Prophylactic vs. Therapeutic Efficacy of Thrombopoietin-mimetics in Mitigating Lethal Irradiation and Attenuating Cardiac Atrophy

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Disclaimers

The views expressed in this presentation reflect the results of research conducted by the authors and do not necessarily reflect the official policy or position of the Defense Health Agency, Department of War, nor the U.S. Government.

The experiments reported herein were conducted in compliance with the Animal Welfare Act and per the principles set forth in the "Guide for Care and Use of Laboratory Animals," Institute of Laboratory Animals Resources, National Research Council, National Academy Press, 2011.

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Integrative Systems Biology

Core Capabilities & Strategic Ecosystem

Deep Discovery

- Next-Gen Sequencing
- Single Cell Omics
- Spectral Assays (LC/MS, OLINK)
- Automated Liquid Handling

Advanced Models

- 3D Cell Culture
- Gnotobiotic Vivarium
- Space Biology/ISS

Data Maneuvering

- DoD HPC Access
- Custom Scripts/Libraries
- Big Data Management

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Countermeasure landscape of radiation

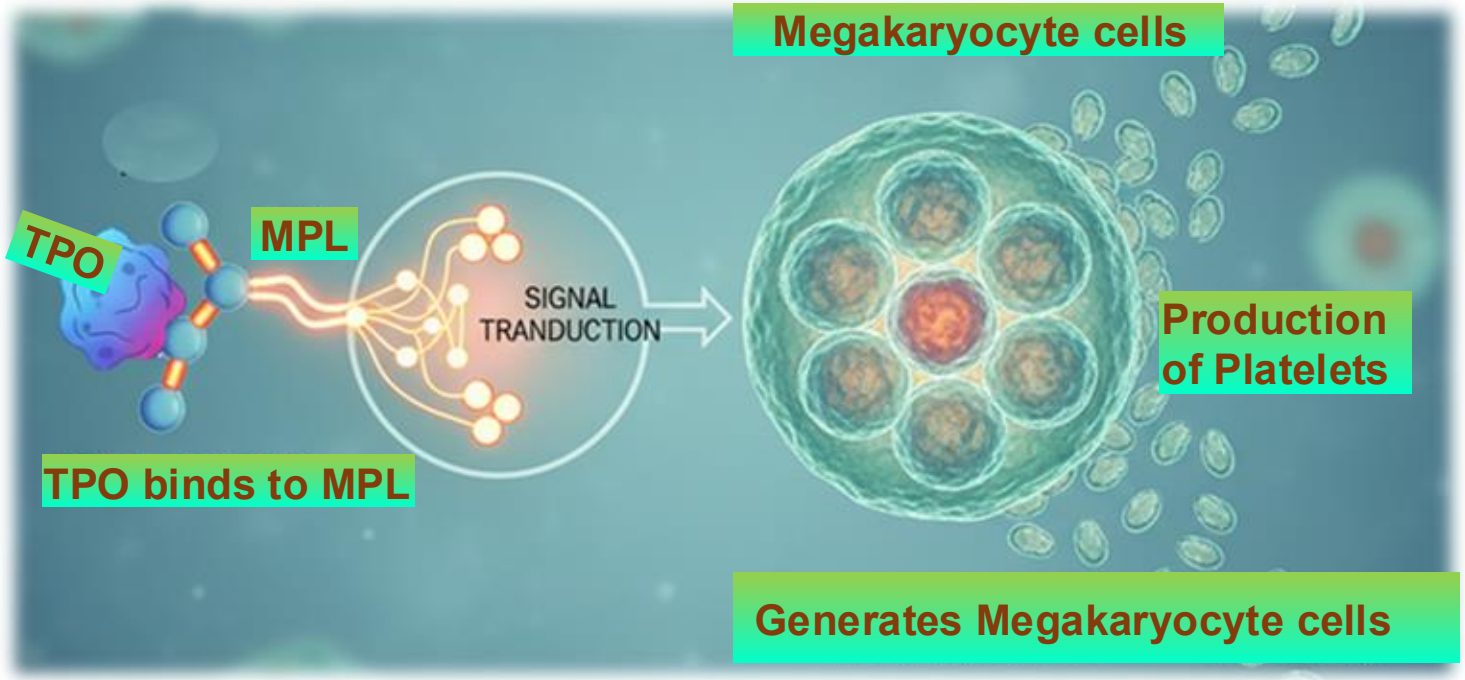
FDA approved nine mitigators of Hematopoietic of ARS (H-ARS):

- Only NPLATE or Romiplostim (approved on 2021) is a TPO mimetic

➢ None of them are approved for prophylactic treatment

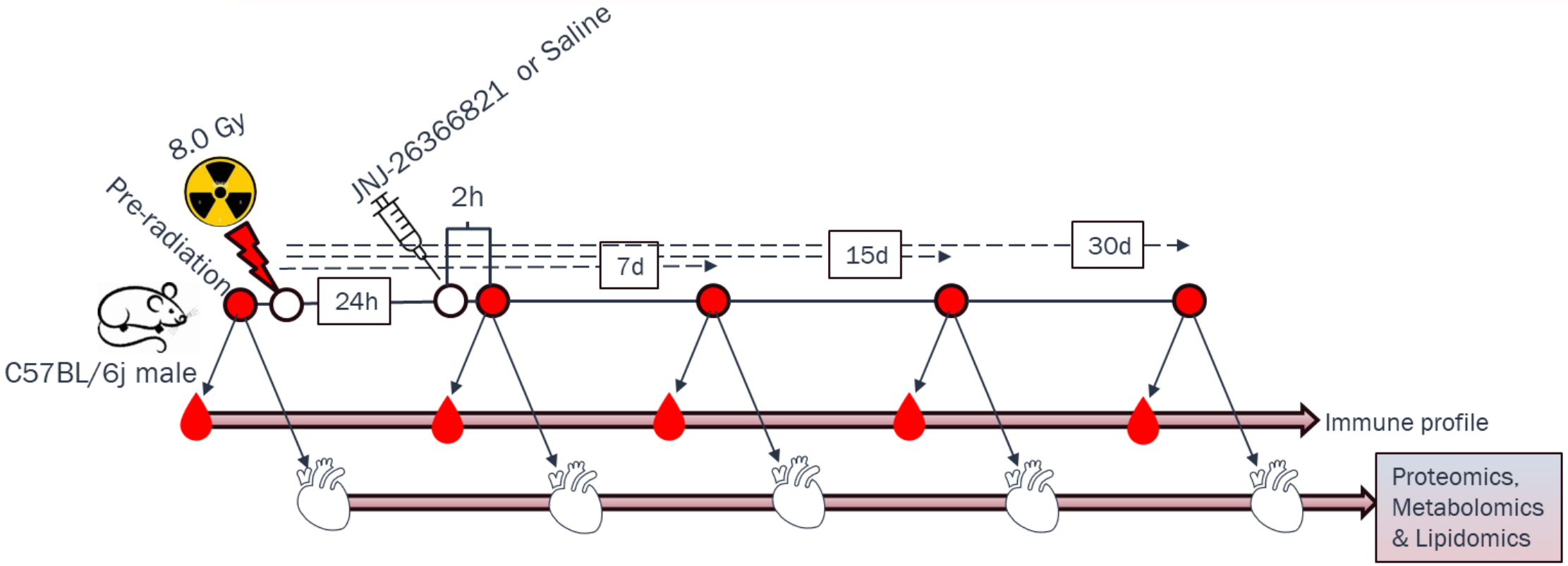
➢ Prophylactic treatment could be significantly useful for the first responders, military personnel, and individuals undergoing radiotherapy

Thrombopoietin (TPO) and hematopoietic cell regeneration



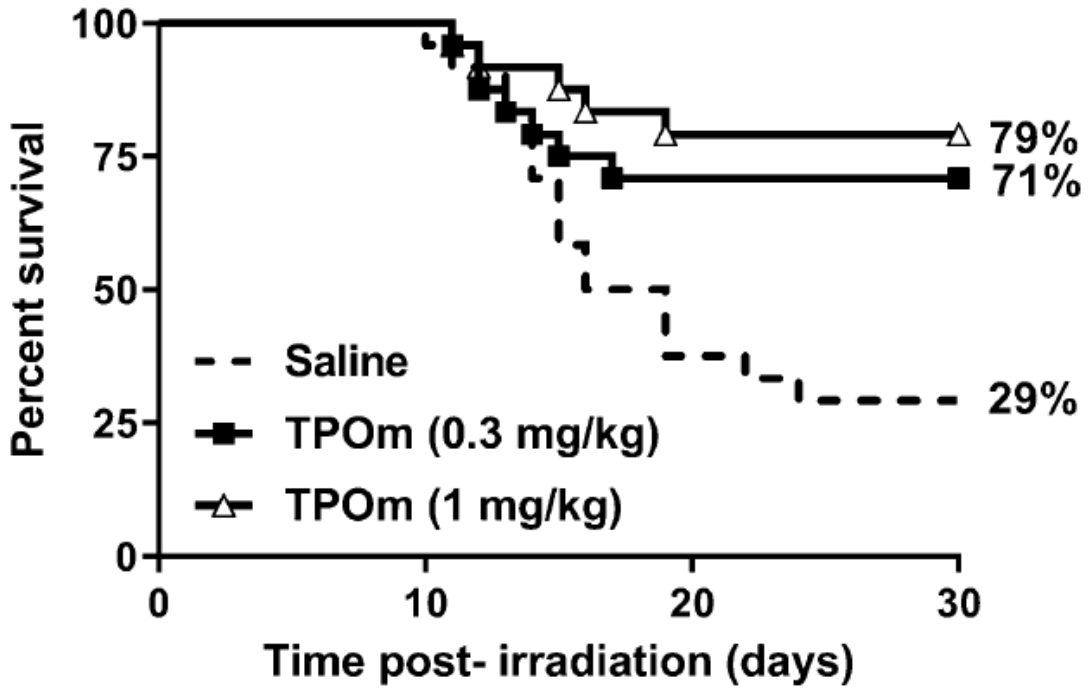
- TPO promotes hematopoietic cell regeneration and attenuates thrombocytopenia, leukopenia, and anemia.
- Hematopoietic Acute radiation syndrome (H-ARS) is characterized by blood cell loss and anemia; a potential target for TPO based treatment
- Current study explored TPO mimetic, namely JNJ-26366821- **its prophylactic vs. mitigating efficacy**, particularly in the context of **cardiovascular disorder**, since cardiomyopathy is a leading cause of mortality because of delayed radiotoxic effects.
- JNJ-26366821 is a PEGylated peptide that embodies a 29 amino acid-long sequence doubly-conjugated to two polyethylene glycol (PEG) structures. Like Romiplostim, JNJ-26366821 shares no sequence homology to endogenous TPO, thus the risk to auto-trigger antibody generation is minimal.

JNJ-26366821: Mitigator of lethal dose of radiation



Single dose of 1.0 mg/kg JNJ-26366821 administered 24h post radiation

Mitigation efficacy: Dose dependent survival curve



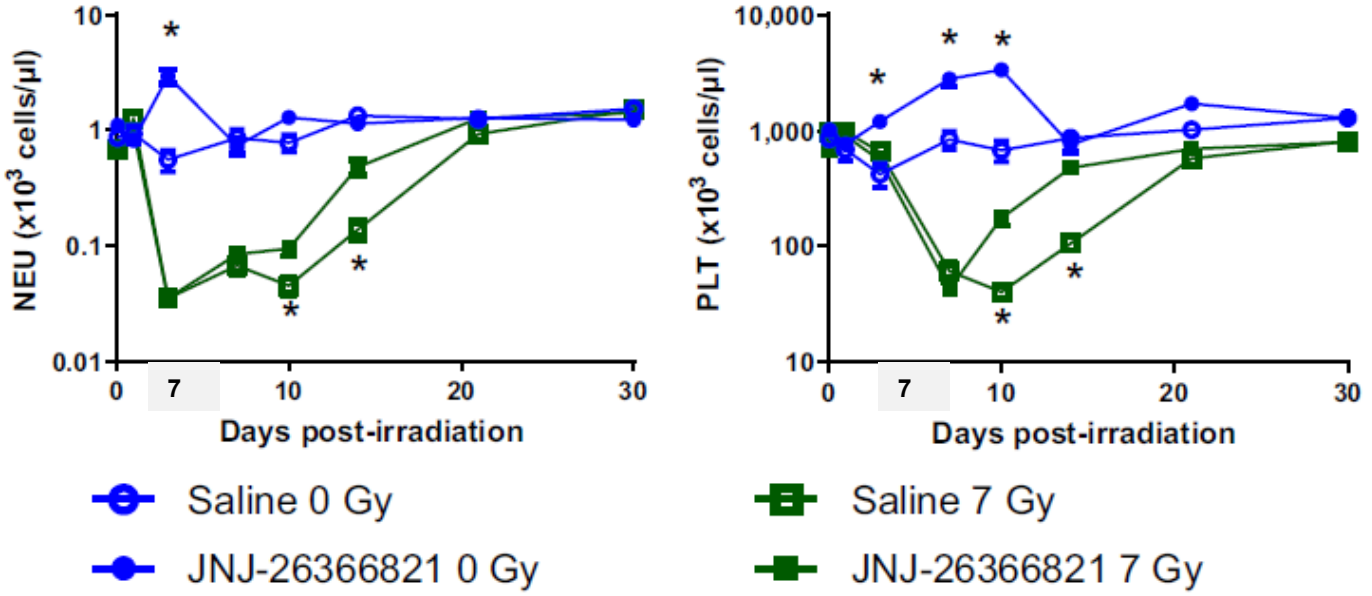
Survival of CD2F1 mice following TBI with 9.35 Gy.
(Log-rank test p = 0.0002) ,
A single dose of JNJ-26366821

- 0.3 mg/kg (■) or
- 1.0 mg/kg (Δ) or
- Saline as a vehicle (dashed line)

JNJ-26366821 significantly enhanced the chances to survive- *dose independent efficacy*

Reference: Kumar VP, Holmes-Hampton GP, Biswas S, Stone S, Sharma NK, Hritzo B, Guilfoyle M, Eichenbaum G, Guha C, Ghosh SP. Mitigation of total body irradiation-induced mortality and hematopoietic injury of mice by a thrombopoietin mimetic (JNJ-26366821). Scientific Reports. 2022 Mar 3;12(1):3485.

Mitigation efficacy: Regeneration of hemopoietic cells

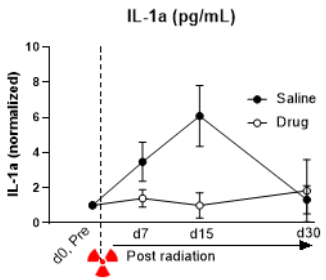


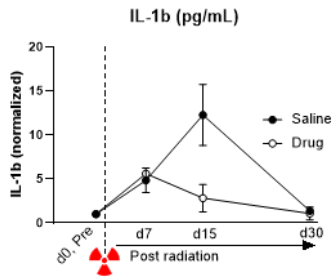
JNJ-26366821 was able to trigger the regeneration by 7d post-TBI

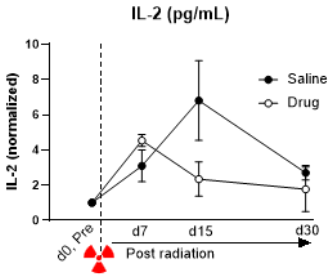
Reference: Kumar VP, Holmes-Hampton GP, Biswas S, Stone S, Sharma NK, Hritzo B, Guilfoyle M, Eichenbaum G, Guha C, Ghosh SP. Mitigation of total body irradiation-induced mortality and hematopoietic injury of mice by a thrombopoietin mimetic (JNJ-26366821). Scientific Reports. 2022 Mar 3;12(1):3485.

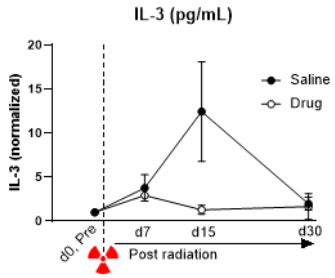
Mitigation efficacy: Blood inflammation panel

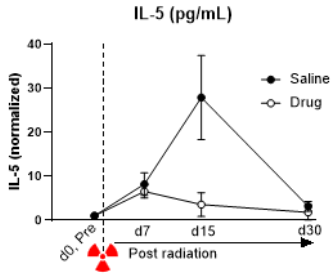
Representative Pro-inflammatory panel

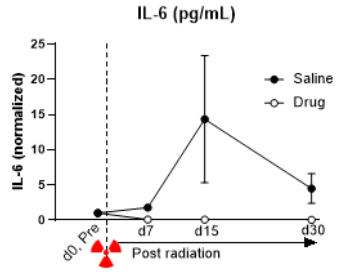




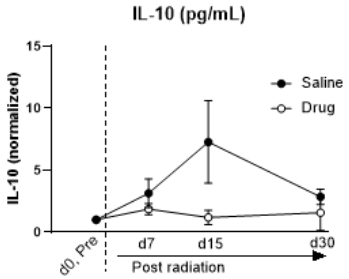


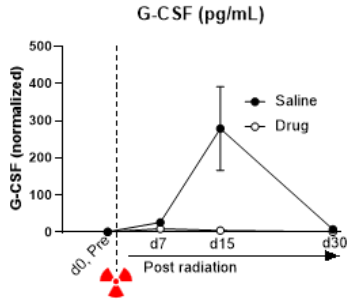






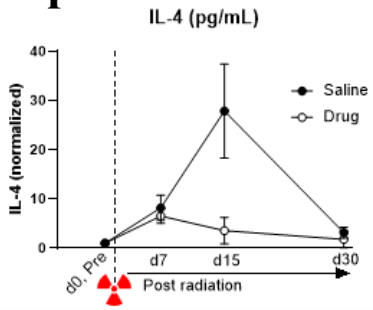
Representative Anti-inflammatory panel

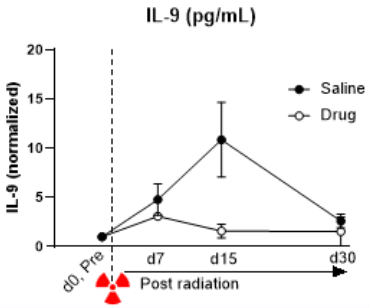


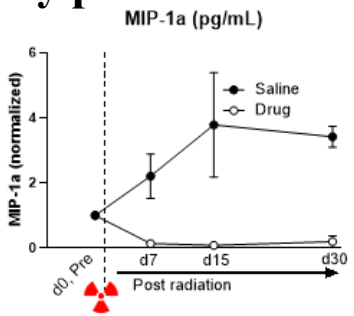


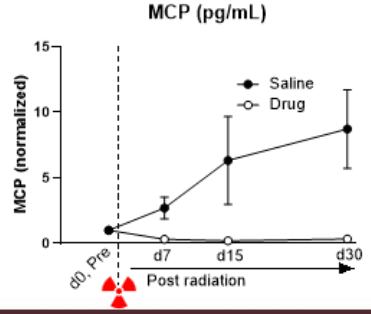
A spike of inflammation at d7 post-TBI was ultimately attenuated by JNJ-26366821

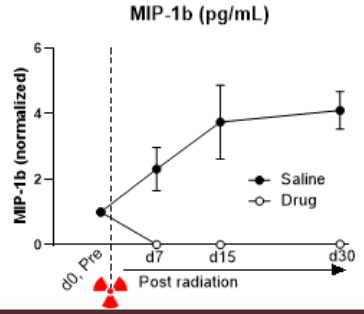
Representative Pro- and Anti-inflammatory panel



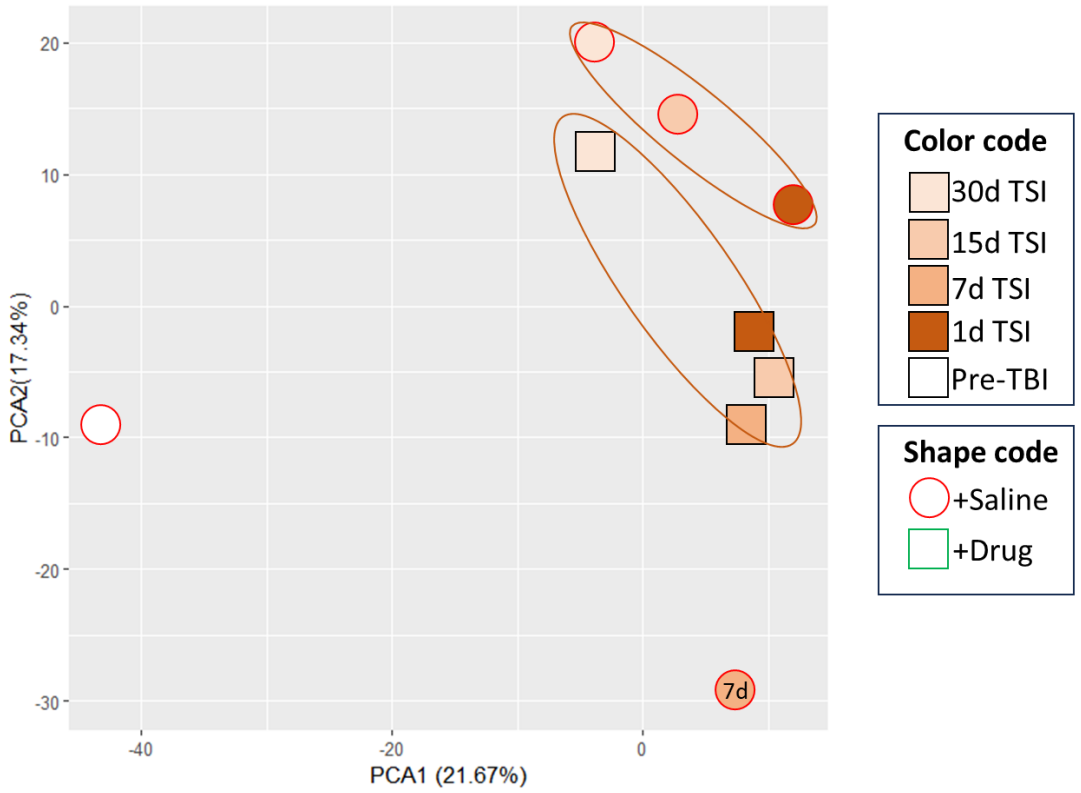








Principal Component Analysis (PCA): Proteomics profile in heart



Both radiated and JNJ-26366821-treated samples clustered away from the pre-TBI baseline – failed to reach baseline; 7d TBI sample clustered away

Mitigation efficacy: Protein-metabolite networks in heart tissue

	Diseases or Functions	Z-score
Day 1 Post-TBI	Necrosis	-2.25
	Vasculogenesis	-2.01
	Migration of endothelial cells	-1.90
	Angiogenesis	-1.73
	Cellular homeostasis	1.82

	Diseases or Functions Annotation	Z-score
Day 7 Post-TBI	Cachexia Signaling Pathway	-2.00
	Differentiation of adipocytes	1.97
	Endocytosis	1.68
	Secretion of protein	1.67
	Transport of molecule	2.05

- By 7 days post-TBI, JNJ-26366821 mobilized molecules in heart tissue to reconstitute cellular development and maintenance.

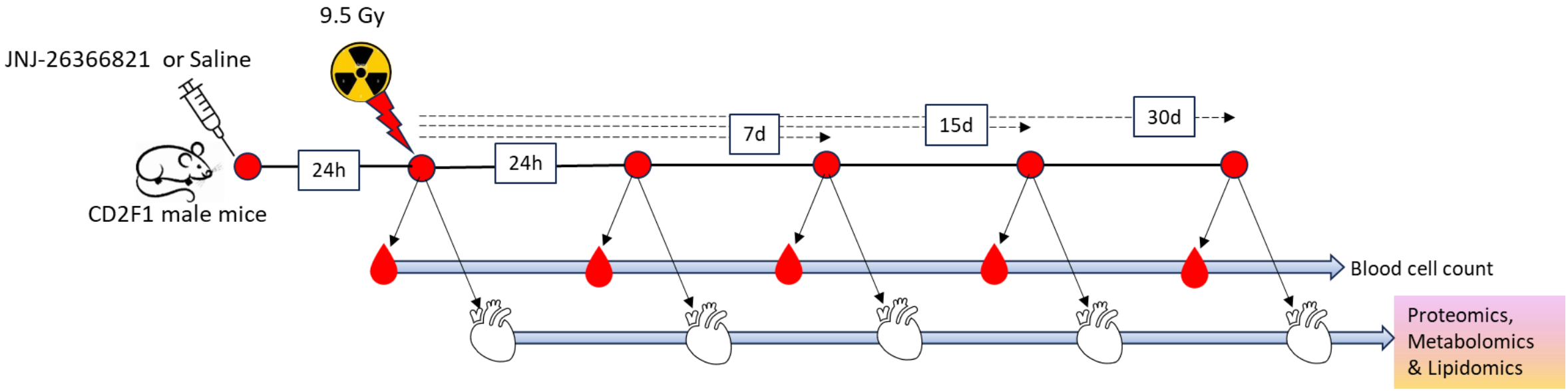
- Protein synthesis and metabolism were activated between 15 and 30 days post-TBI, potentially compensating for radiation-induced muscle wasting.

Impact of JNJ-26366821 on sham mice: Step towards prophylactic measure

Diseases or Functions	Z-score
Activation of gene	1.54
Cellular homeostasis	1.55
Free Radical Scavenging	1.56
Assembly of organelle	1.75
Transcription of RNA	1.89
Transcription of DNA	2.01
Cell viability	2.46

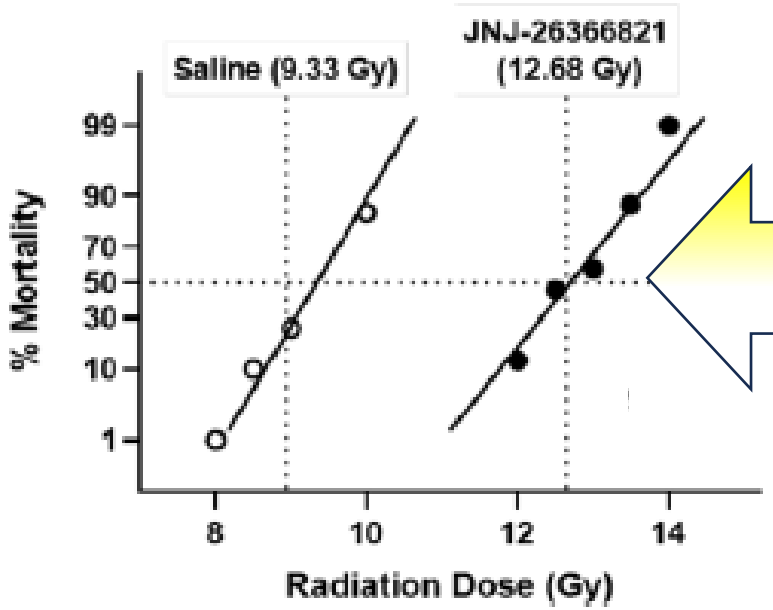
- Single dose of 1.0 mg/kg JNJ-26366821 showed an overall positive impacts in sham mice.
- The results underlines the potential prophylactic applicability of JNJ-26366821

JNJ-26366821:
Prophylactic drug of lethal dose of radiation



Single dose of 1.0 mg/kg JNJ-26366821 administered 24h before total body irradiation

Prophylactic efficacy: Dose dependent survival

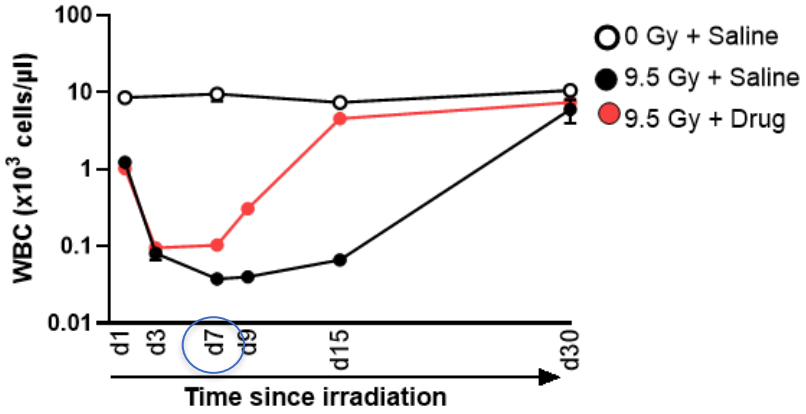


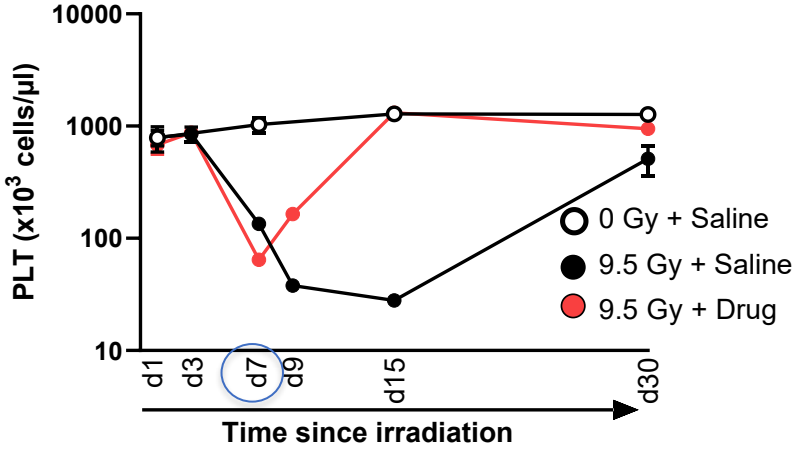
JNJ-26366821 achieved 50% chance to survive after 12.68 Gy TBI

Mortality rate vs. Radiation dose underlined a promising applicability of JNJ-26366821 as a prophylactic drug

Reference: Holmes-Hampton GP, Kumar VP, Biswas S, Stone S, Sharma NK, Legesse B, Vercellino J, Guha C, Eichenbaum G, Ghosh SP. PEGylated thrombopoietin mimetic, JNJ-26366821 a novel prophylactic radiation countermeasure for acute radiation injury. Scientific reports. 2023 Sep 14;13(1):15211.

Prophylactic efficacy: Regeneration of hemopoietic cells

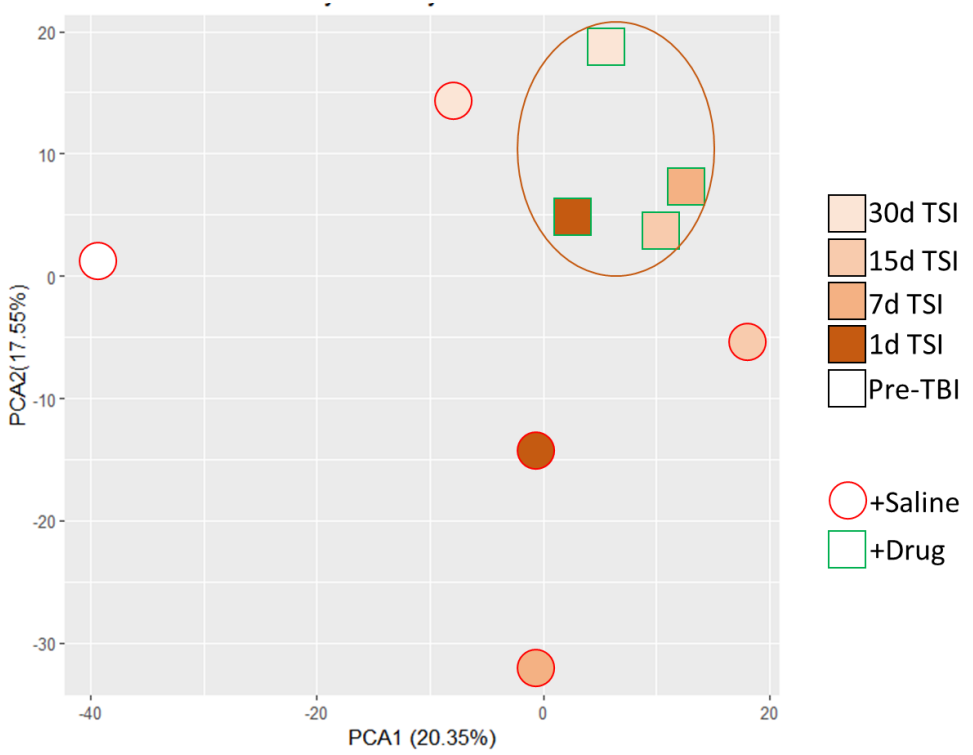




JNJ-26366821 was able to trigger the regeneration by 7d post-TBI –

A nearly similar longitudinal profile as mitigation approach

PCA: Proteomics profile in heart



Both radiated and JNJ-26366821-treated samples clustered away from the pre-TBI baseline – failed to reach baseline;

Mitigation efficacy: Protein-metabolite networks in heart tissue

	Diseases or Functions	Z-score
Day 1	Cyclophilin Signaling Pathway	-1.63
	Metabolism of protein	-1.55
	Internalization of cells	1.51
	Immune response of cells	1.51
	Phagocytosis of cells	1.98

	Diseases or Functions	Z-score
Day 7	Quantity of reactive oxygen species	-2.02
	Activation of gene	1.54
	Cellular homeostasis	1.75

- Prophylactic administration activated immune response immediately after TBI
- By 7 days gene function networks were activated, and ROS quantity was reduced
- By 15-30 days post-TBI, JNJ-26366821 mobilized molecules in heart tissue to reconstitute cellular development and maintenance.

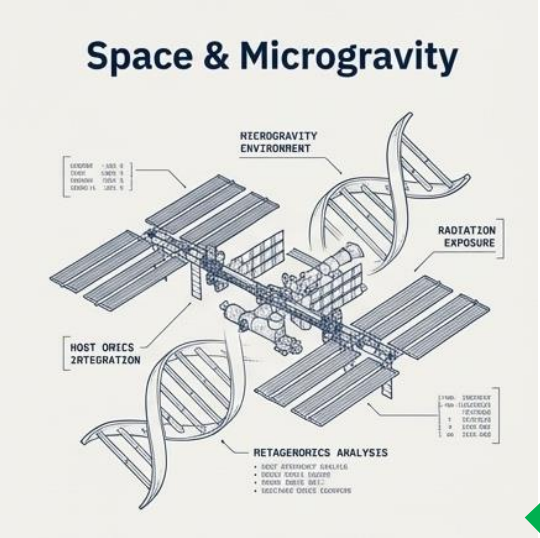
Conclusions

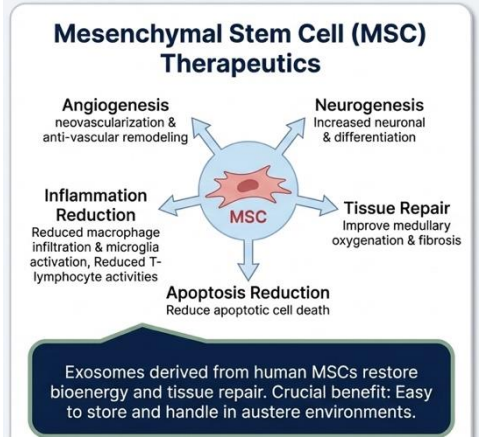
- JNJ-26366821 administration after radiation exposure (TBI) promoted recovery of hematopoietic cells and reduced inflammatory surges by day 7.
  - The drug rapidly decreased cell death, though cardiovascular-supporting networks (angiogenesis, vasculogenesis) remained suppressed at 2 hours post-treatment.
  - By day 7 post-TBI, JNJ-26366821 mobilized heart tissue molecules to restore cellular development and maintenance.

- JNJ-26366821 treatment on Sham mice showed positive impacts highlighting its potential prophylactic application.

- Prophylactic use of JNJ-26366821 resulted in hematopoietic recovery similar to mitigation dosing.
  - The drug activated pro-survival biofunctions, such as free radical scavenging and cell survival, supporting delayed radio-resistance in cardiac tissue.
  - JNJ-26366821 demonstrates potential as a prophylactic agent for radiation injury, aiding both hematopoietic and cardiac recovery.

Thank You





Review of our five Space studies

Session: Current Challenges in DoW Aerospace Medicine
Time: Monday, 1300-1500

hMSC-ex in Cold stress

Session: Human Performance Optimization in Cold-Weather & High-Altitude Environments
Time: Monday, 1530-1730

hMSC-ex in ASD

Session: Cellular Therapeutics for Trauma
Time: Thursday, 1115-1315

TBI Biomarker

Session: Managing the Golden Hour & Beyond: Innovative TBI Care in Contested Combat Environments
Time: Wednesday, 0830-1000

Radiation Therapeutics

Session: Ops in a Nuclear Environment: Ensuring Medical Readiness & Preparing for Complex Injuries
Time: Wednesday, 1530:1730

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