# Combined Radiation Injury Impacts Development of Radiation Countermeasures and Biodosimetry

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- I and my family members have **NO financial interest** in any commercial product, service, or organization providing financial support for this research.
- The research protocols in the presentation **were reviewed and approved** by the *institutional animal care and use committee (IACUC)* according to all applicable Federal regulations governing the protection of animals in research.

# *Outline*

- Background / Introduction
- Animal model: RI+Skin-wound CI and survival,
- Survival, wound healing and weight loss
- Bone marrow histopathology
- GI histopathology
- Underlying mechanisms
- Medical countermeasures (MCMs)
- Biomarkers for triage
- Biomarkers for biodosimetry

# *Background*

- Large-scale radiation exposure events in history have shown that irradiated victims are also often subjected to other trauma such as wounds, burns, hemorrhage, or infection.
- Preparedness for medical responses to major radiation accidents and increasing threat of nuclear warfare worldwide necessitates an understanding of the complexity of combined radiation injury (CI) and
- Identifying drugs to treat CI.
- Biomarkers that remain the same changes between CI and radiation alone are inevitably critical for biodosimetry and triage.

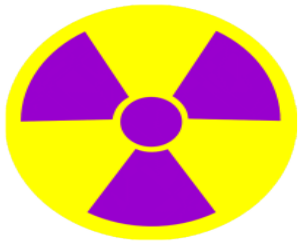
# Percentage of victims exposed to atomic bombs with numbers of injury

| | Little Boy-$U^{235}$<br>Hiroshima, Aug 6, 1945 | Fat Man-$Pu^{239}$<br>Nagasaki, Aug 9, 1945 |
|---|---|---|
| | (N = 5185) | (N = 4107) |
| **Single injury** | 60.5 % | 57.5 % |
| **Two injuries** | 34.5 % | 37.1 % |
| **Three injuries** | 5.0 % | 5.2 % |

Data from Joint Commission of USA and Japanese Physicians collected from victims exposed to 20-KT fission devices (1946).

Kiang and Blakely. 2023 PMID: 36947602; PMCID: PMC10947598

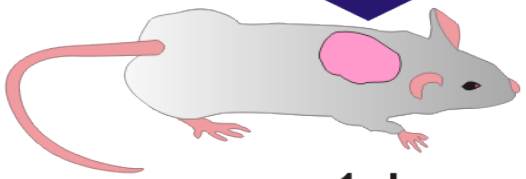
# Mouse Model for Combined Injury Studies



Co-60 radiation
0.4 Gy/min

15 % dorsal
skin-wound or burn
20% hemorrhage
Bacterial inoculation

Wound healing
Body weight
Cytokine
Infection
Survival



0 hr

+1 hr

30-day survival

B6D2F1/J female mice, 12-20 wks old

# CI Hallmarks

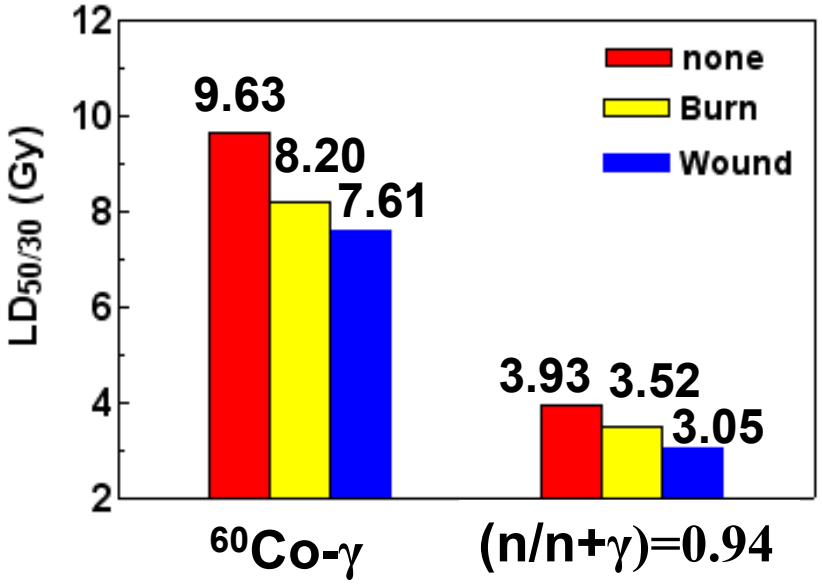
## Combined Injury Models

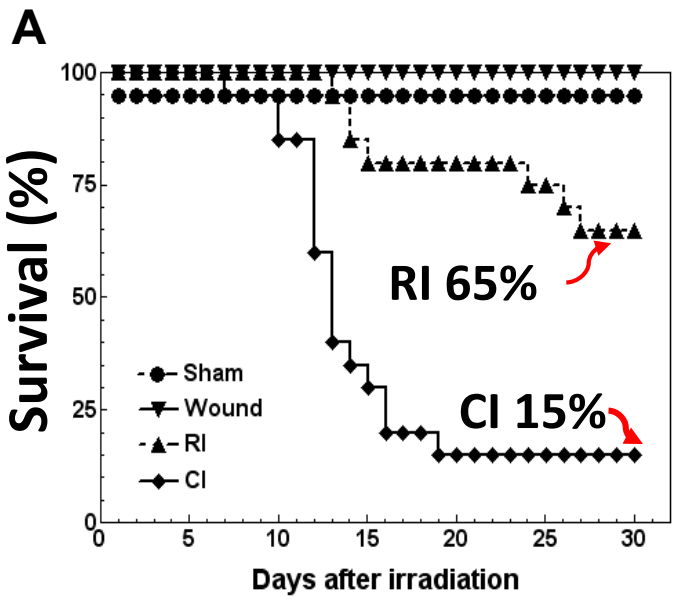
**A. In vivo**

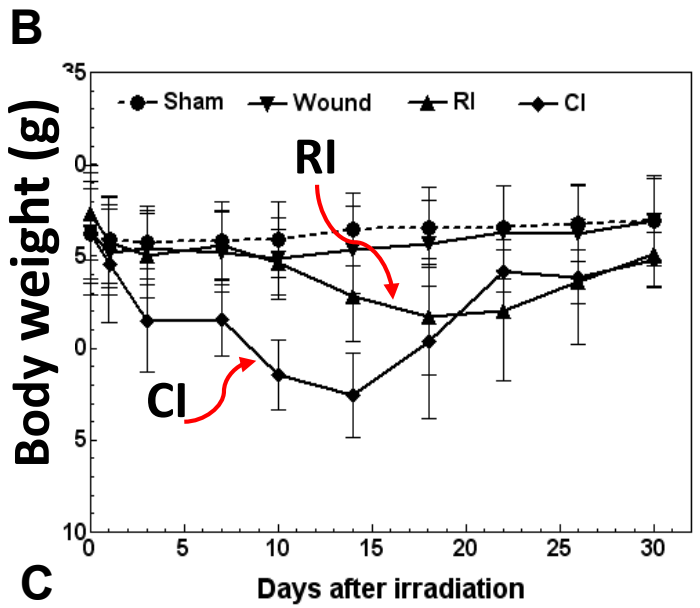
- Radiation + Wound
- Radiation + Burn
- Radiation + Hemorrhage
- Radiation + Infection

**B. In vitro**

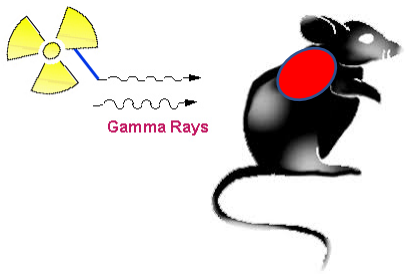
- Radiation + Scratch
- Radiation + Burn

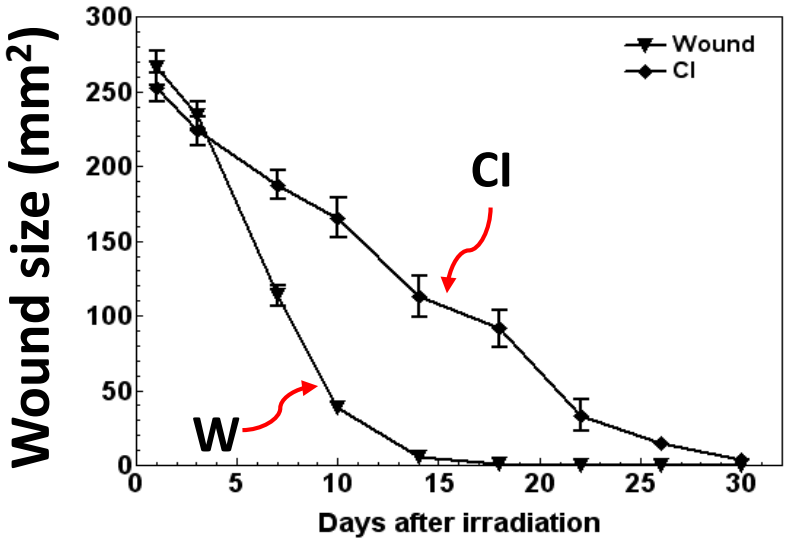



**B6D2F1 mice**
**9.75 Gy + wound**




Kiang and Blakely. 2023 PMID: 36947602; PMCID: PMC10947598

# CI: Poly-organ Hit

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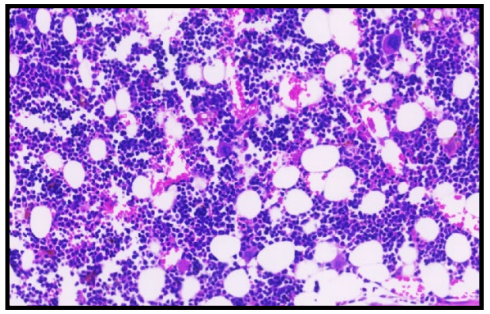
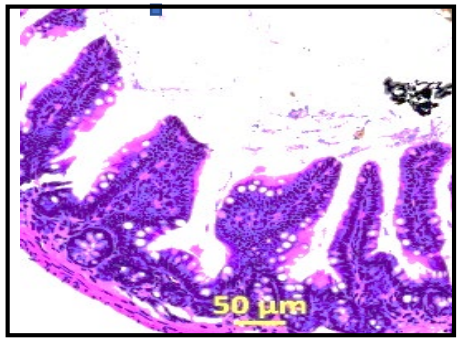
**Hematopoietic ARS (< 1 day)**



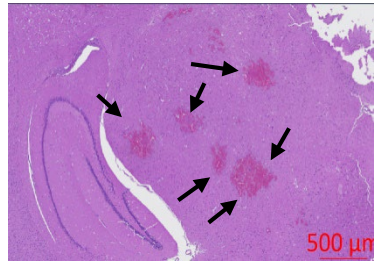
**GI ARS (< 7 days)**




**CI Acute Radiation Syndrome**

**Immunodeficiency (<1 day then >25 days)**

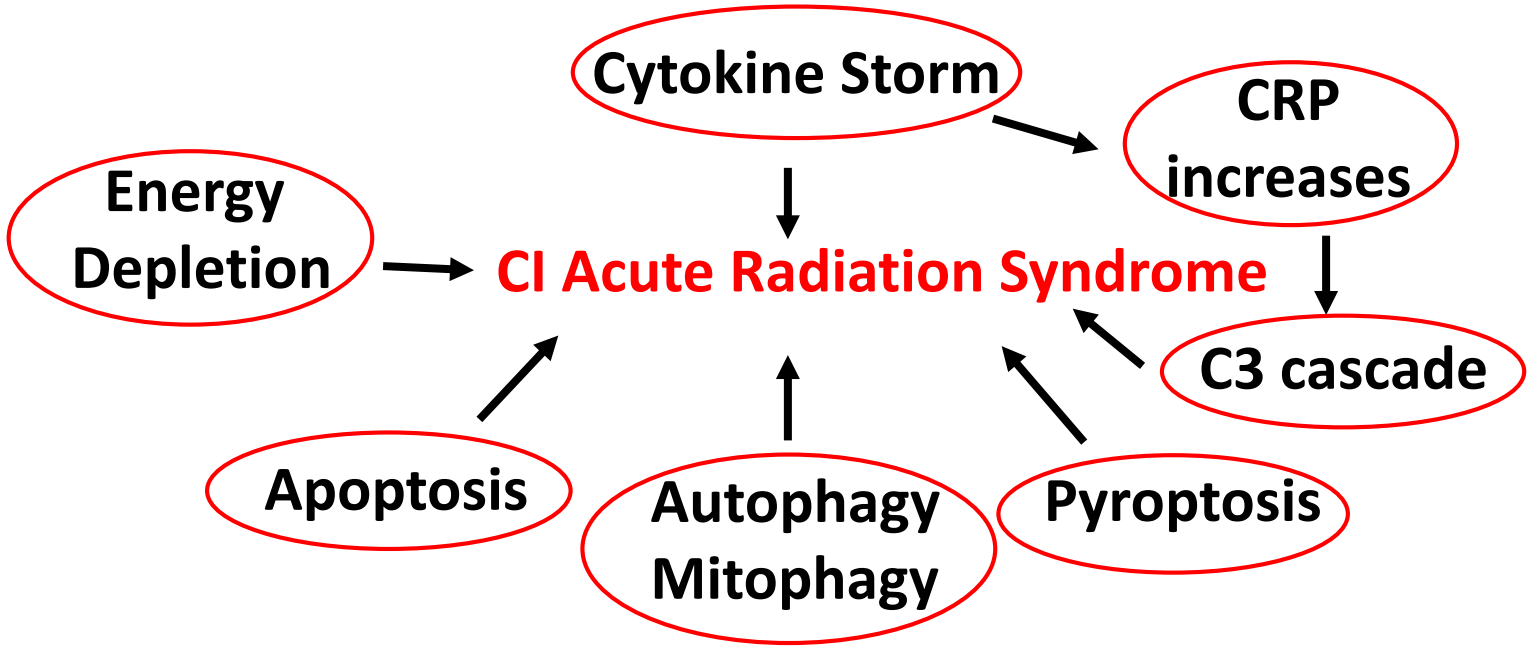

**Cranial ARS (>10 days)**

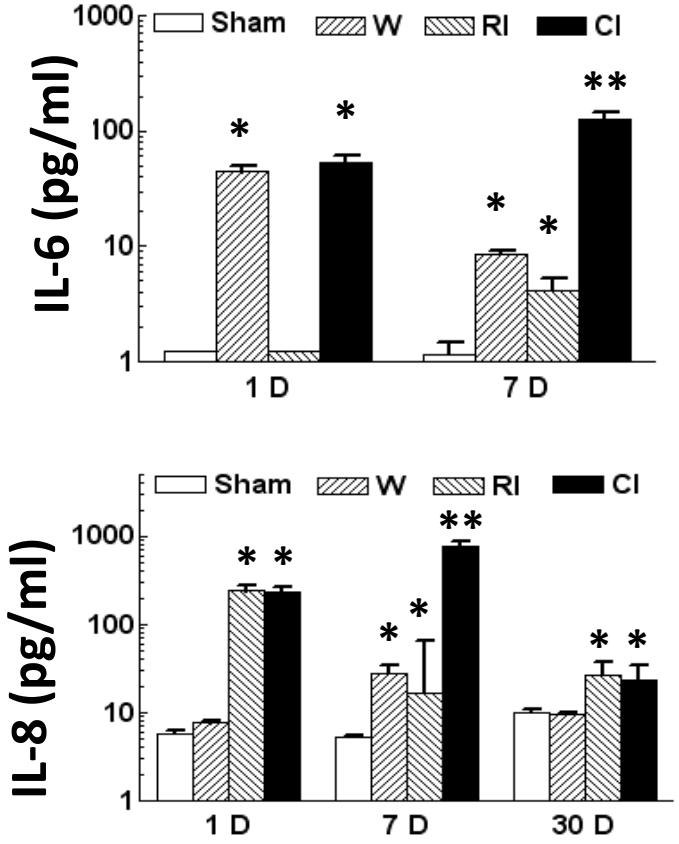



**Day 13**

Kiang and Olabisi, Cell Biosci 9:25, 2019, PMID: 30911370, PMCID: PMC6417034
Kiang and Blakely, Intl J Radiat Biol 1-11, 2023, PMID: 36947602, PMC: PMC10947598

# CI: Poly-signaling Hits




Kiang and Olabisi, Cell Biosci 9:25, 2019, PMID: 30911370, PMCID: PMC6417034
Kiang and Blakely, Intl J Radiat Biol 1-11, 2023, PMID: 36947602, PMCID: PMC10947598

# FDA-approved Drugs/Agents Are Not Effective to Treat CI

**RI Mitigators – (H-ARS)**

- **Neupogen (G-CSF)**
- **Neulasta (peg-G-CSF)**
- **Leukine (Gm-CSF)**
- **Nplate**
- **Stimufend (peg-fpgk)**
- **Udenyca (peg-cbqv)**

Kiang and Blakely, Intl J Radiat Biol 99(7):1055-1065, 2023, PMID: 36947602, PMCID: PMC10947598

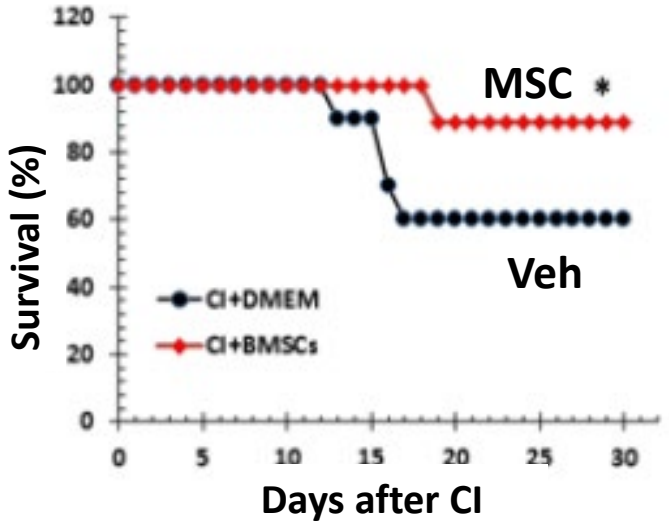
# Drugs/Agents that Mitigate Combined Injury

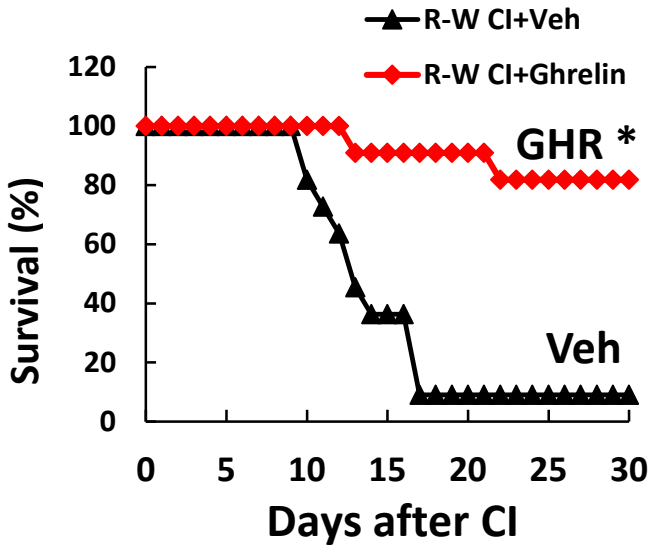
**CI Mitigators –**

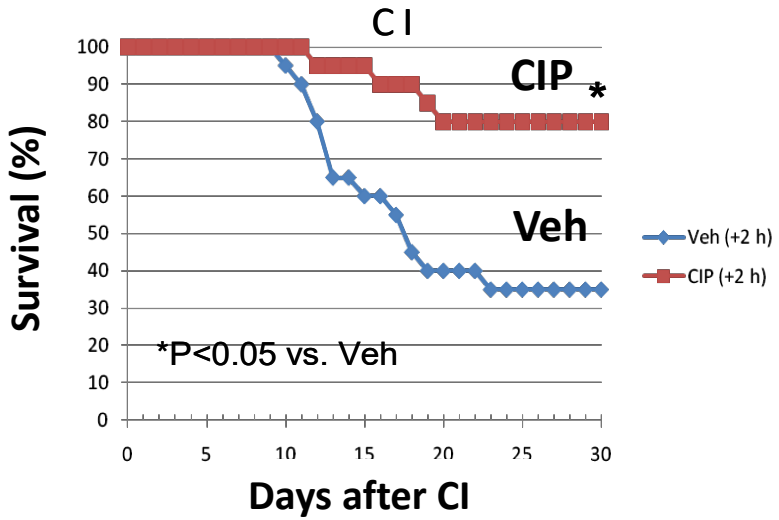
- Mesenchymal Stem cells
- Ghrelin: hunger hormone
- Alxn4100TPO: TPO receptor agonist
- Ciprofloxacin: IL-3 and RBC promoter
- Neulasta+Alxn4100TPO

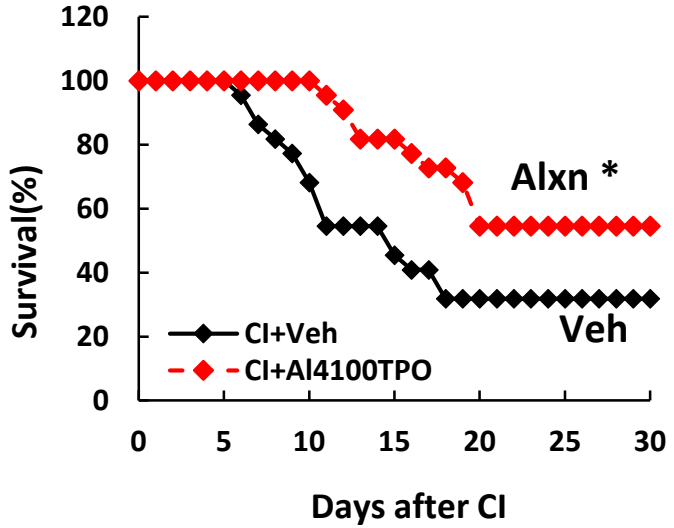
**CI Radioprotectant –**

- L-histidine



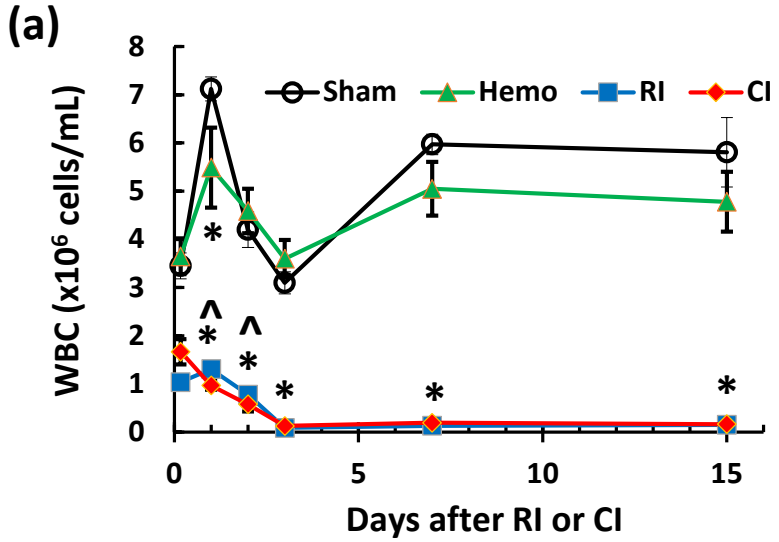



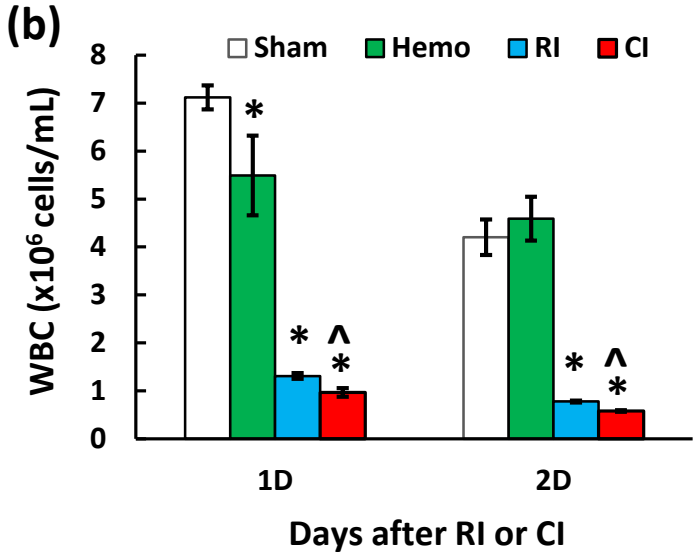



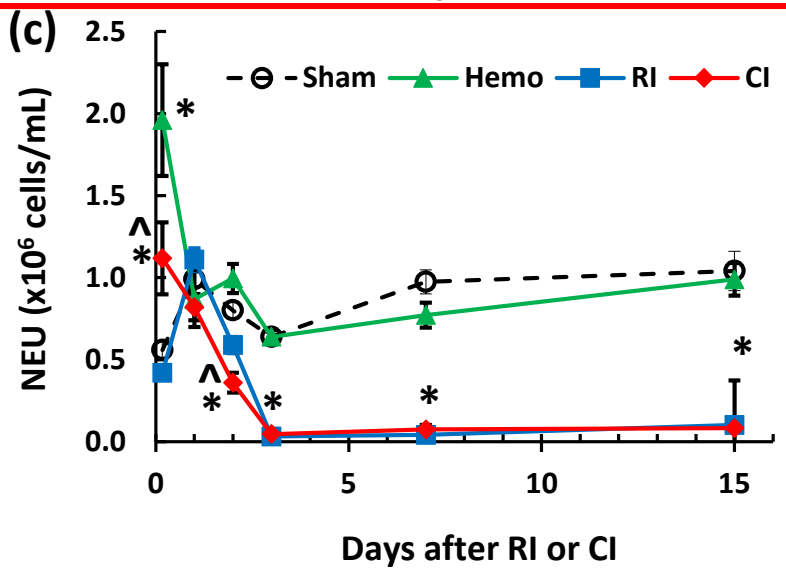

Kiang and Blakely, Intl J Radiat Biol 99(7):1055-1065, 2023, PMID: 36947602, PMCID: PMC10947598

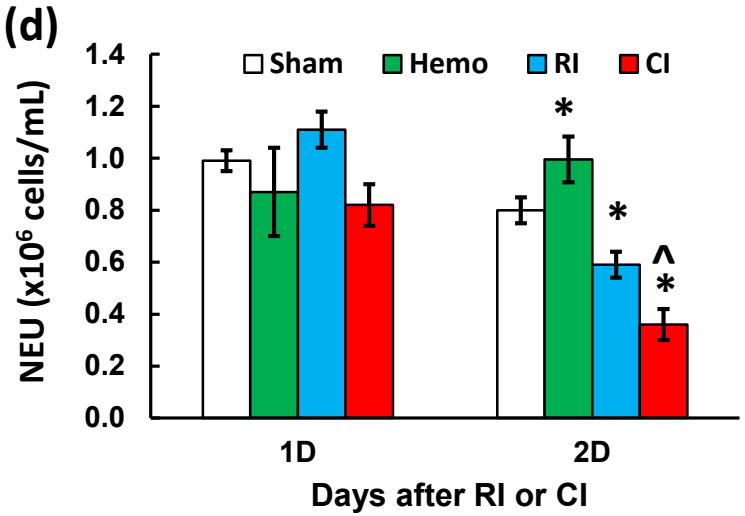
## CI Depletes WBCs More Than RI on Day 1 and Day 2



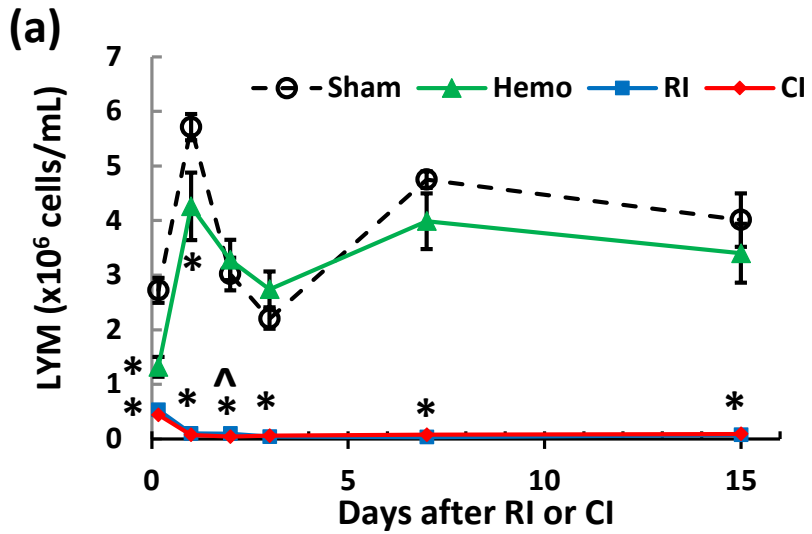

## CI Depletes NEU More Than RI on Day 2

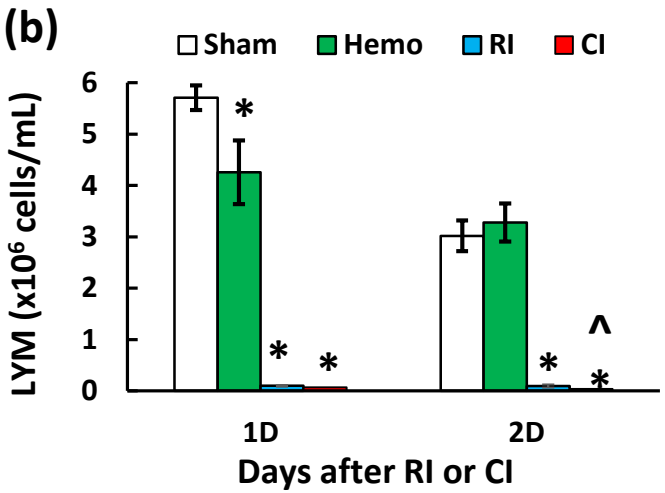


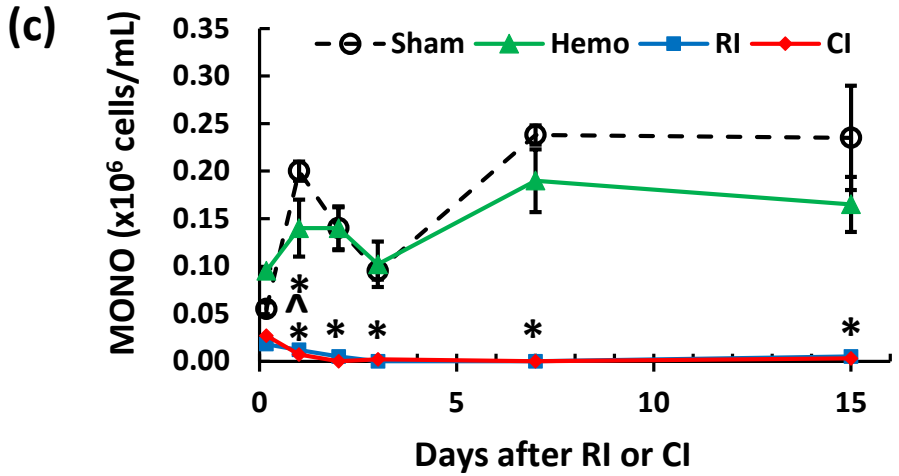

Kiang et al. 2024 PMID: 38474235; PMCID: PMC10932428

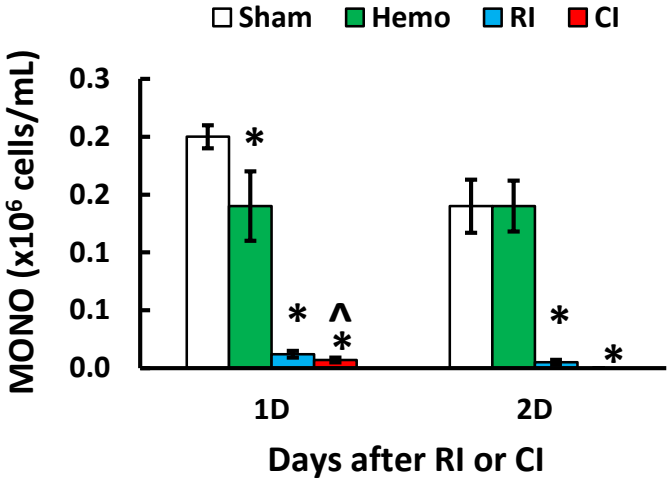
# *CI Depletes LYM More Than RI on Day 2*



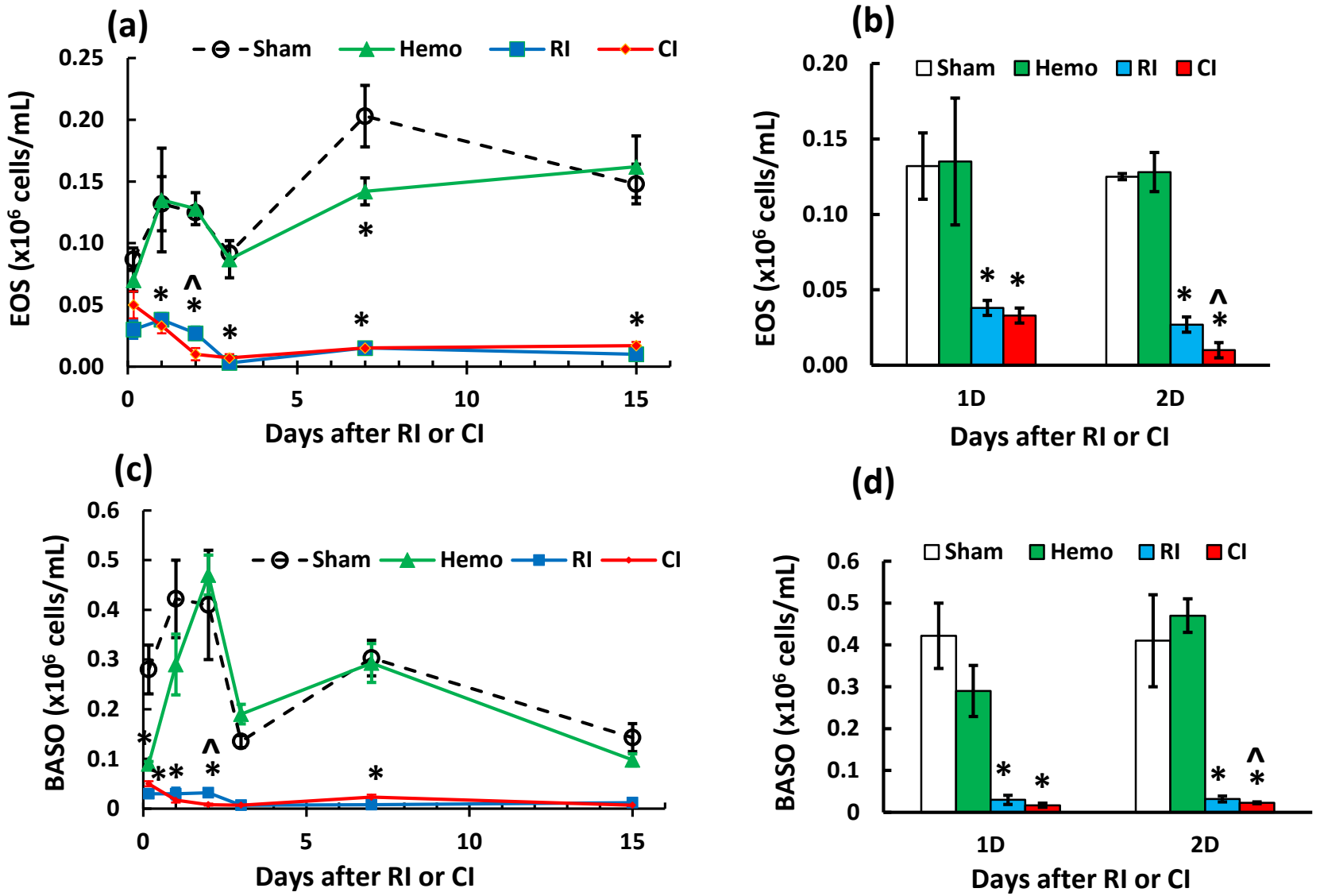




## CI Depletes MONO More Than RI on Day 1



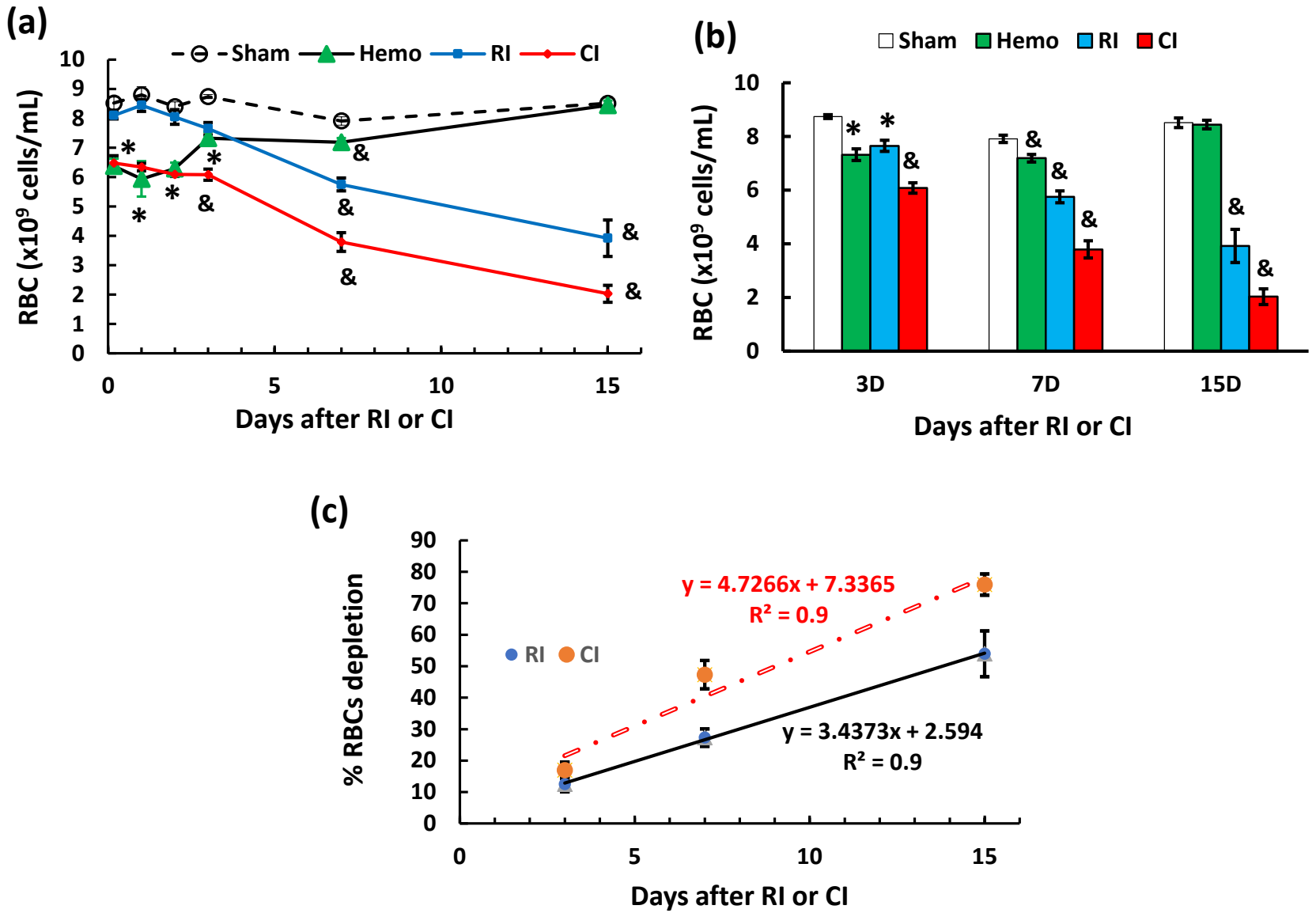



# *CI Depletes EOS and BASO More Than RI on Day 2*



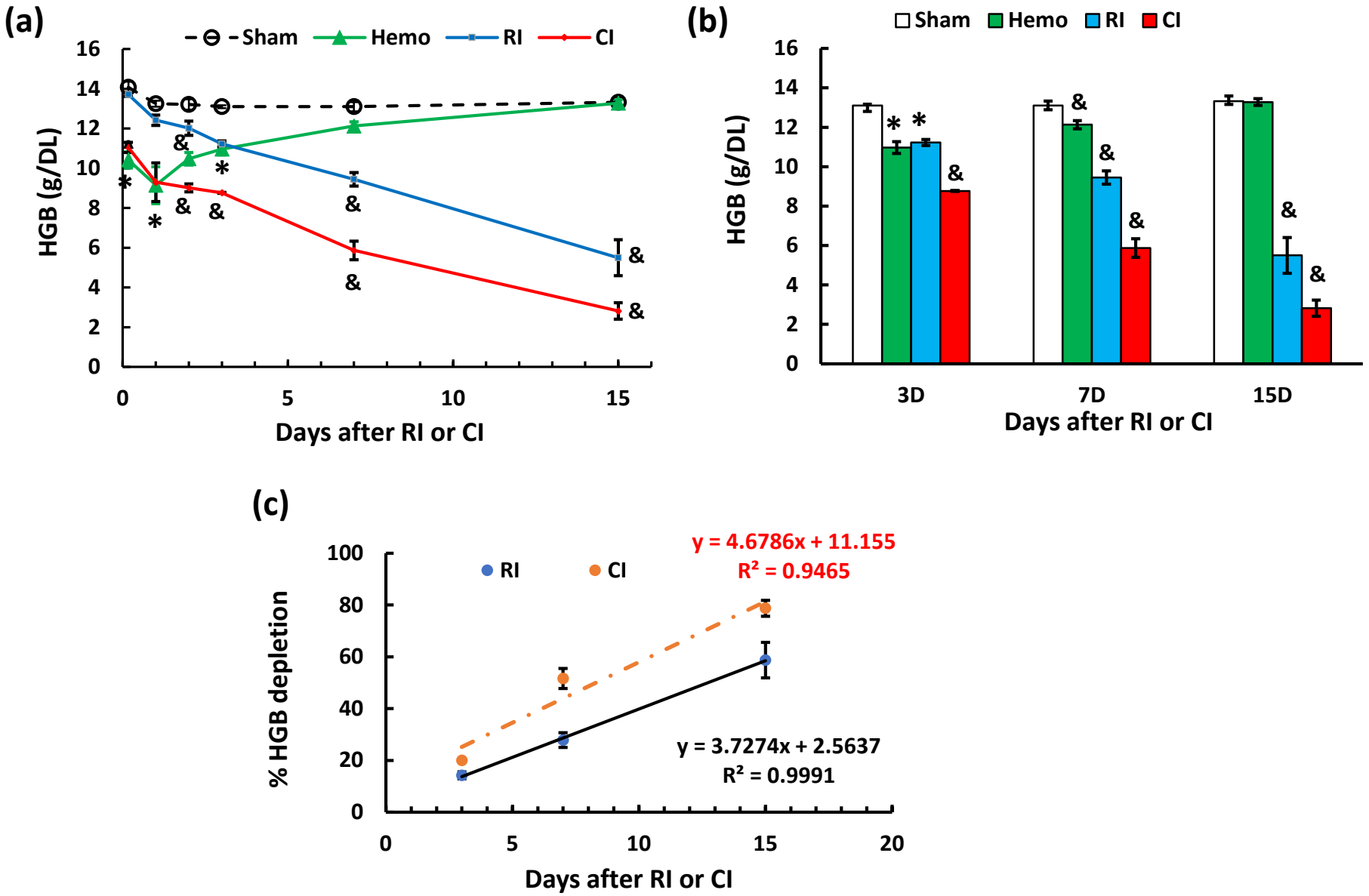

Kiang et al. 2024 PMID: 38474235; PMCID: PMC10932428

# *CI Depletes RBCs More Than RI on Days 3-15*



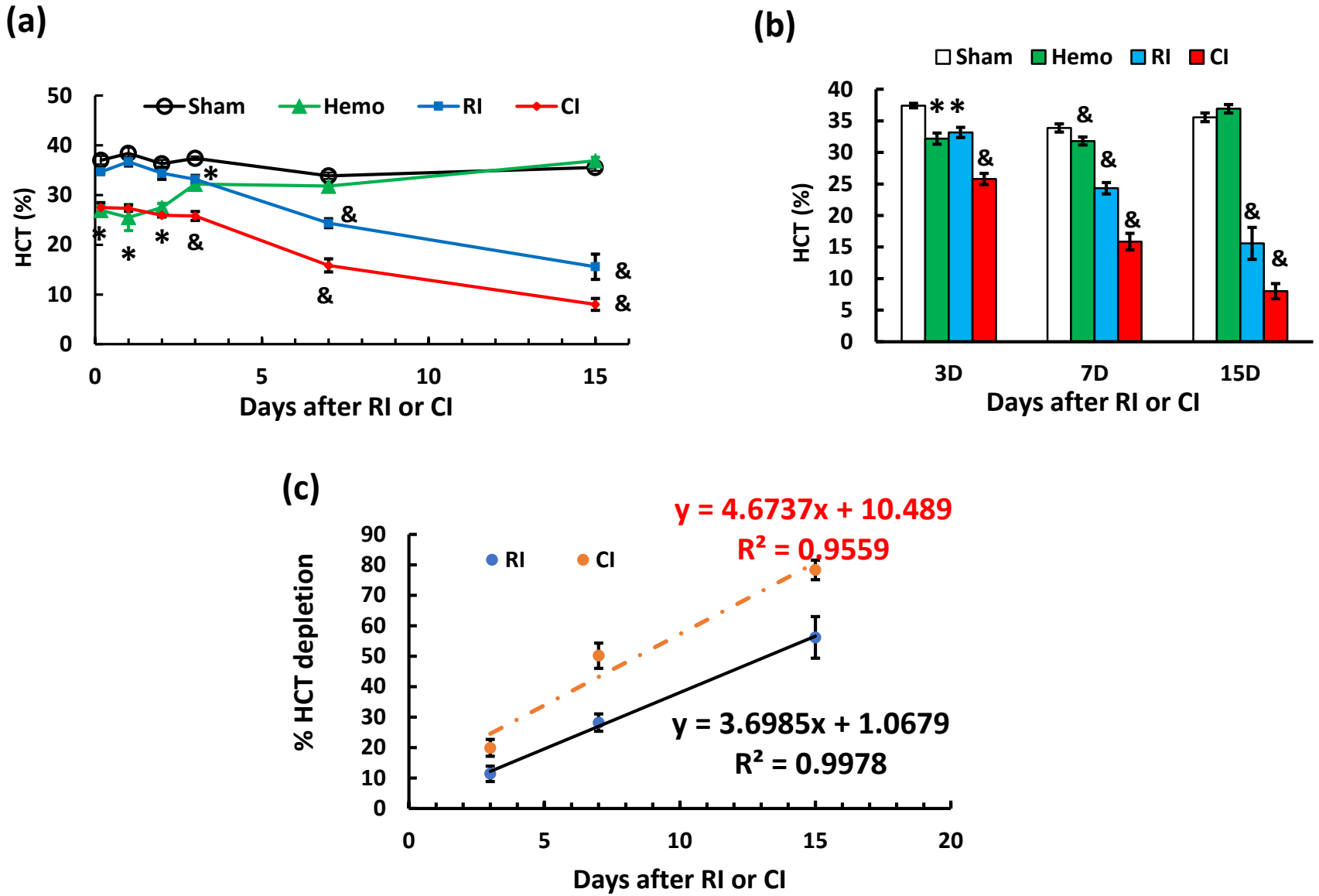

Kiang et al. 2024 PMID: 38474235; PMCID: PMC10932428

# CI Depletes Hemoglobin More Than RI on Days 3-15



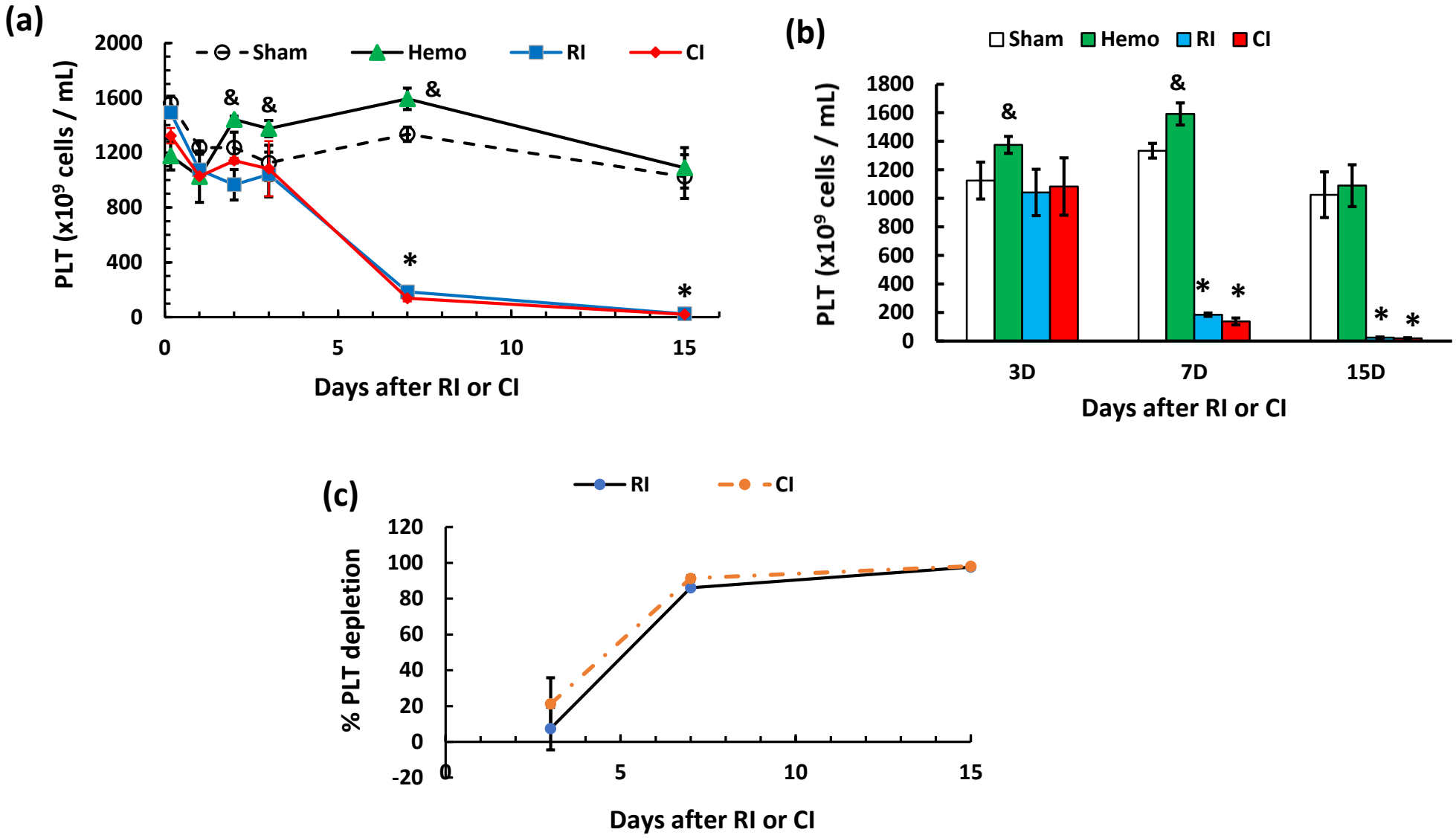

Kiang et al. 2024 PMID: 38474235; PMCID: PMC10932428

# CI Depletes Hematocrits More Than RI on Days 3-15



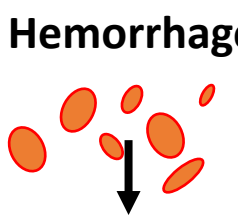

Kiang et al. 2024 PMID: 38474235; PMCID: PMC10932428

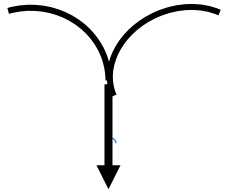
# *Hemorrhage Increases Platelets More Than RI and CI on Days 3-7*

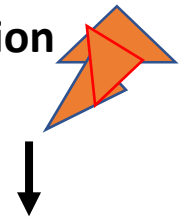



Kiang et al. 2024 PMID: 38474235; PMCID: PMC10932428

# *Biomarkers for Triage*



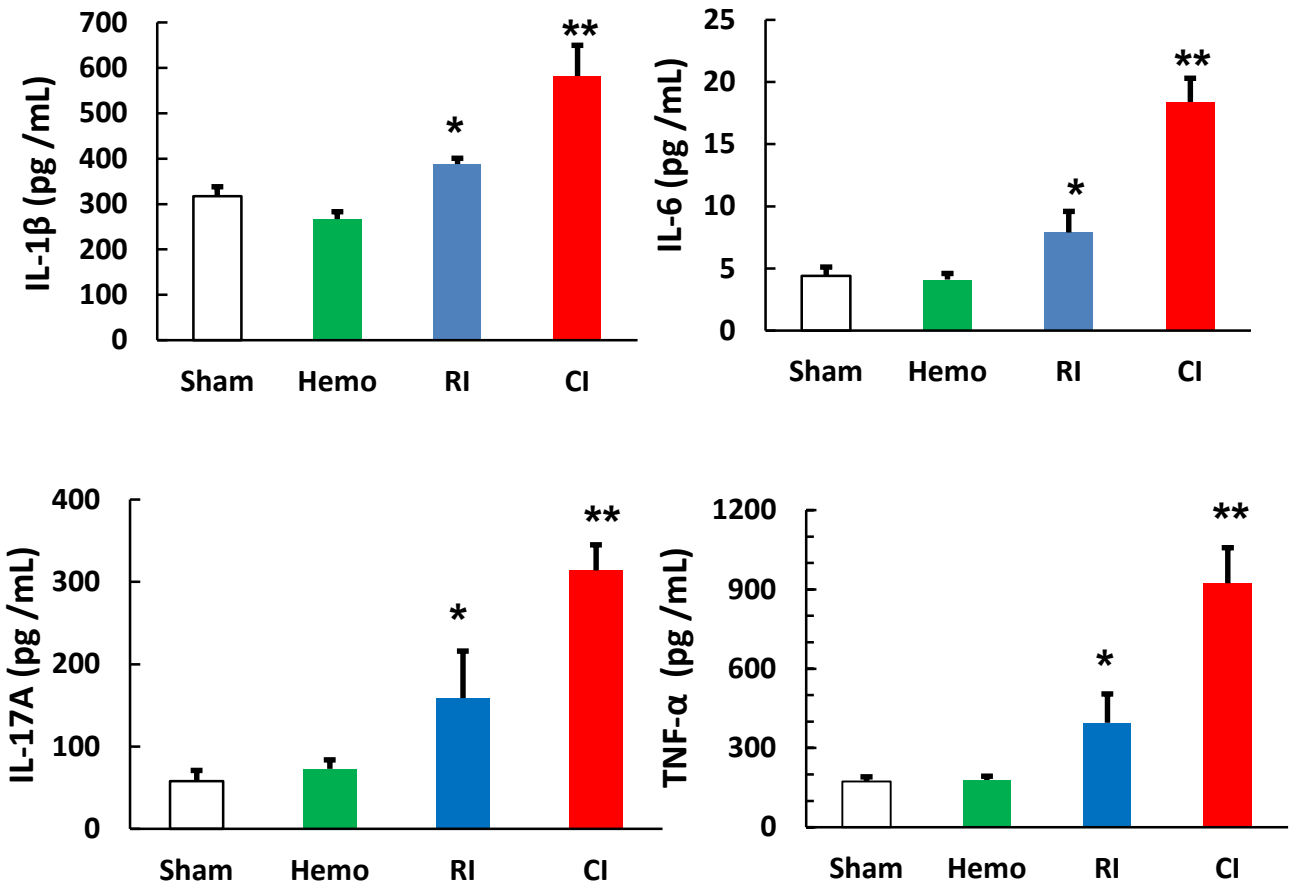




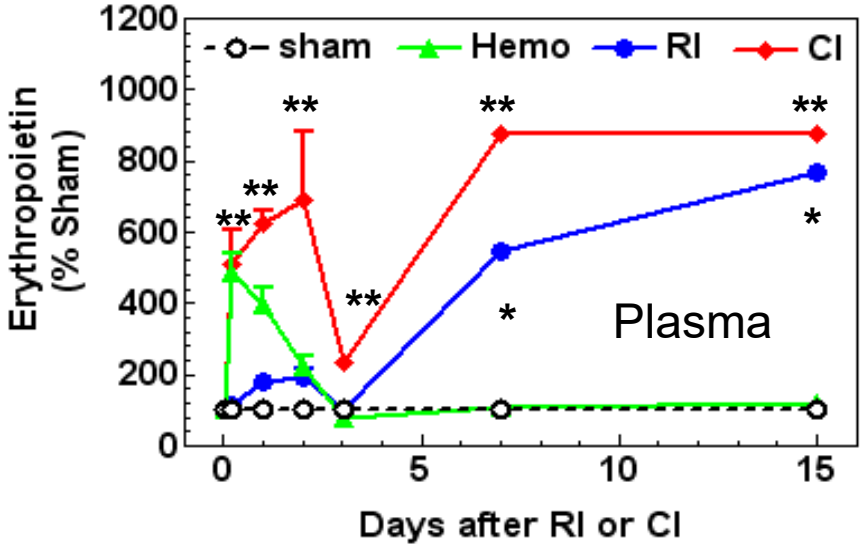
| | Hemorrhage | CI | Radiation |
|---|---|---|---|
| | **HEMO** | **CI** | **RI** |
| 4-5 hr | **Neutrophils up**<br>**Monocytes up**<br>Platelets low | **Neutrophils up**<br>Monocytes low<br>Platelets low | **Neutrophils low**<br>**Monocytes low**<br>Platelets normal |
| Day1 | WBCs low<br>RBCs low<br>Platelets normal | **WBCs lower**<br>RBCs low<br>Platelets normal | **WBCs low**<br>**RBCs normal**<br>Platelets normal |
| Day2 | WBCs normal<br>RBCs low<br>**Platelets up** | **WBCs lower**<br>RBCs low<br>Platelets normal | **WBCs low**<br>RBCs low<br>Platelets low |
| Day 3 | WBCs normal<br>RBCs normal<br>**Platelets up** | WBCs low<br>**RBCs lower**<br>Platelets normal | WBCs low<br>RBCs low<br>Platelets normal |
| Day 7 | WBCs normal<br>RBCs normal<br>**Platelets up** | WBCs low<br>**RBCs lower**<br>Platelets low | WBCs low<br>RBCs low<br>Platelets low |
| Day 15 | WBCs normal<br>RBCs normal<br>Platelets normal | WBCs low<br>**RBCs lower**<br>Platelets low | WBCs low<br>RBCs low<br>Platelets low |

Kiang et al. 2024 PMID: 38474235; PMCID: PMC10932428

# *A Biomarker Panel for Triage including IL-1β, IL-6, IL-17A, TNF-α, and EPO*

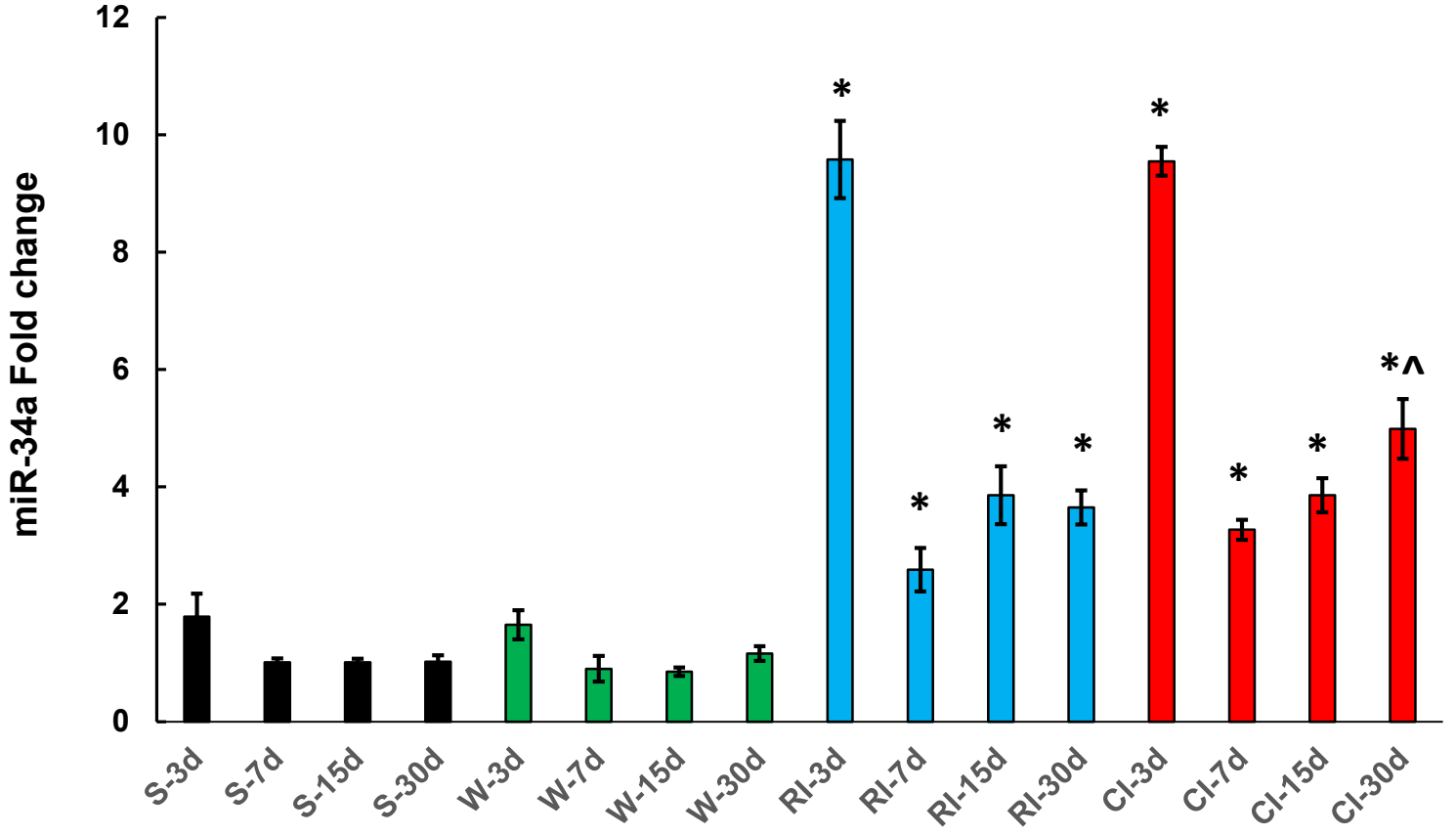



Serum on day 1



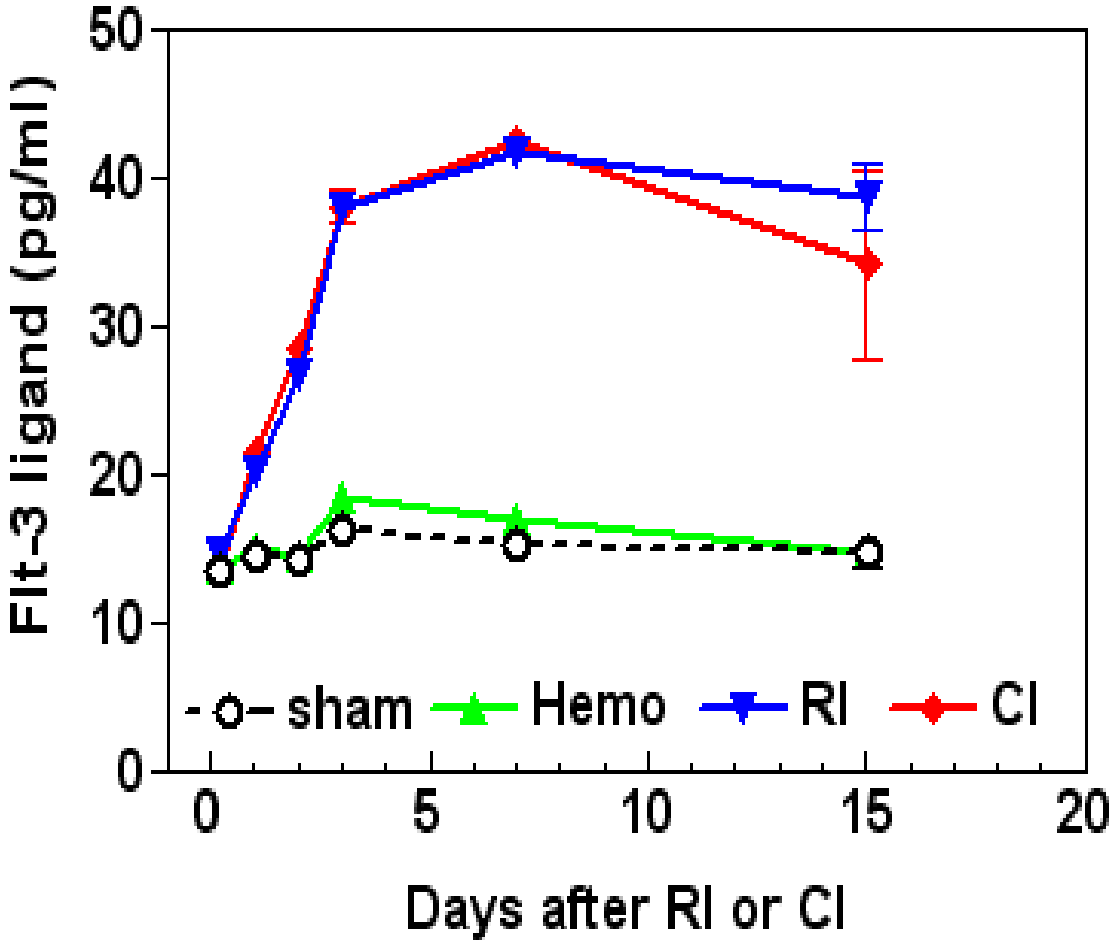

Kiang et al. 2017 PMID: 28934227 PMCID: PMC5608216

# *Biomarkers for Biodosimetry (no Disparity between RI and CI): miR-34a*

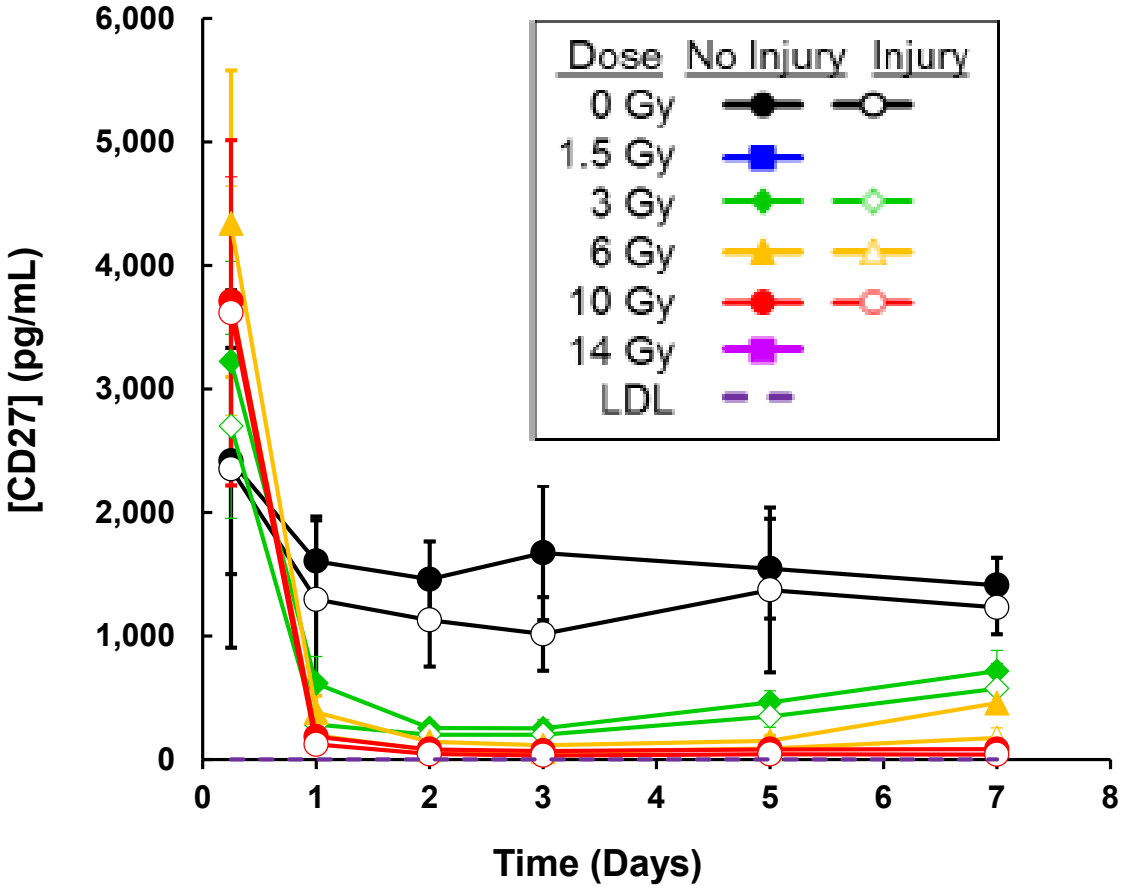



Kiang and Blakely. 2023 PMID: ; PMCID:

# *Biomarkers for Biodosimetry (no disparity between RI and CI): Flt-3 ligand and CD27*



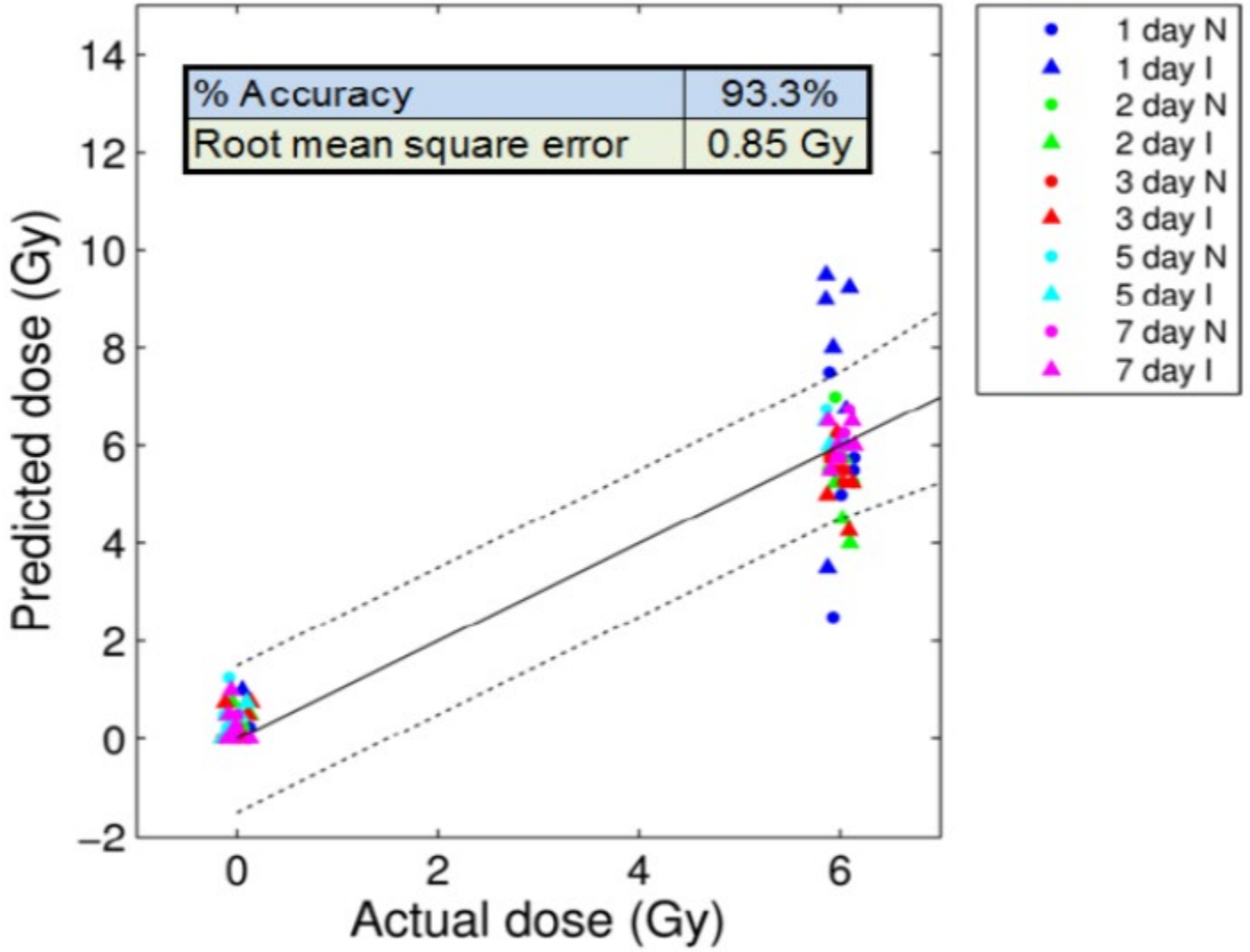

Kiang et al. 2017 PMID: 28934227 PMCID: PMC5608216




Kiang and Blakely. 2023; PMID: 36947602; PMCID: PMC10947598

## *Effect of CI (radiation plus wounding) on radiation dose prediction accuracy*

Multivariate algorithm using proteomic plasma biomarkers (i.e., CD27, Flt-3L, GM-CSF, CD45, IL-12, TPO) used to assess radiation dose that are negligibly affected by wounding.




Kiang and Blakely. 2023;
PMID: 36947602;
PMCID: PMC10947598

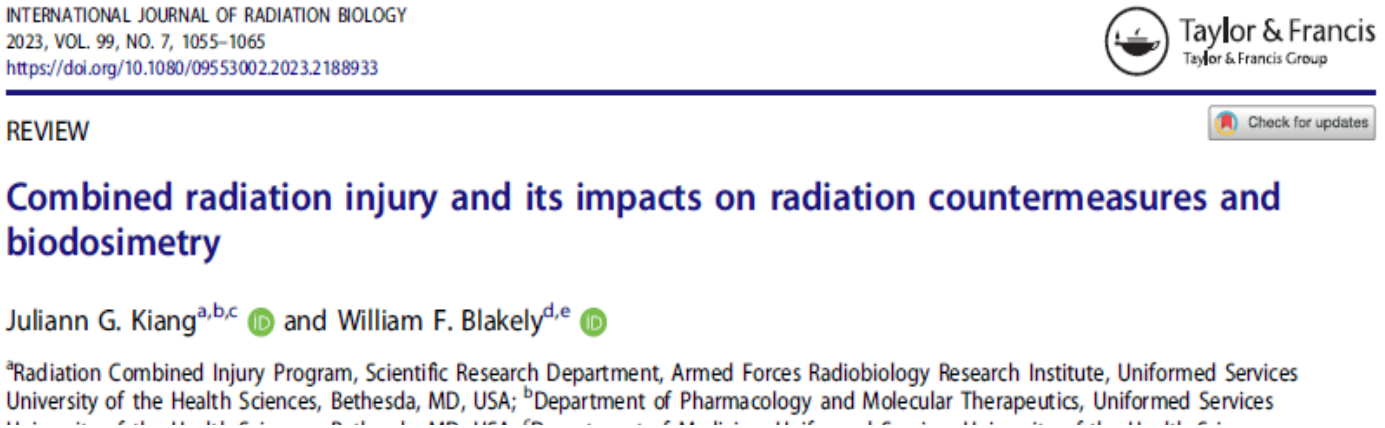
# Take Home Messages

- For triage, WBCs, RBCs and platelets are biomarkers to distinguish a victim apart from sham, irradiation only, or combined irradiation with other trauma.

- Erythropoietin, IL-1β, IL-6, IL-17A, and TNF-α can be a supplemental support to blood cell data.

- For radiation dose assessment, Flt-3 ligand, CD27, miR-34a, GM-CSF, CD45, IL-12, and TPO are biomarkers that display no disparity between radiation alone and CI.

1. Kiang JG, Blakely WF. Int J Radiat Biol 99(7): 1055-1065, 2023. PMID: 36947602, PMCID:PMC10947598



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https://doi.org/10.1080/09553002.2023.2188933

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REVIEW

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## Combined radiation injury and its impacts on radiation countermeasures and biodosimetry

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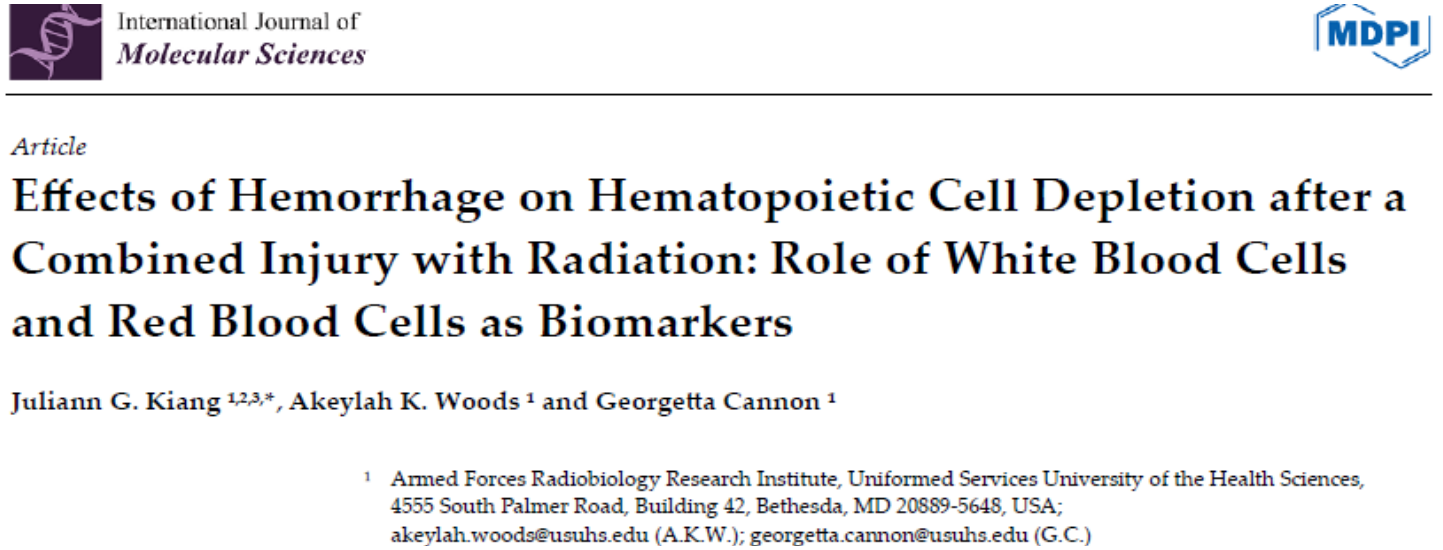
2. Kiang JG, Woods AK, Cannon G. Int J Mol Sci 25:2988, 2024. PMID: 38319684 PMCID: PMC10932428



International Journal of *Molecular Sciences*

MDPI

*Article*

## Effects of Hemorrhage on Hematopoietic Cell Depletion after a Combined Injury with Radiation: Role of White Blood Cells and Red Blood Cells as Biomarkers

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