Thrombopoietin Mimetic as Radioprotectant against High Energy Radiation Exposure

Venkat Dronamraju PhD

Scientist, HJF

AFRRI
Uniformed Services University

Ghosh-Kumar-Holmes Hampton Lab

Armed Forces Radiobiology Research Institute

Uniformed Services University of the health Sciences

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Conflict of Interest Statement

Neither I nor my family have any financial interest in any commercial product, service, or organization providing financial support for this research.

This presentation includes confidential data.

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BACKGROUND

OPERATIONAL CONTEXT: THE NEED FOR NOVEL COUNTERMEASURES

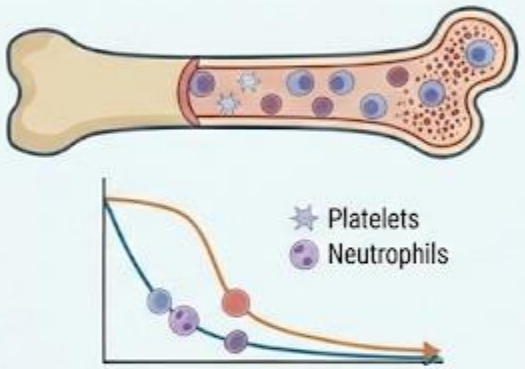
THREAT: RENEWED GEOPOLITICAL & ACCIDENTAL RISK

Asymmetric Warfare
(Improvised Nuclear Devices)

Resurgence of Tactical Weapon Rhetoric

Civilian Infrastructure Accidents
in Conflict Zones

RELEVANCE: HEMATOPOIETIC ACUTE RADIATION SYNDROME (H-ARS)

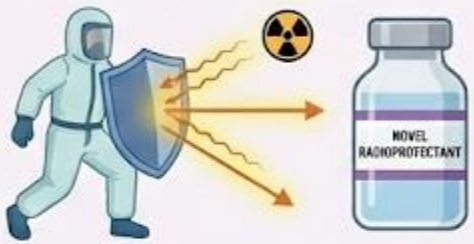


Massive Bone Marrow Destruction
(Pancytopenia)

Primary Cause of Death < Day 30

Leads to Lethal Hemorrhage & Infection

GAP: UNMET MEDICAL NEED FOR COUNTERMEASURES



Lack of FDA-Approved Radioprotectants
(Preventative options are non-existent)

Logistical Limitations
(Cold Chain, Daily Injections)

Lineage-Specific Rescue
(Mostly Neutrophils, Ignores Platelets/RBCs)

No Protection Against Delayed Effects
(e.g., Lung Fibrosis)

A CRITICAL NEED EXISTS FOR A SHELF-STABLE, SINGLE-DOSE, MULTI-LINEAGE MEDICAL COUNTERMEASURE.

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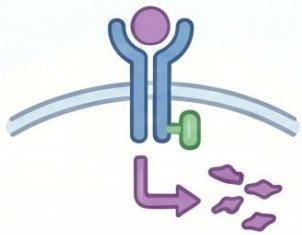
JNJ-26366821: A Thrombopoietin Mimetic (TPOm)

WHAT IS TPOm & WHO MADE IT

Small molecule mimetic of Thrombopoietin (TPO) peptide, Developed by Janssen Pharmaceuticals (Johnson & Johnson).



MECHANISM OF ACTION: c-Mpl PATHWAY

Binds to and activates the c-Mpl receptor on hematopoietic stem cells and megakaryocytes, stimulating platelet production.

ADVANTAGES OF TPOm

Stable, non-immunogenic, shelf-stable, potentially single-dose effective for acute radiation syndrome.

CURRENT WORK AT AFRRI

Funding from JWMRP and NIAID U01.

DOSE USED & ROUTE OF ADMINISTRATION

In mice given as single subcutaneous injection at 1 mg/kg.

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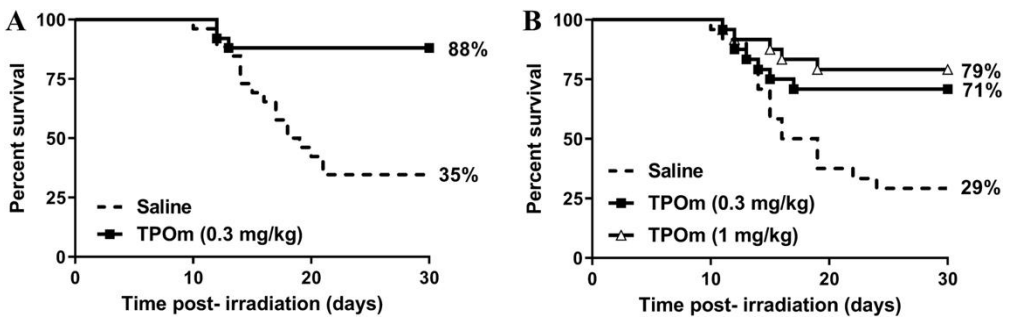
JNJ-26366821, a PEGylated thrombopoietin mimetic (TPOm)

CD2F1 male mice, TBI (gamma)



4h post-TBI 24h post-TBI

Mitigation of total body irradiation-induced mortality and hematopoietic injury of mice by a thrombopoietin mimetic (JNJ-26366821)

Vidya P Kumar [1,#], Gregory P Holmes-Hampton [1,#], Shukla Biswas [1], Sasha Stone [1], Neel Kamal Sharma [1], Bernadette Hritzo [1], Mary Guilfoyle [2], Gary Eichenbaum [2], Chandan Guha [3], Sanchita P Ghosh [1,✉]

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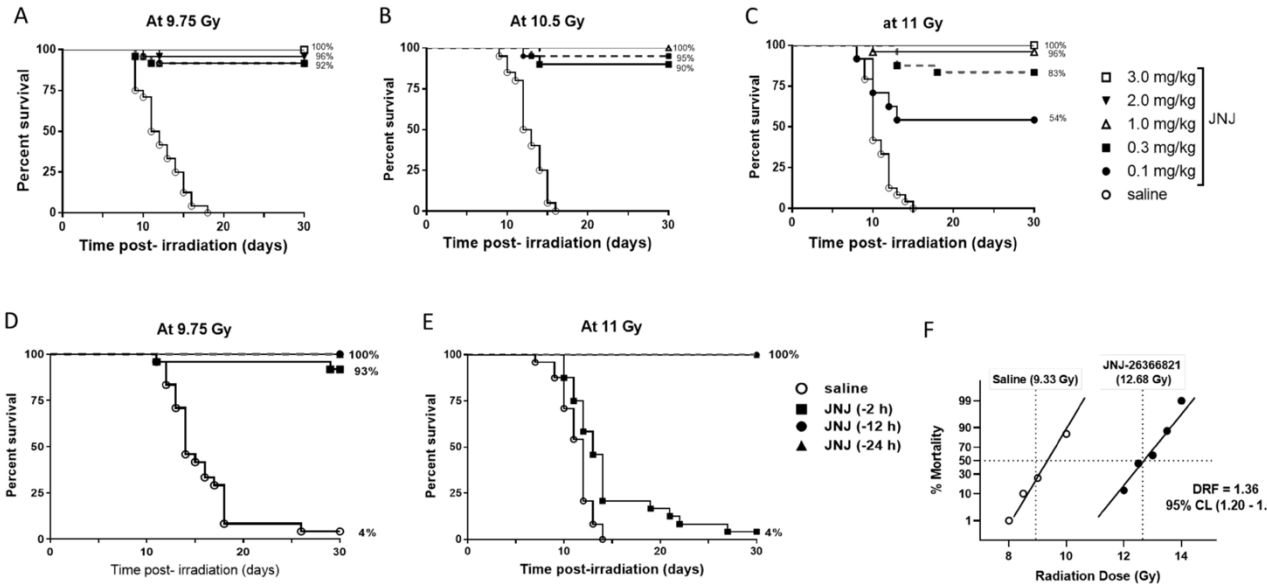
PMCID: PMC8894488 PMID: 35241733

CD2F1 male mice, TBI (gamma)



Pre-TBI

PEGylated thrombopoietin mimetic, JNJ-26366821 a novel prophylactic radiation countermeasure for acute radiation injury

Gregory P Holmes-Hampton [1,#], Vidya P Kumar [1,#], Shukla Biswas [1], Sasha Stone [1], Neel K Sharma [1], Betre Legesse [1], Justin Vercellino [2], Chandan Guha [2], Gary Eichenbaum [3], Sanchita P Ghosh [1,✉]

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PMCID: PMC10502090 PMID: 37709916

In the following studies TPOm was administered as prophylactic at 6h to 12h pre-TBI in both gamma and mixed field radiation exposure models

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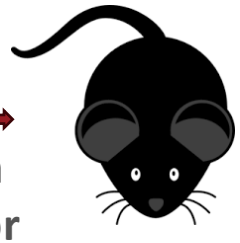
1. SURVIVAL

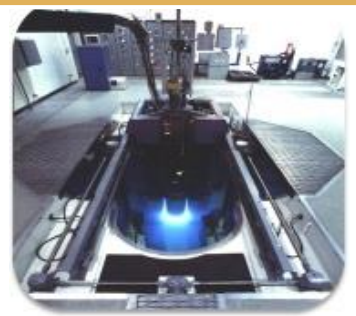
TPOm
at 6h or
12h Pre-TBI



Day 0

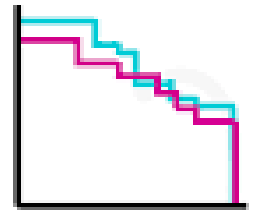
Co-60 (Gamma)

TRIGA (Mixed field*)



*65% neutron and 35% gamma

30-days



KAPLAN-
MEIER CURVE

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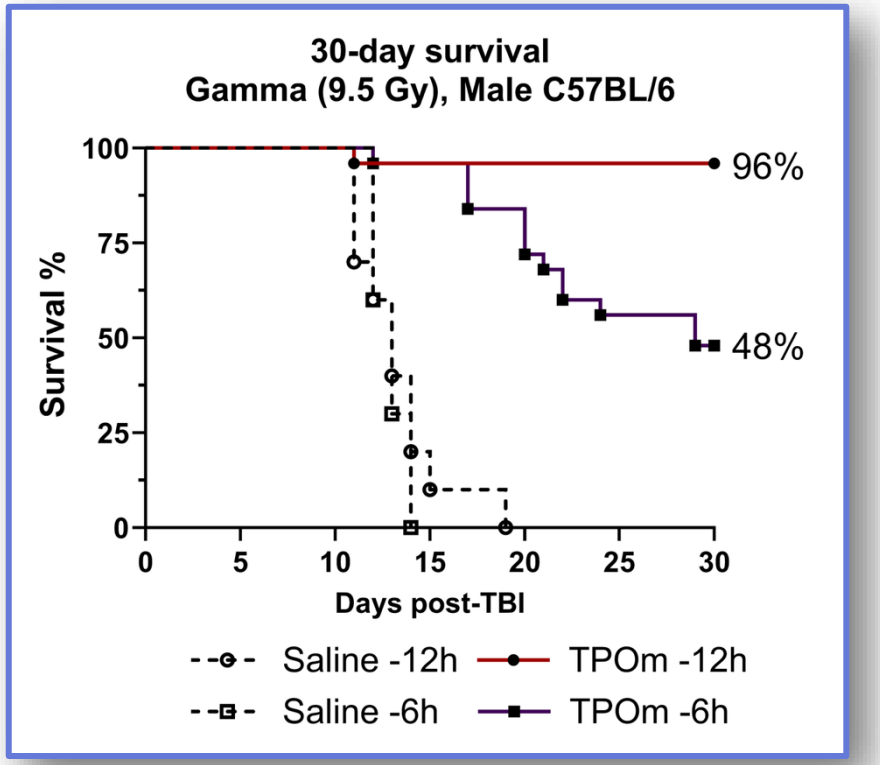
Pre-treatment with TPOm improves survival in low LET scenario

Co-60 (Gamma)



Statistics	For -6h	For -12h	-6h Vs -12h
Log-rank test (Mantel Cox)	p< 0.0001	p< 0.0001	p= 0.0002
Fisher's exact test	p= 0.0069	p< 0.0001	p= 0.0003

n= 10 for saline, n=25 for TPOm

- TPOm given prior to LD100/30 radiation (9.5) Gy
- Higher survival in TPOm treated animals
- Validated in female mice (data not shown)

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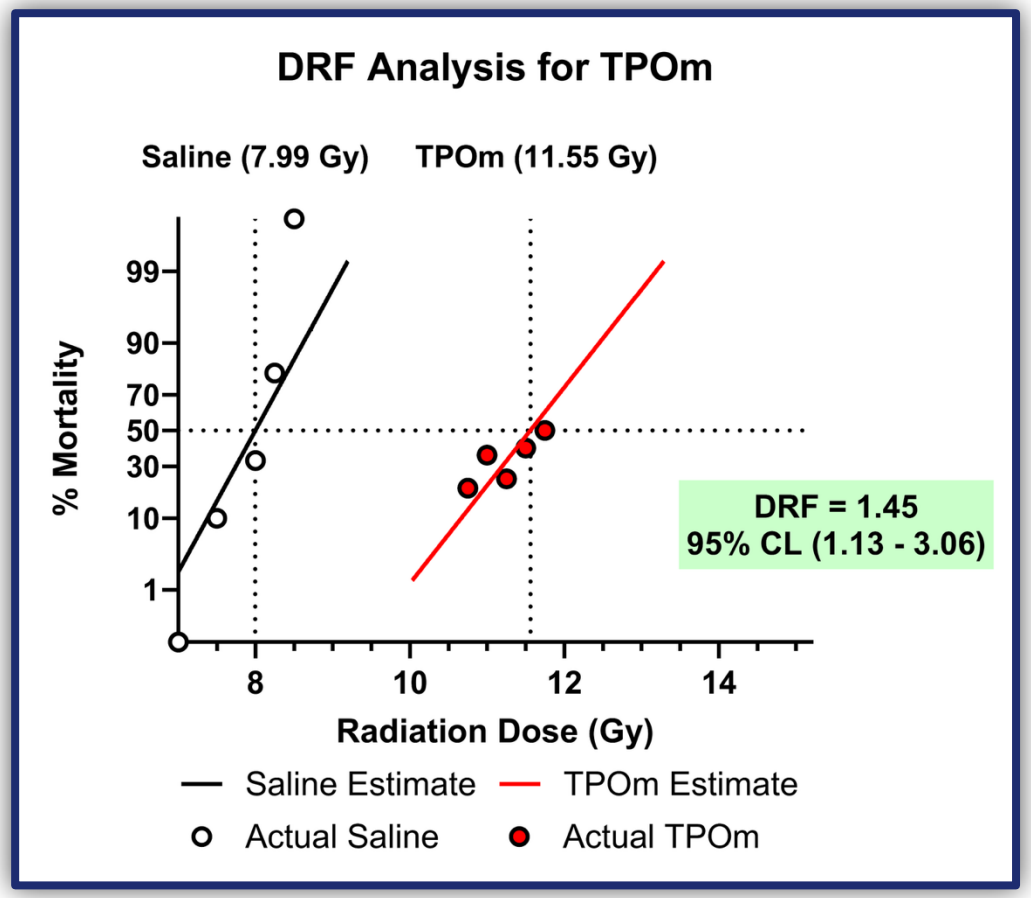
Dose Reduction Factor in low LET

(Survival data)

Co-60 (Gamma)



LD50/30 Summary Table

Group	LD50/30 (Gy)	95% CI
Vehicle	7.99 Gy	7.69 – 8.33
TPOm	11.55 Gy	11.27 – 12.04

n=25 for vehicle and TPOm at lower doses.
At higher doses n=15 was used for vehicle and n=20 for TPOm
Data fitted using parallel slopes probit model (Pearson-goodness of fit), p=0.063

DRF = LD50 (Countermeasure) / LD50 (Vehicle)

- Dose reduction factor was found to be 1.45 in male mice exposed to TBI in Co-60 (gamma).
- To be validated in female mice.
- Previous studies in CD2F1 mice showed DRF of 1.36 when TPOm was given 24h pre-TBI

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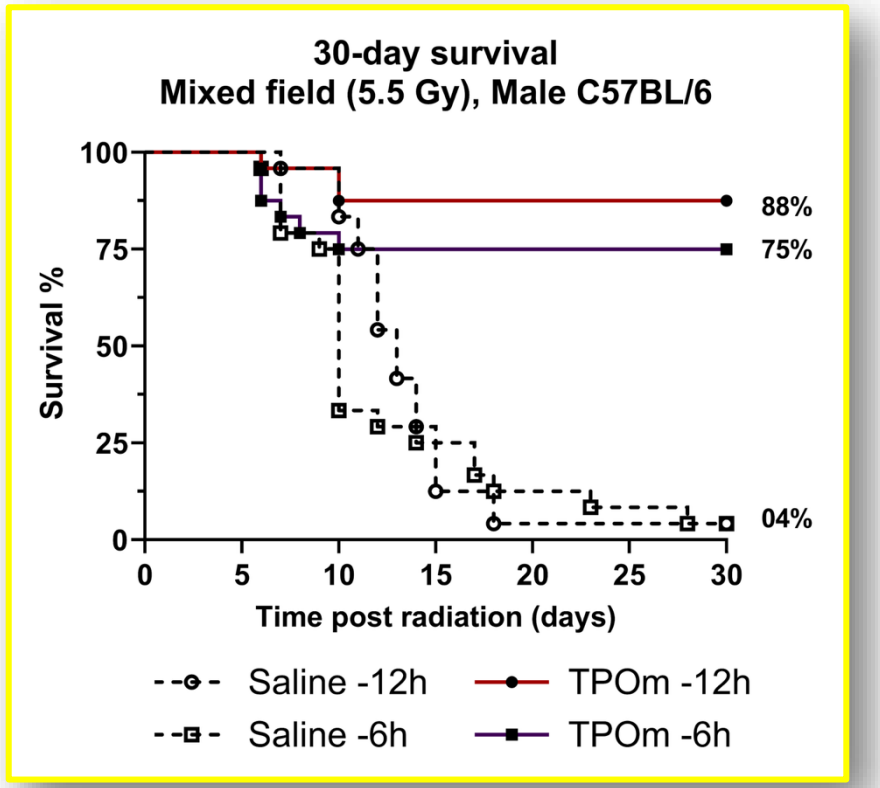
Pre-treatment with TPOm improves survival in high LET scenario

TRIGA (Mixed field*)

*65% neutron and 35% gamma



Statistics	For -6h	For -12h	-6h Vs -12h
Log-rank test (Mantel Cox)	p< 0.0001	p< 0.0001	p= 0.2452 (ns)
Fisher's exact test	p< 0.0001	p< 0.0001	p= 0.4614 (ns)

n= 24 for saline, n=24 for TPOm

- **TPOm given prior to LD90/30 radiation (5.5) Gy**
- **Higher survival in TPOm treated animals in high LET scenario as well**
- **To be validated in female mice**

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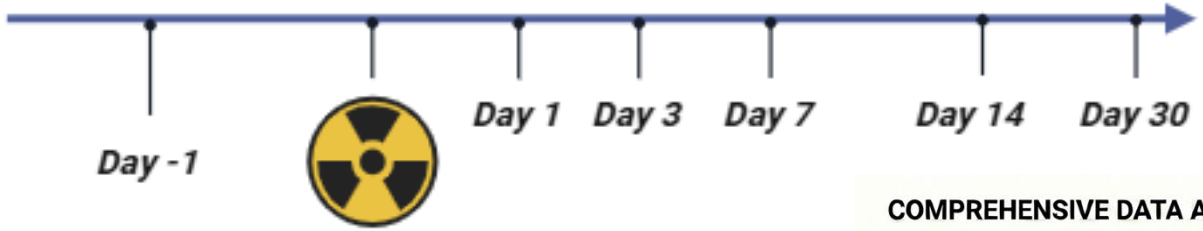
2. RECOVERY

TPOm administered s.c.
12 hours prior to
irradiation

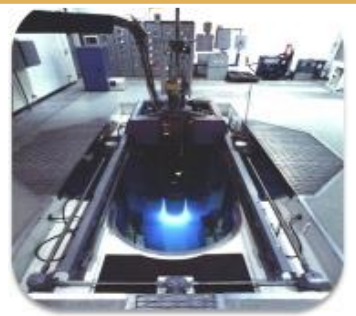
Blood sample collected
through cardiac puncture

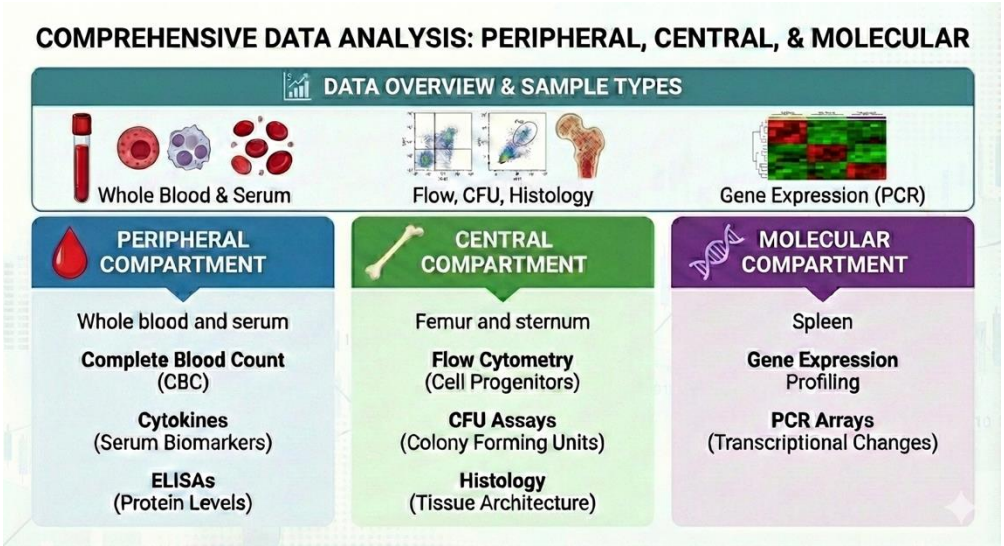
After blood sample collection at each time point:
Sternum, spleen, thymus and Bone Marrow were collected (n=5) per timepoint



LD30/30 @ 4.8 Gy
High LET (65% neutron +35% gamma)

TRIGA (Mixed field)





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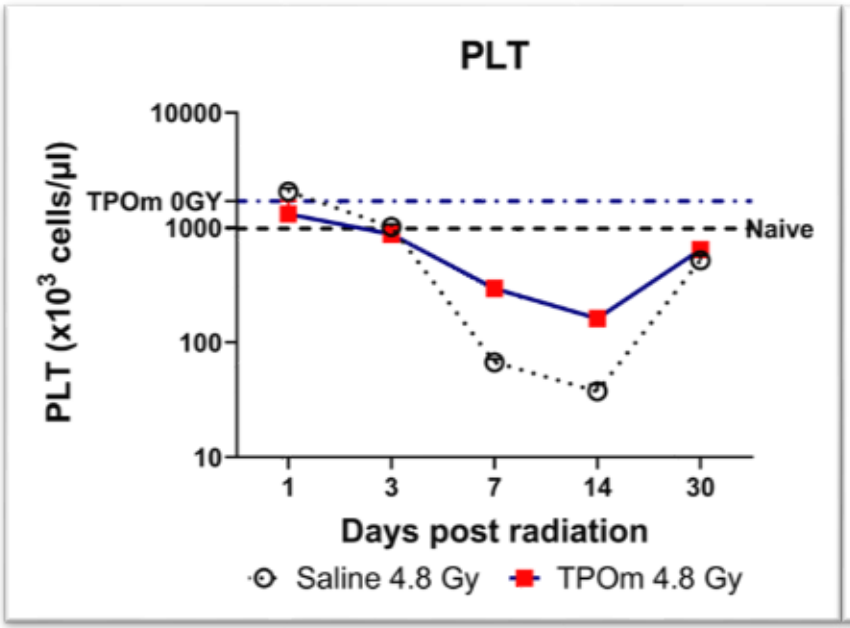
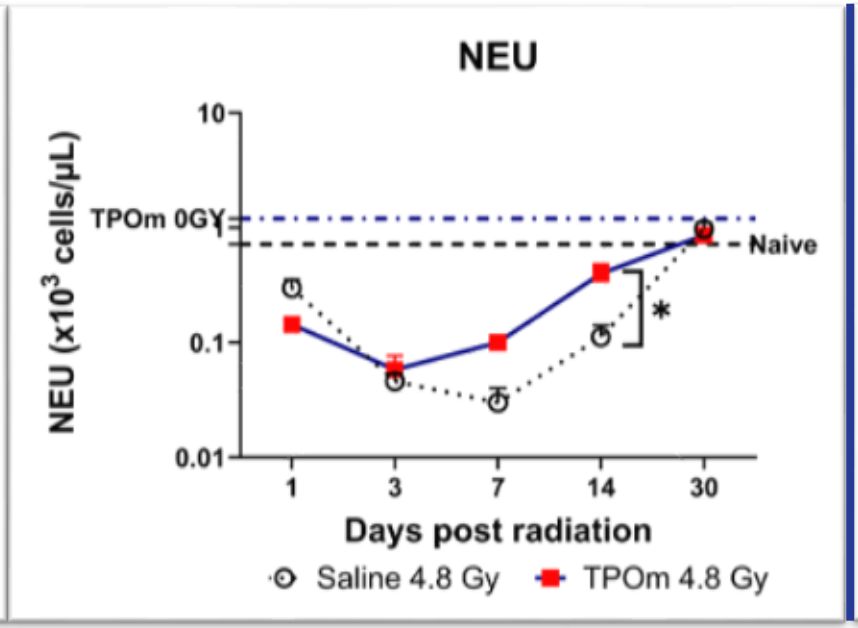
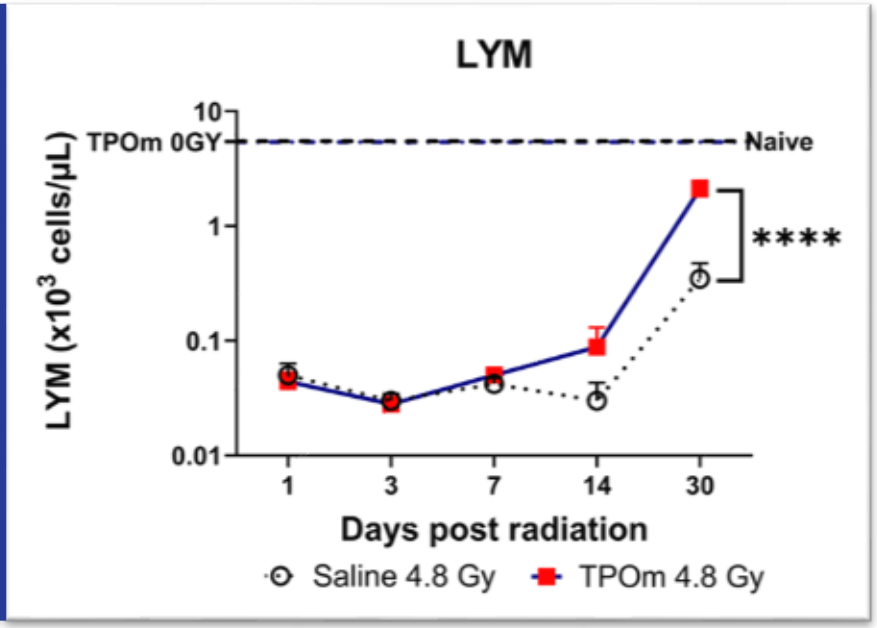
TPOm accelerated peripheral blood cell recovery

(Complete blood cell count)

TRIGA (Mixed field)







Myeloid (PLT, NEU) and Lymphoid (LYM) Lineages increased.
Erythroid (RBC): No change (not shown)

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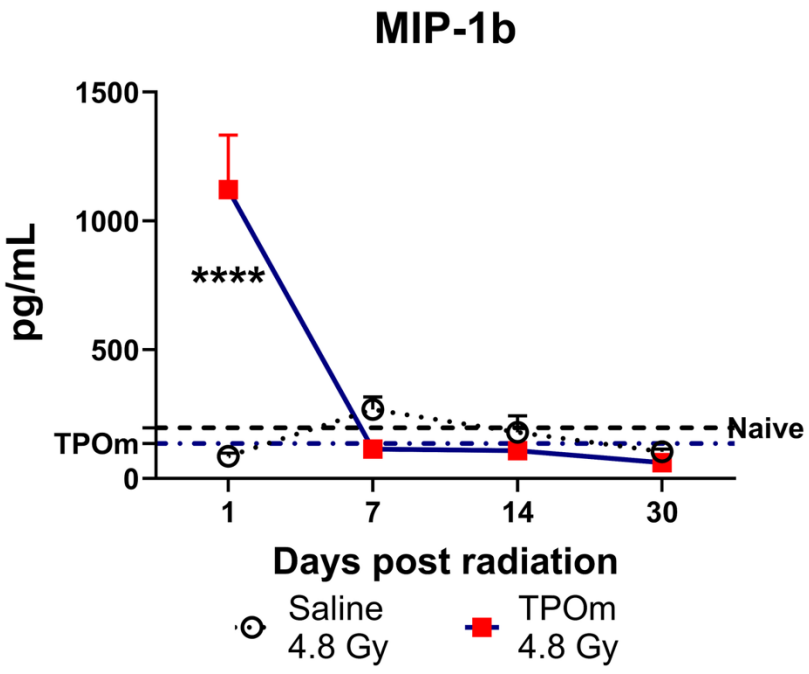
Restoration of Chemotactic and Mucosal Cytokine Signaling

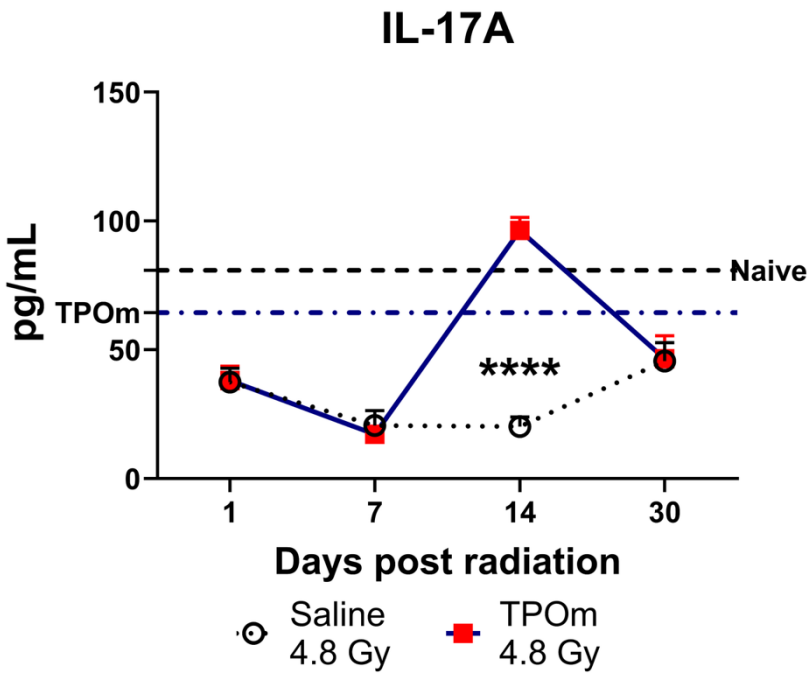
(Bio plex assay)

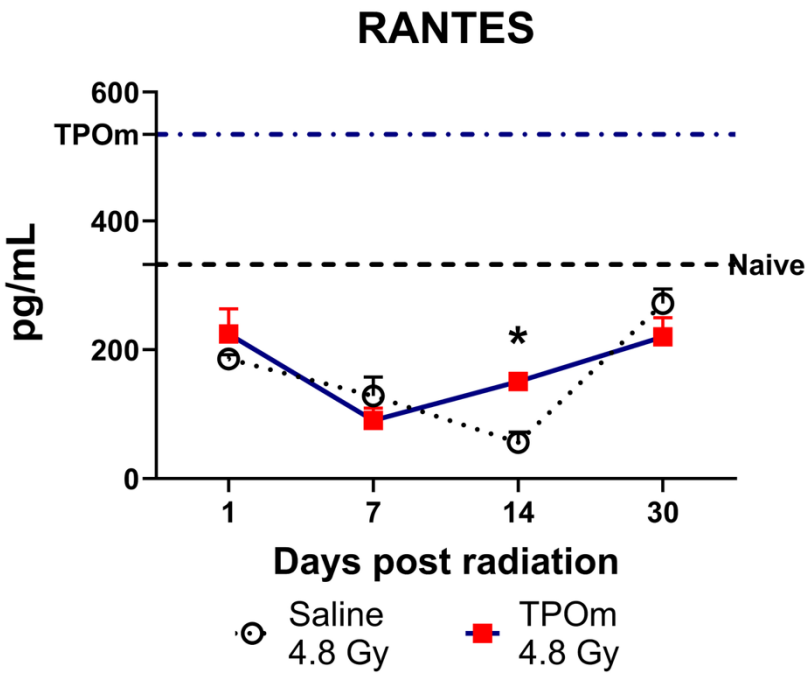
TRIGA (Mixed field)

IMMEDIATE IMMUNE MOBILIZATION

GRANULOPOIESIS AND TRAFFICKING SIGNALS







Increased early response signal (MIP-1b) as well as late recovery signals (IL-17A and RANTES) seen in response to TPOm treatment

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TPOm Accelerates Recovery of Sternum BM

(H&E staining)

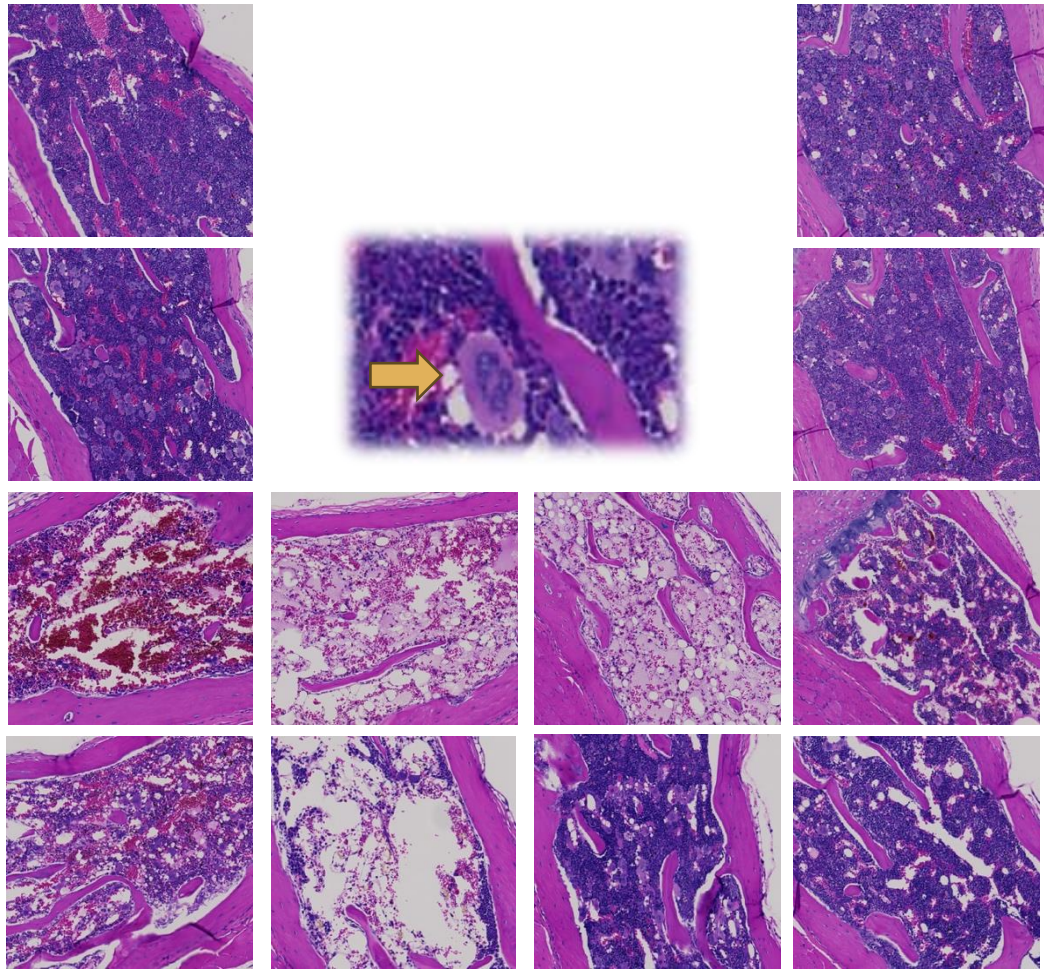
TRIGA (Mixed field)

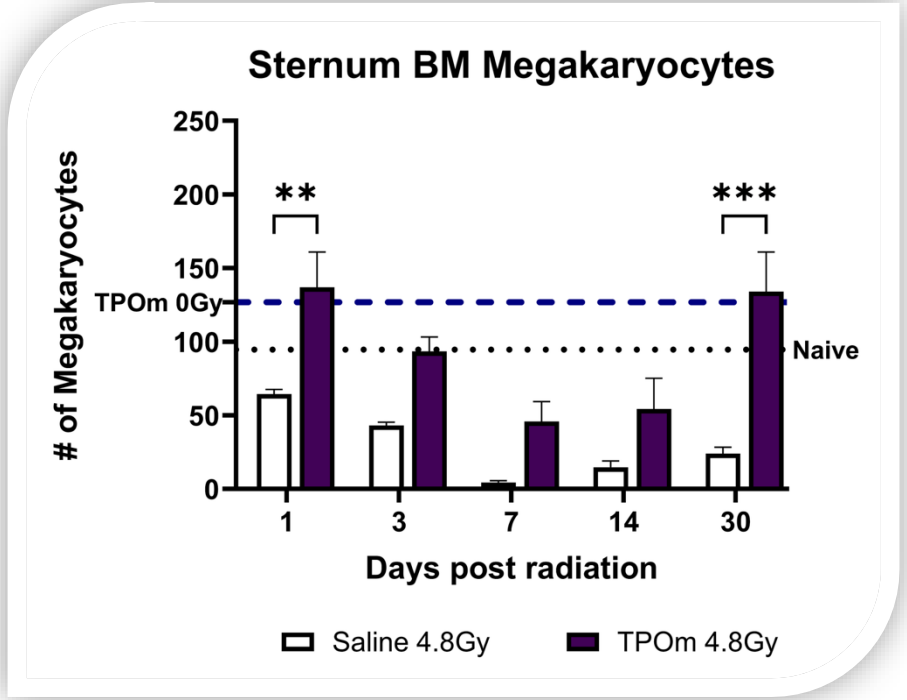
Naive

TPOm 0 Gy

Saline 4.8 Gy

TPOm 4.8 Gy





TPOm induces megakaryocyte prodcution and accelerates recovery of bone marrow cellularity

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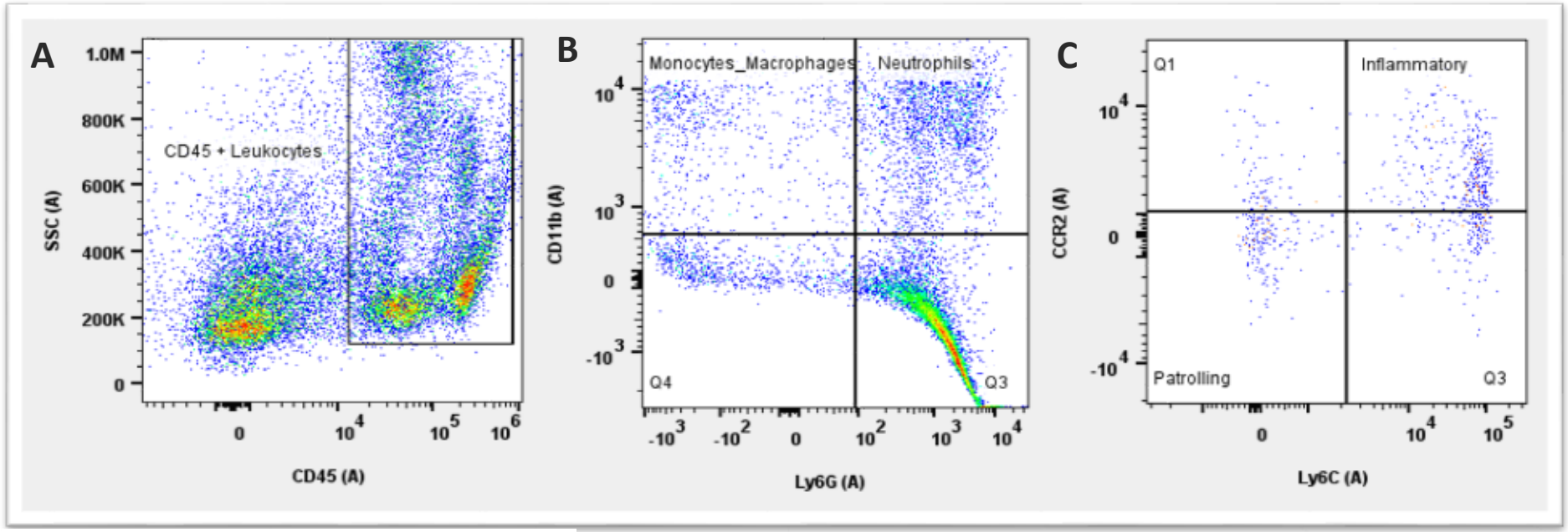
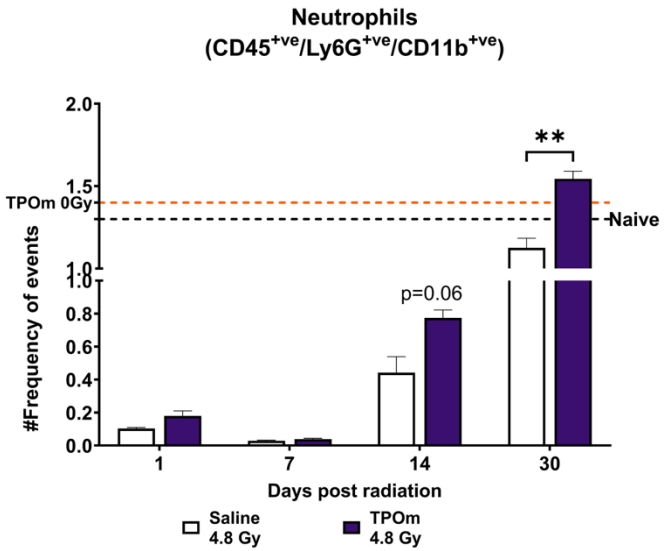
TPOm Drives Neutrophil Differentiation in Femur BM

(Flow Cytometry)

TRIGA (Mixed field)





TPOm treatment drives neutrophil differentiation in the femur bone marrow

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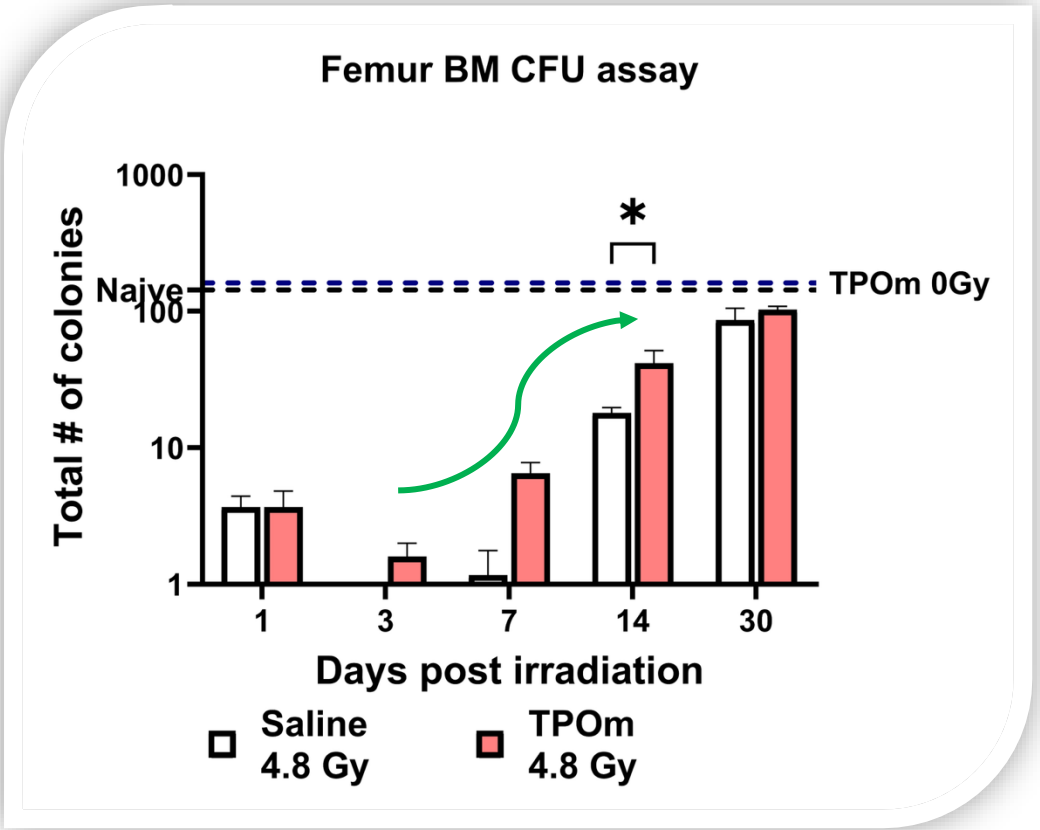
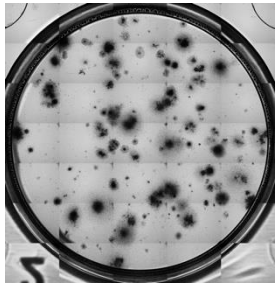
TPOm Preserves Colony Forming Ability of Progenitors in Femur

(CFU assay)

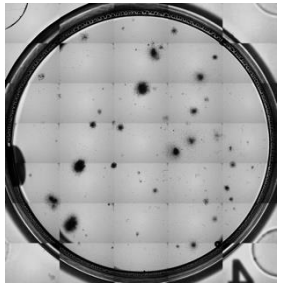
TRIGA (Mixed field)



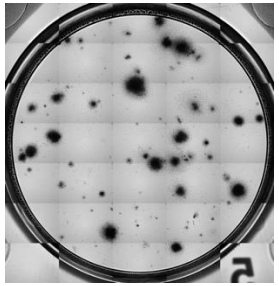
Day 14



Naive
0 Gy



Saline
4.8 Gy



TPOm
4.8 Gy

TPOm preserved the colony forming ability of Femur bone marrow progenitors

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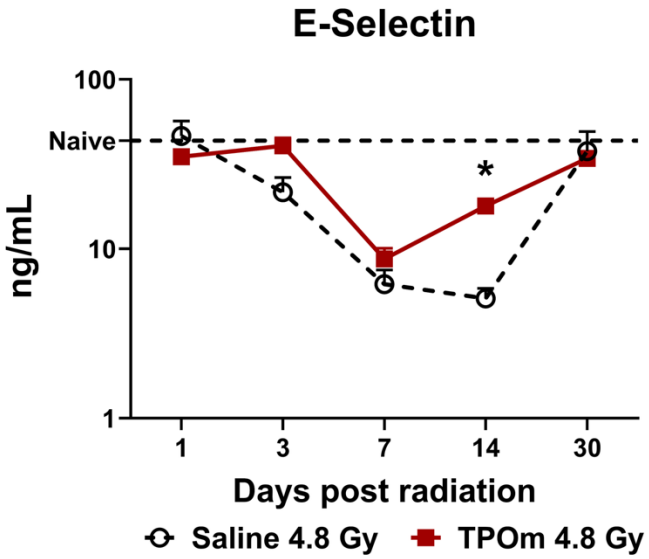
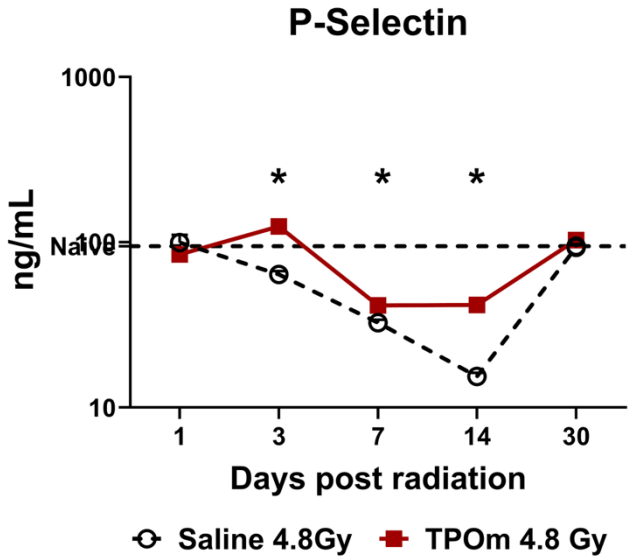
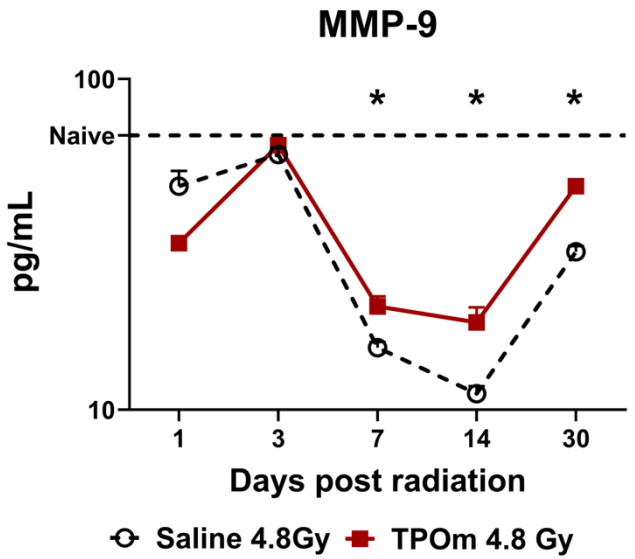
Promotes Vascular Adhesion and Extracellular remodeling

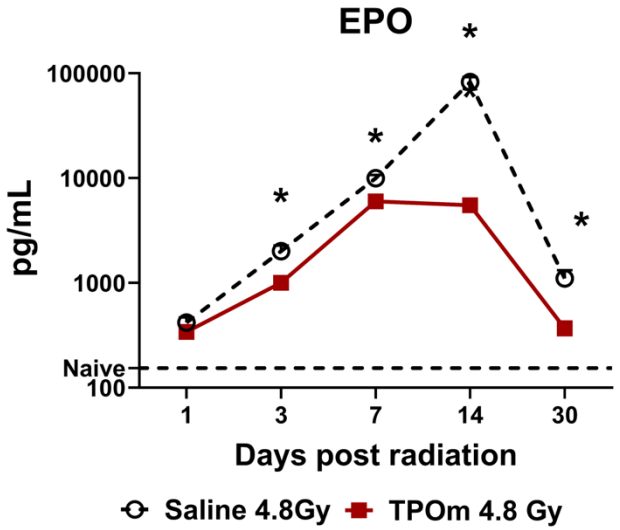
(ELISA assay)

TRIGA (Mixed field)









TPOm promotes a pro-retention vascular phenotype (Selectins) and late-stage matrix remodeling (MMP-9) while mitigating hypoxic stress (EPO)

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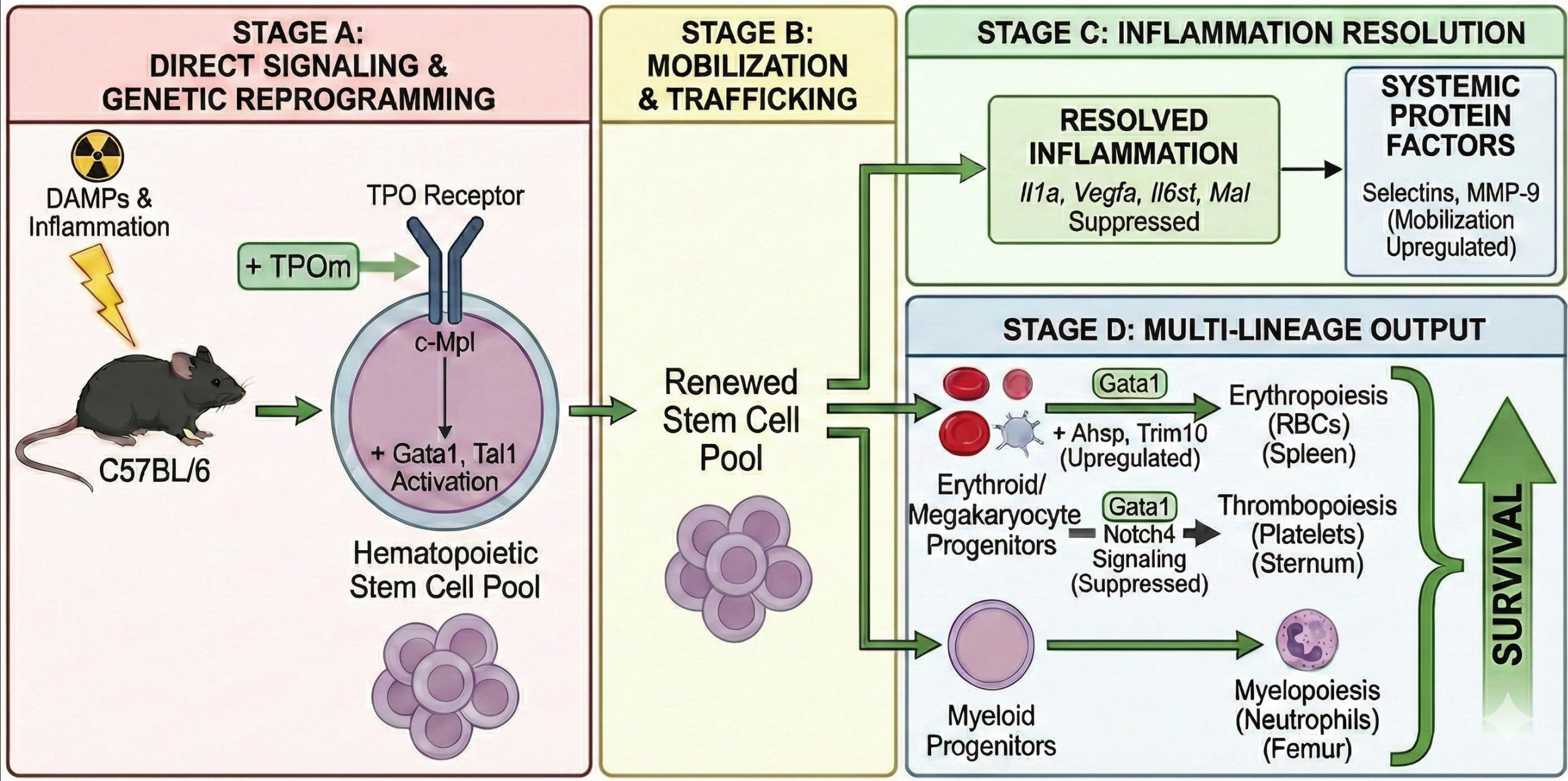
TPOm-Driven Multi-Lineage Recovery Mechanism



SUMMARY & FUTURE DIRECTIONS

SUMMARY OF FINDINGS: SUPERIOR EFFICACY & MECHANISM

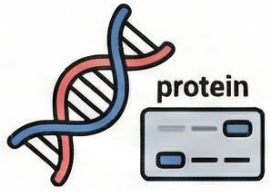
TPOm Confers High DRF of 1.45 ($LD_{50/30}$ shift from 7.99 to 11.55 Gy)

Mechanism Driven by Rescuing Stem Cell Self-Renewal & Resolving Inflammation

Operational Value: Shelf-Stable, Single-Dose, Multi-Lineage Rescue

FUTURE DIRECTIONS: VALIDATION & LONG-TERM STUDY

Sex-Difference Validation: DRF & Mixed-Field Studies in Female Mice



Molecular Deep Dive: Spleen miRNA (TaqMan) & Western Blot Confirmation

Long-Term Sequelae: Assess Delayed Effects (DEARE), specifically Lung Fibrosis

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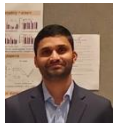

Dr. Venkat Dronamraju PhD
(Scientist 1)

Dr. Brandon Jones PhD
(Scientist 1)

Kefale Wuddie, Zemenu Aschenake, Fetene Dagnew

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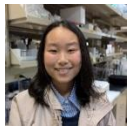

Emily Gu

(Research Assistant)

Previous team members
Carmela Doroteo
Asma Shariff

Dubravka Trakic

(Project Coordinator)

AFRRI Leadership
CAPT Burke
Col Whiteway
CDR King
MAJ Patel

Biomedical Research Imaging Core
Dr. Maureen Hood, PhD
Nikolai Rakhilin, PhD
Salsabila Puronomo

HJF
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Venkat Dronamraju PhD
Scientist, HJF
Ghosh-Kumar-Holmes-Hampton Lab
Venkateshwara.dronamraju.ctr@usuhs.edu

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