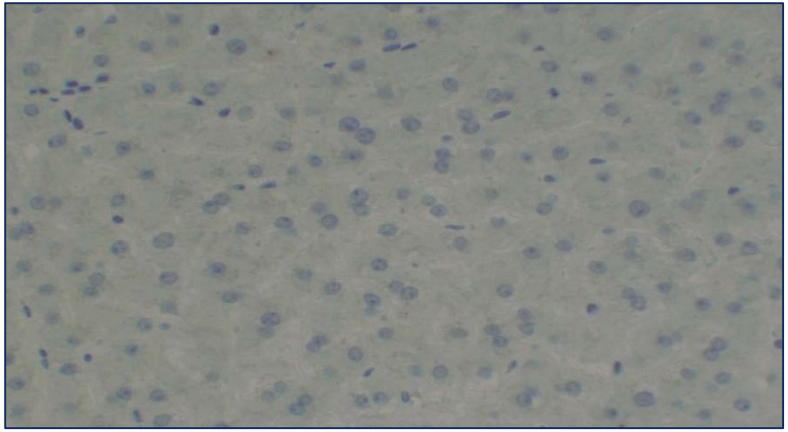
Dysregulation of all Coagulation Factor Levels in the Irradiated Göttingen Minipig

SNBL USA

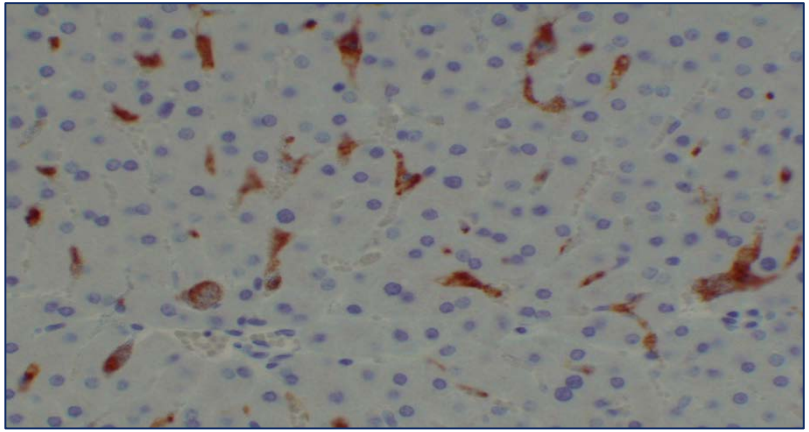
Altasciences CLINICAL RESEARCH



Deposition of Fibrin in Livers of Irradiated Rabbits



Control animal,
not irradiated
200x



10 Gy
Sacrifice on day 12
200x

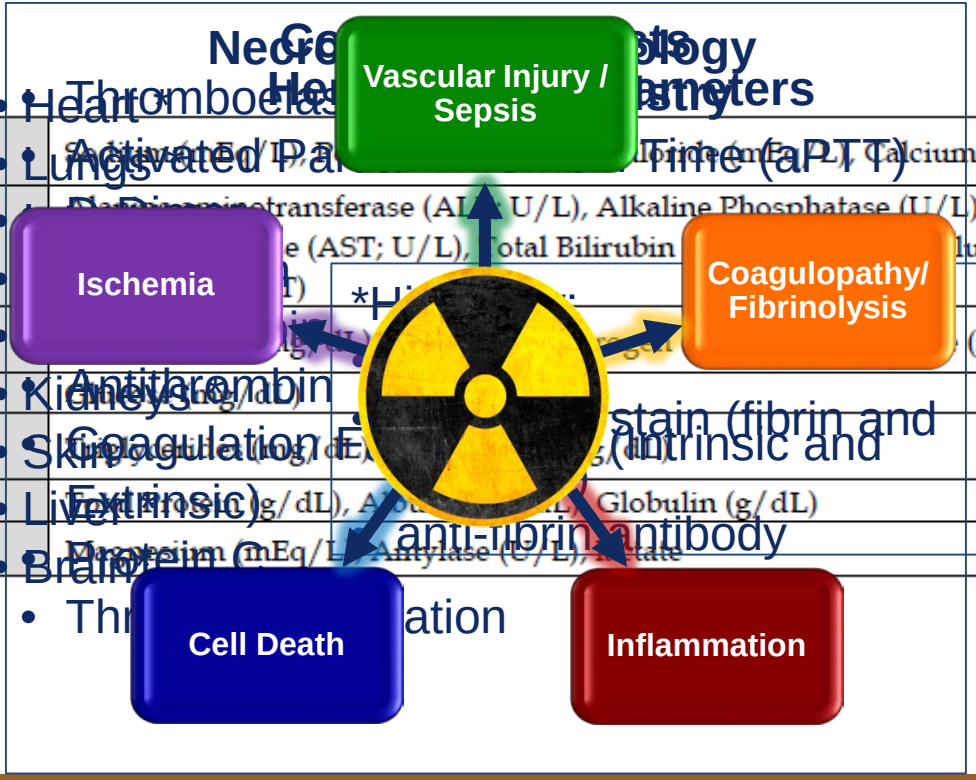
UIC University of Illinois at Chicago

Additional Assays to Characterize Natural History

Pa	Electrolytes	Sodium (mEq/L), P… …loride (mEq/L), Calcium (mg/dL)
Re	Liver function	Aminotransferase (AL… U/L), Alkaline Phosphatase (U/L), Aspartate …e (AST; U/L), Total Bilirubin … …lutamyl …
Pla	Renal function	… (mg/dL)
He	Blood glucose	…
He	Lipid profile	…
Me	Protein	… Globulin (g/dL)
Me	Other	Magnesium (mEq/L), Amylase (U/L), Lactate
he		

- Heart
- Lungs
- Kidneys
- Skin
- Liver
- Brain

- Thrombocytes
- Activated Pa… Time (aPTT)
- Antithrombin
- Coagulation F… stain (fibrin and …(intrinsic and Extrinsic)
- Thr… ation



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How to Contact BARDA

medicalcountermeasures.gov/home.aspx
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!