Developing a Host-Directed Therapy for Multiple Threats and Complex Combined Injuries: Treating Pancytopenia and Resulting Infection, Sepsis, and Hemorrhage Due to Acute Radiation or Sulfur Mustard Exposure Plus Trauma with Leukine®

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MILITARY HEALTH SYSTEM RESEARCH SYMPOSIUM - AUGUST 2023

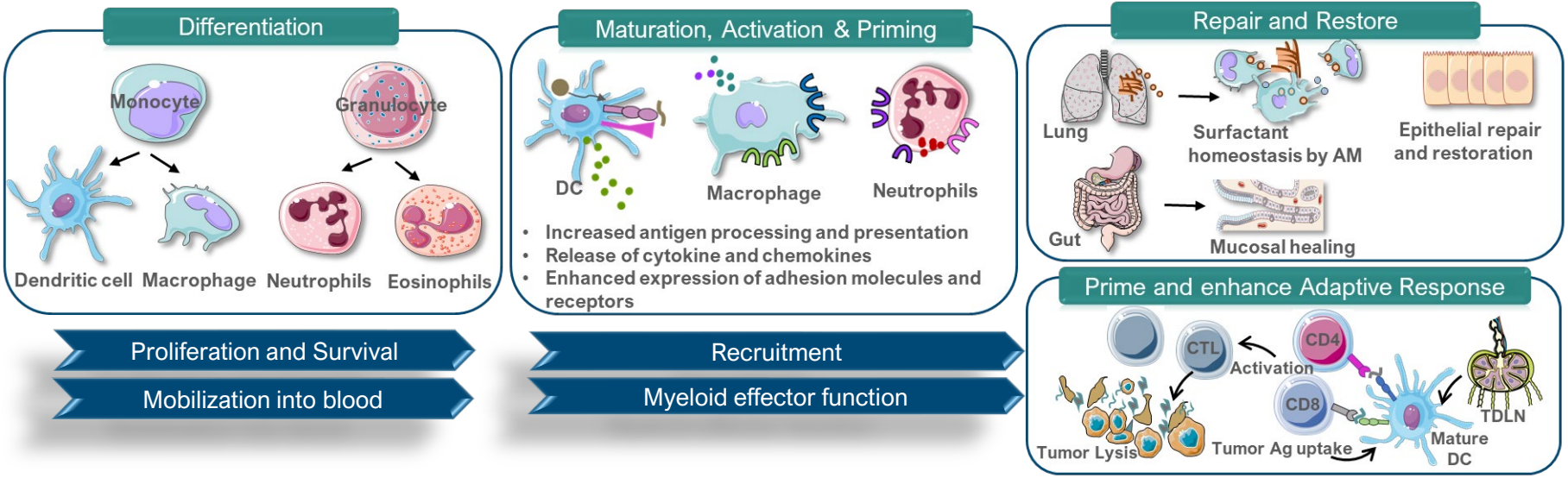
The views expressed are those of PTx and should not be construed to represent the positions of the U.S. Army or the Department of Defense. The data and opinions presented are the presenter's own, and do not reflect the view of the U.S. government.

Disclosures

- Ila Joshi, PhD, Debasish Roychowdhury, MD, Sanjeev Ahuja, MD, and John McManus are Partner Therapeutics, Inc., employees and have received salary and stock options from the Company
- Melanie Doyle-Eisele, PhD and Danielle Adney, DVM are employees of Lovelace Biomedical Research Institute (LBRI) and LBRI is the primary subcontractor for PTx's sulfur mustard contract and received research funding from this project.
- Isabel Lauren Jackson, PhD is CEO of TrueNorth Biopharm, LLC and received consulting fees for this project.

Data and opinions presented are those of the authors and should not be construed to represent positions of NIH/NIAID, AFRRI/USUHS, the U.S. Army, Department of Defense, or U.S. government.

LEUKINE (rhu GM-CSF) Multilineage Biology Provides Rationale for Use Beyond Traditional Growth Factor Settings



*Ag, antigen; AM, alveolar macrophage, TDLN, Tumor draining Lymph Node; DC, Dendritic Cell; CTL, Cytotoxic T lymphocytes; *Leukine Package Insert, Dranoff, et al Proc Natl Acad Sci (1993); Bernsconi, et al, Inflamm Bowel Dis (2010); Rosler, et al, Mol Cell Pediatr (2016).*

LEUKINE® (sargramostim; rhu GM-CSF)

Host-directed therapeutic that augments immune response and promotes function, repair and restoration

- **Host-Based Therapeutic** that mitigates immune dysregulation
- **Boosts** pathogen-specific immune response
- **Restores** alveolar gas exchange / diffusion capacity
- **FDA-Approved** for use in 6 Indications
- **Available / Held** for use by the US Government

- Immune dysregulation/suppression induced by radiation or sulfur mustard (HD) drives infection, sepsis, and multi-organ damage, which are exacerbated when accompanied by wounds (combined injury or CI).
- Leukine accelerates recovery of immune response and promotes repair and restoration of barrier integrity, thereby mitigating the pathophysiology underlying morbidity and mortality from H-ARS, HD, wounds, or CI.

Established Ability for Initial Deployment and Use to Protect the Warfighter

- ✓ Obtained FDA approval of Leukine to treat radiation-induced myelosuppression in 2018 with support from the Biomedical Advanced Research and Development Authority (BARDA)
- ✓ ASPR added Leukine to the Strategic National Stockpile in 2019
- ✓ FDA designated Leukine an Essential Medicine for H-ARS
- ✓ DoD Clinical Practice Guidelines recommend Leukine for use in H-ARS
- ✓ DoD added Leukine to Joint Deployment Formulary and assigned a National Stock Number

Leukine Improves Survival after Radiation Exposure by Accelerating Recovery of Immune Response Reducing Frequency and Severity of GI Damage and Sepsis

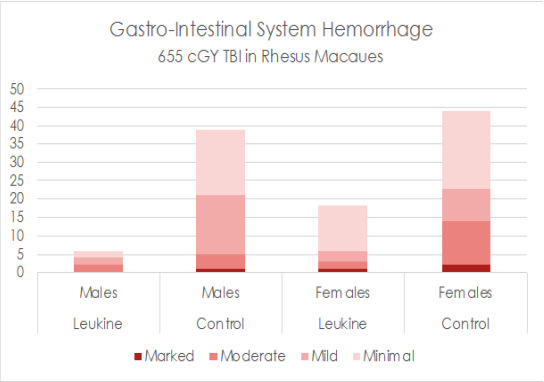
Primary cause of death: sepsis or septicemia (observed in 95% of decedents) with hemorrhage from thrombocytopenia contributory

60-Day Survival after Total Body Irradiation

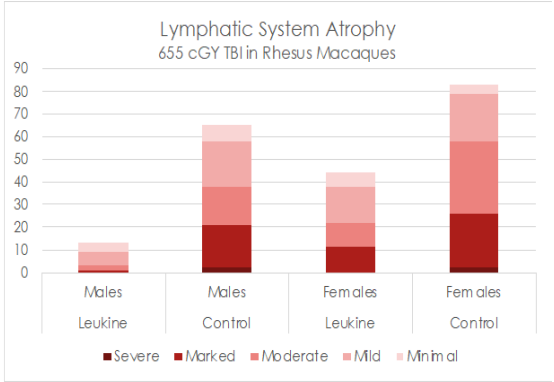
	Radiation Exposure (cGy)				
	655	670	680	713	730
Control	42% (36)	42% (12)	29% (35)	17% (18)	33% (12)
Leukine (24 Hour)			49% (35)		58% (12)
Leukine (48 Hour)	78% (36)	67% (12)	60% (35)	61% (18)	

Treatment Benefit up to 96-Hours Post-Exposure

	Control	Leukine 48 hours	Leukine 72 hours	Leukine 96 hours	Leukine 120 hours
% Survival	9%	32%	25%	32%	16%

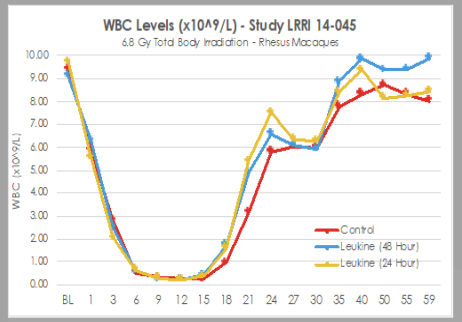


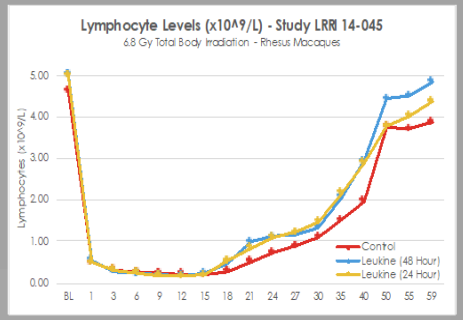
- Severe lymphatic system atrophy and GI damage; bone marrow hypocellularity in >90% of deceased control animals
- Hemorrhage and bacteria across tissues and necrosis of tissues associated with bacteria in decedents

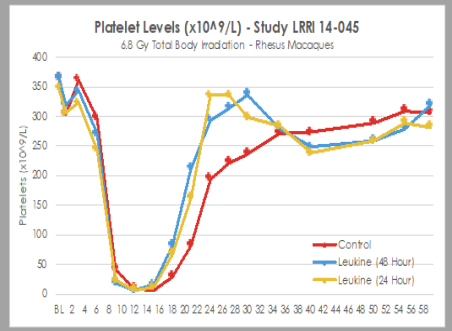


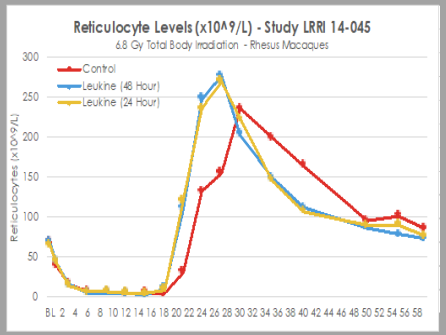
Sources: Doyle-Eisele M, Study 14-045 Final Report (2015); Clayton NP, et al, Rad Res 195, 191-199 (2021); Zhong Y, et al. Int J Radiat Biol. 2020:1-17; Sanofi communications; Final Study Report TSK-0143; Final Study Report TSK-0144, Final Study Report 1017-3493. Funding: Office of the Assistant Secretary for Preparedness and Response (ASPR), Biomedical Advanced Research and Development Authority (BARDA), Contract# HHSO1002013000051

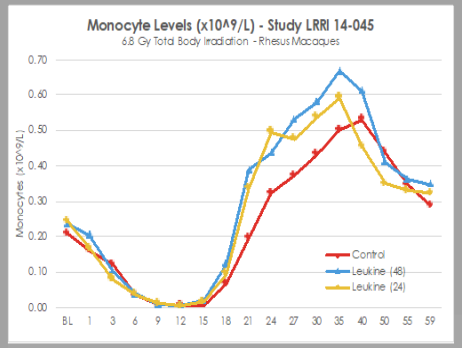
Leukine Reduces Duration of Radiation–Induced Leukopenia, Thrombocytopenia and Anemia

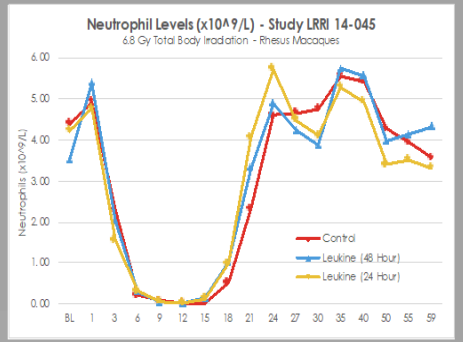


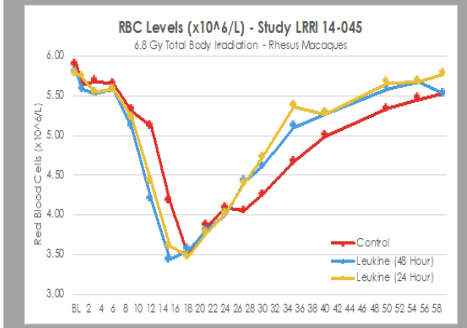


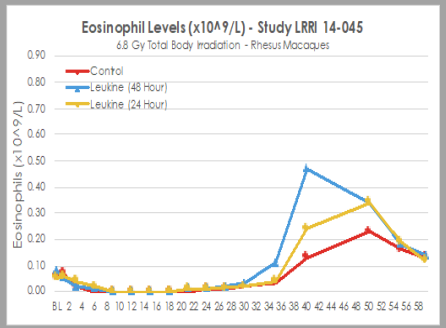












Source: Doyle-Eisele M, Study 14-045 Final Report (2015).

Funding: Office of the Assistant Secretary for Preparedness and Response (ASPR), Biomedical Advanced Research and Development Authority (BARDA), Contract# HHSO1002013000051

Generate Data to Expand Use to Treat Warfighter Complex Injuries

- ✓ Establish Leukine efficacy in HD-induced myelosuppression model
- ✓ Establish Leukine efficacy in Armed Forces Radiation Research Institute (AFRRI) murine combined injury (CI) model
- Conduct confirmatory CI studies in mouse and select appropriate large animal model (ongoing)
- Provide data from HD and CI studies to JPM CBRN Medical to support Clinical Practice Guideline submissions

Systemic / Hematological Effects of Sulfur Mustard (HD) Exposure

Bone Marrow Suppression and Lymphatic Damage Drives Pancytopenia / Immune Suppression

Clinical management of mustard gas casualties

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- 170 HD Casualties evacuated to European hospitals during 1984-1986
- Clinical files of 65 patients were analyzed
- Hospitalization occurred between day 4 to 17 post–exposure
- **Leukopenia** occurred in 29 of 65 HD casualties
- 9 of the other 65 HD casualties had **lymphopenia**
- 9 patients died – 7 of 9 had severe **Leukopenia** (WBC ≤ 200/ml)
- High frequency of septicemia

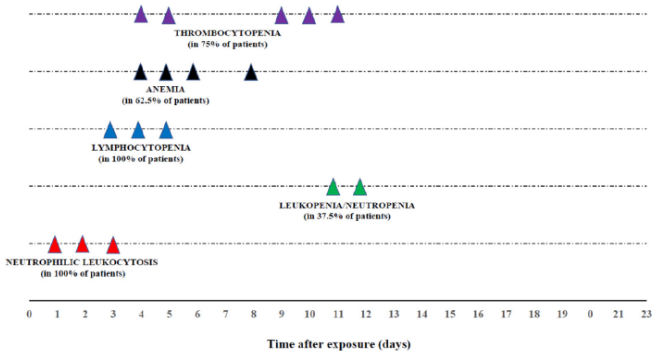
It is of interest that older observations report that leukocyte counts started to drop on the third to fourth day after exposure (Alexander, 1947) and that a minimum was obtained at 9 days (Krumbhaar, 1919; Krumbhaar and Krumbhaar, 1919). Alexander (1947) further states that cell counts of 100/μ1 or below were recorded and that all patients with extremely low leukocyte counts died. In our series also, all patients who had minimum counts of 200 cell/μl or less died.

"Mustard acts at different sites in the body as a radio-mimetic. The resulting symptoms are headache, nausea, vomiting, anorexia, epigastric pain, **leukopenia, thrombocytopenia and anemia**."

Myelosuppression and acute hematological complications of sulfur mustard exposure in victims of chemical terrorism

Sermet Sezigen*, Rusen Koray Eyison, Mesut Ortatatli, Ertugrul Kilic, Levent Kenar
University of Health Sciences, Dept. of Medical CBRN Defense, Etlik, 06010, Ankara, Turkey

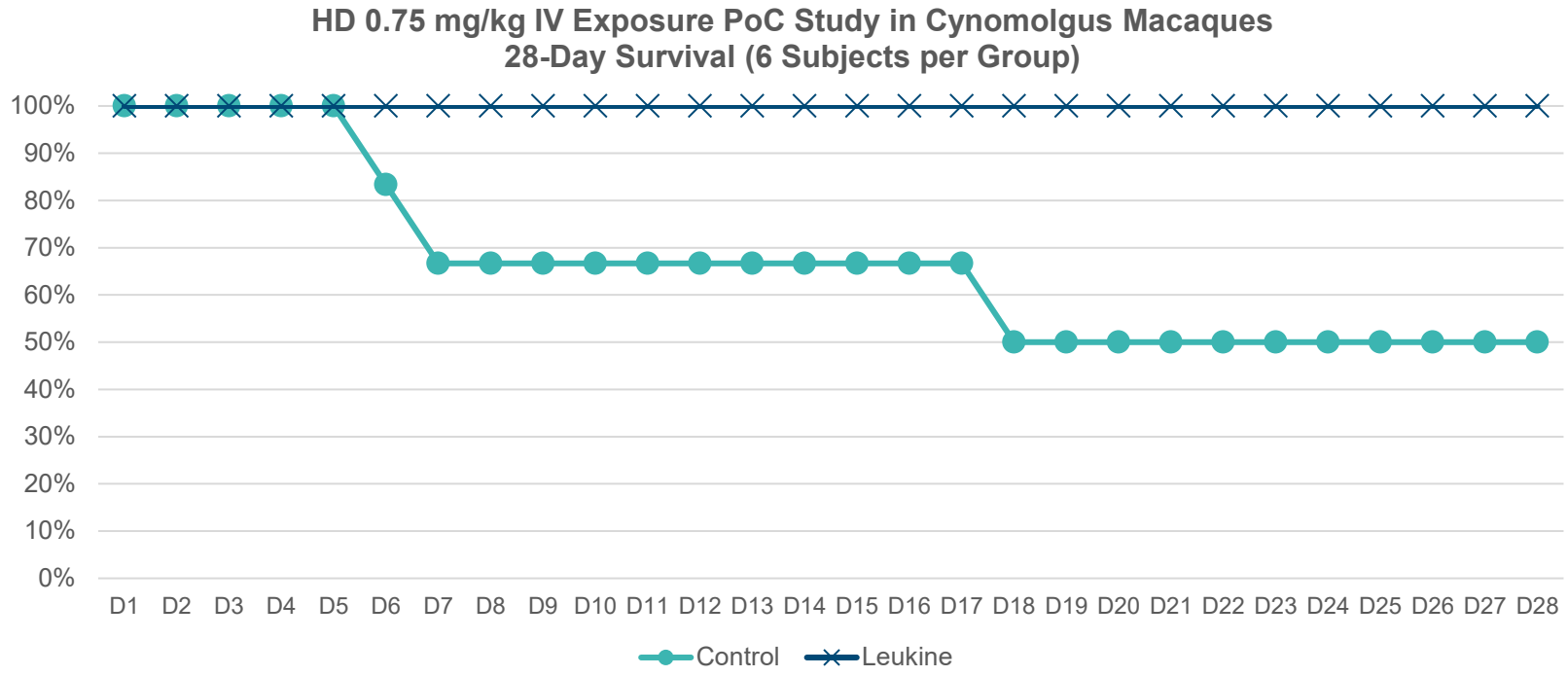
Onset of Pancytopenia after HD Exposure



Pancytopenia:	severity increases with exposure
Leukopenia:	**serious** at highest exposure
Lymphopenia:	**severe** in all patients
Neutropenia:	mild to none
Thrombocytopenia:	moderate at highest exposure
Anemia:	moderate at highest exposure

There are no FDA-approved MCMs to treat HD-induced myelosuppression, which is the primary driver of morbidity and mortality in human exposures

Sulfur Mustard (HD) Proof of Concept Study

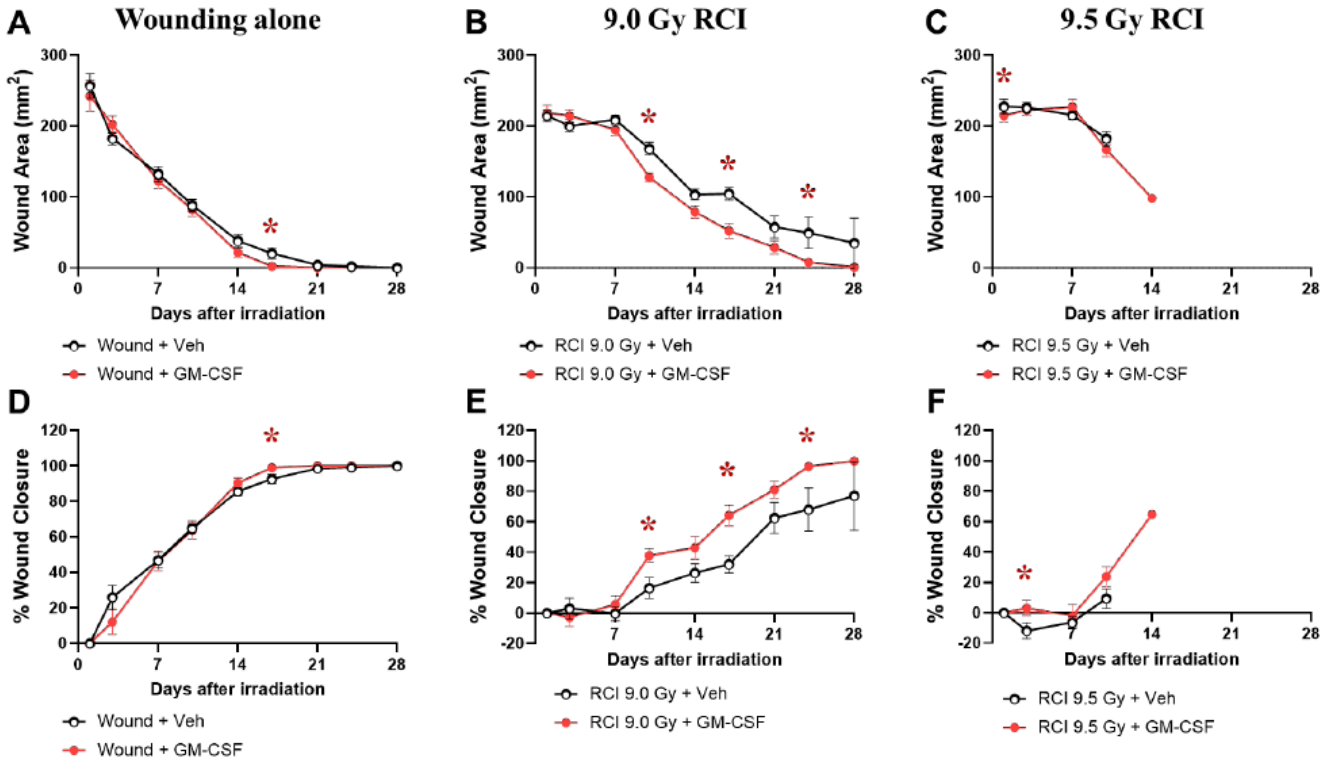


Leukine is Technology Readiness Level 7B for HD

Source: Preliminary Results from Proof-of-Concept Efficacy Study conducted by LBRI in 2023
Funding: US Department of Defense (DoD) Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense (JPEO-CBRND) under Agreement W911SR229000

Combined Injury (Radiation with Puncture Wound)

GM-CSF Accelerates Wound Closure



** Indicates P <0.05*

- There are no FDA-approved MCMs to treat CI.
- Many H-ARS victims would also suffer blast wounds.
- Animal studies suggest that wounds exacerbate radiation effects by degrading barrier integrity and further dysregulating immune response, thus elevating risk of infection and sepsis.
- AFRRI evaluated GM-CSF in a murine CI model funded and found that GM-CSF improved survival and accelerated wound healing.

Leukine is at TRL 6C for CI

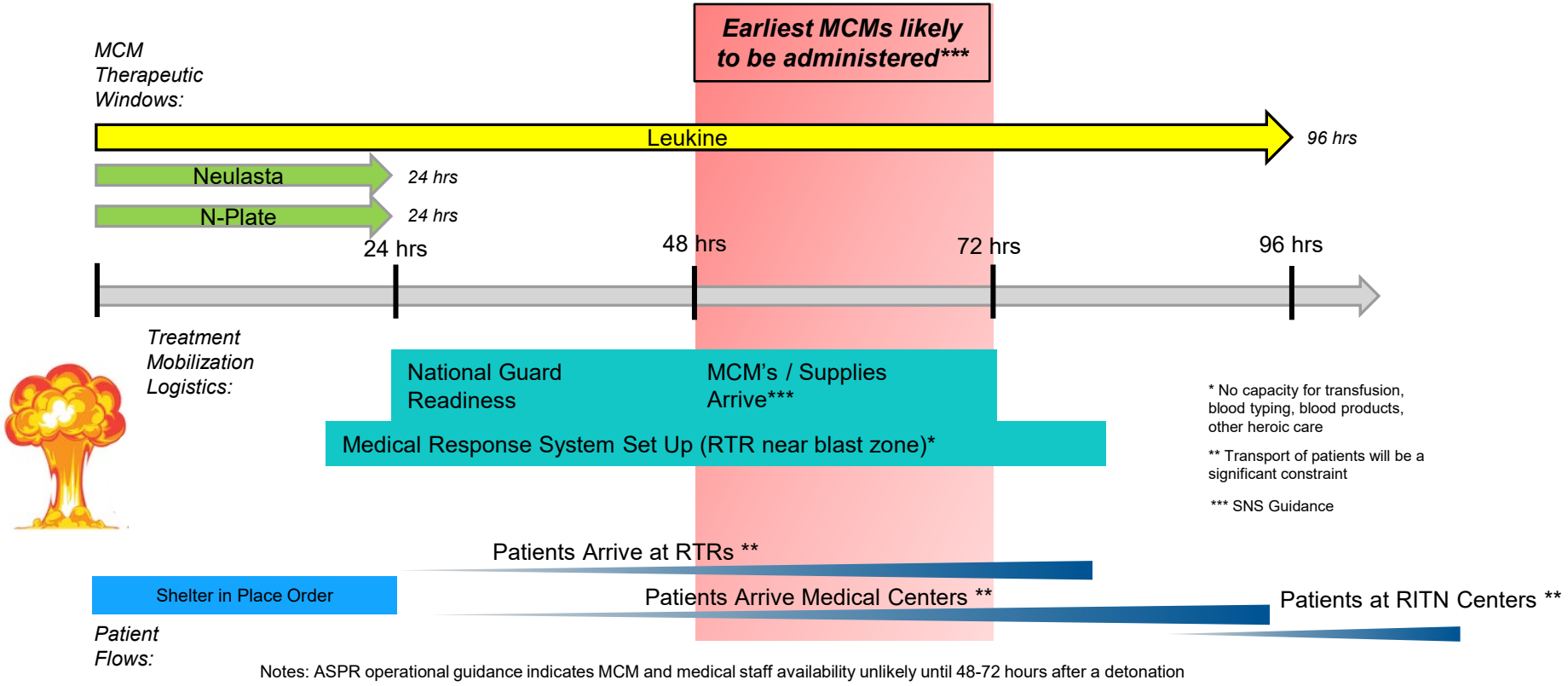
Final Study Report: Xiao, M., MD; Armed Forces Radiation Research Institute (May 2023)

Obtain FDA Approvals to Expand Leukine Label / CPGs

- Conduct adequate and well-controlled (AWC) studies after FDA consultation in HD and CI
- Add treatment of HD-induced myelosuppression and CI to label
- Pursue approval and/or CPGs for additional unmet needs to enhance warfighter protection

- Results from HD and CI studies will be provided to DoD for review and submission to support CPGs.
- Meetings will be held with the FDA to obtain concurrence on AWC study designs to support inclusion of HD and CI in the Leukine label.
- The HD AWC study will be conducted under the CET RAIDR HD contract.
- A CI AWC study would be conducted in an established large animal CI model for which funding will be required.

ARS Deployment Challenges: Post-Detonation Operational Realities will Prevent Administration of Treatments Prior to 48 Hours-post Detonation



Notes: ASPR operational guidance indicates MCM and medical staff availability unlikely until 48-72 hours after a detonation

Sources: Exploring Medical and Public Health Preparedness for a Nuclear Incident, National Academies Press (2019); US Dept of Health & Human Services Radiation Emergency Management https://remm.hhs.gov/RTR.htm

Applicability to Medical Roles of Care

Comparison of Key Attributes of FDA-Approved Medical Countermeasures for Acute Radiation Syndrome (NHP TBI H-ARS Model)				
	Leukine® (Sargramostim)	Neupogen™ (Filgrastim)	Neulasta™ (Pegylated Filgrastim)	Nplate™ (Romiplastim)
Effective without Blood Transfusions	Yes	No	No	Yes
Reduces Infection	Yes	Yes	Yes	No
Reduces Hemorrhage	Yes	No	No	Yes
Improves Anemia	Yes	No	No	No
Accelerates Lymphocyte Recovery	Yes	No	No	No
Accelerates Monocyte Recovery	Yes	No	No	No
Accelerates Neutrophil Recovery	Yes	Yes	Yes	No
Accelerates Eosinophil Recovery	Yes	No	No	No
Accelerates Platelet Recovery	Yes	No	No	Yes
Accelerates Erythrocyte/Reticulocyte Recovery	Yes	No	No	No
Treatment Effective when Administered up to:	96 hours	24 hours	24 hours	24 hours

Notes: Based on Non-Human Primate Studies Supporting FDA-Approval
ASPR operational guidance indicates MCM and medical staff availability unlikely until 48-72 hours after a detonation

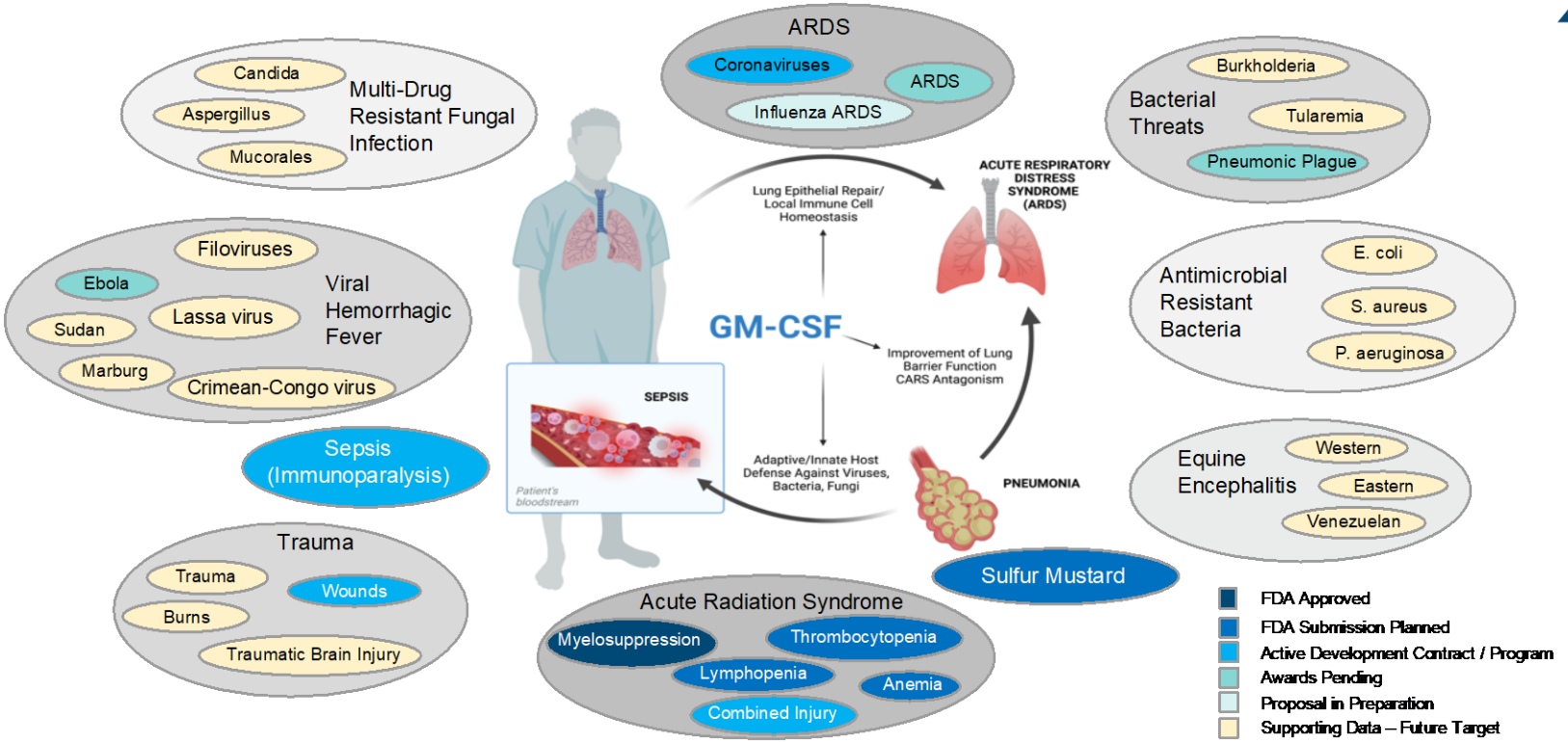
- ✓ Leukine's availability to protect warfighters from H-ARS represents an advancement in medical care over previously approved H-ARS treatments (Neupogen® and Neulasta®) which must be administered within 24 hours of radiation exposure and require concomitant administration of blood products to improve survival.
- ✓ Leukine improves survival when started up to 96 hours after exposure, providing critical time to overcome operations area complexity.
- ✓ Efficacy without blood transfusions simplifies response given that blood products will be limited or unavailable.
- **Expanding CPGs and Leukine's label to include HD-induced myelosuppression will enhance warfighter protection by addressing the primary driver of HD hospitalization and mortality.**
- **Confirming Leukine's efficacy in wound healing and addressing complex combat trauma further extends warfighter protection and does so rapidly and economically with CET RAIDR and NIH-NIAID.**

Lazarus H, McManus J, Gale RP (2022): Sargramostim in acute radiation syndrome, Expert Opinion on Biological Therapy 2022, DOI:10.1080/14712598.2022.2143261

Impact to the Warfighter / Significance

- Expanding the utility of Leukine as a host-directed medical countermeasure provides enhanced warfighter protection against chemical, biological and radiological-nuclear threats.
- Further exploration of the product offers potential for expanding this protection against additional threats and represents a promising tool for addressing unknown threats by offering a frontline defense and buying time to develop or modify targeted MCMs.
- This protection can be provided with the knowledge that Leukine has been safely used in more than 538,000 patients.

Host-Directed Therapy to Protect the Warfighter from Known and Unknown Threats



Acknowledgements

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- Studies supporting Leukine's FDA-approval as a MCM to treat H-AR were funded by the Office of the Assistant Secretary for Preparedness and Response (ASPR), Biomedical Advanced Research and Development Authority (BARDA), under contract number HHSO1002013000051.
- Combined injury work was supported by funds from NIH/NIAID-AFRRI IAA Work Plan A.
- Melanie Doyle-Eisele, PhD and Danielle Adney, PhD, DVM of Lovelace Biomedical Research Institute (LBRI), Lauren Jackson, PhD of TrueNorth Biopharm, LLC (TNB) and Sanjeev Ahuja, MD, Ila Joshi, PhD and John McManus of PTx contributed to the design of the HD exposure studies.

Learning Objectives

1. Describe how radiation or HD-induced myelosuppression drives infection, sepsis, hemorrhage, and multi-organ damage; how wounds exacerbate this; and how Leukine accelerates recovery from myelosuppression and wounds, leading to improved outcomes.
2. Analyze impaired immune response after HD, radiation and wounds, and how host-directed therapy can accelerate recovery of immune response and promote barrier integrity restoration, reducing the pathophysiology underlying morbidity and mortality.
3. Discuss Leukine's potential to treat warfighter combined injury including the cascade of cellular reactions and pathophysiology triggered by the combination of radiation or sulfur mustard and wounds, and its deployment in complex operating environments.