**Developing a broad-spectrum, 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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Introduction

In support of the Department of Defense (DoD) Chemical and Biological Defense (CBD) program's objectives, Partner Therapeutics (PTx) is collaborating with the Joint Project Manager for Chemical, Biological, Radiological, and Nuclear Medical (JPM CBRN Medical) Countering Emerging Threats - Rapid Acquisition and Investigation of Drugs for Repurposing (CET RAIDR) program to expand the utility of an Food and Drug Administration (FDA)-approved medical countermeasure (MCM) that strengthens host immune response to deliver broad spectrum protection against known and unknown, chemical, biological, radiological, nuclear, and combined threats to the warfighter. The initial PTx-CET RAIDR program effort leverages interagency development funded by the Biomedical Advanced Research and Development Authority (BARDA) and the National Institutes of Health, National Institute of Allergy and Infectious Diseases (NIH-NIAID) Radiation Nuclear Countermeasures Program (RNCP) to address high-consequence aspects of polytrauma threats to warfighters and civilians.

Capability Description

Leukine (sargramostim) is an FDA-approved "Essential Medicine" held for use by the Strategic National Stockpile (SNS) and included in the Joint Deployment Formulary (JDF) and Clinical Practice Guidelines (CPGs) to treat the myelosuppressive effects of acute radiation exposure (H-ARS). PTx manufactures bulk drug substance at its Lynnwood, WA facility, and final product is filled at U.S. based facilities. Leukine's shelf-life is four years when stored at 2 to 8°C.

As a yeast-derived recombinant form of human granulocyte-macrophage colony-stimulating factor (GM-CSF), Leukine functions as an immunomodulator and plays a critical role in host defense, immune homeostasis, tissue repair and lung physiology. GM-CSF is classically known for promoting differentiation of immature precursor cells in bone marrow, and stimulating proliferation, differentiation, and maturation of myeloid cells. Equally important are its roles in antigen presentation, T-cell activation and promotion of myeloid cell survival, division, maturation, function, and activation. It also acts on resident macrophages to promote tissue repair and wound healing and is critical for resolution of inflammation. In the lungs, GM-CSF promotes alveolar epithelial cell health, surfactant clearance and maturation of monocytes into alveolar macrophages.

Leukine was developed conventionally as a radiation MCM with BARDA support and received FDA approval to treat H-ARS in 2018. Myelosuppression induced by radiation or sulfur mustard (HD) drives infection, sepsis, hemorrhage, 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.

Methods / Technical Approach

Establish Ability for Initial Deployment and Use to Protect the Warfighter

- Obtain FDA approval to treat radiation-induced myelosuppression.
- Add Leukine to SNS, CPGs and JDF to enable deployment for warfighter protection.

Generate Data Expanding Use to Treat Warfighter Complex Injuries
- Establish Leukine efficacy in HD-induced myelosuppression model.
- Evaluate Leukine efficacy in Armed Forces Radiation Research Institute (AFRRI) murine combined injury model.
- Provide data from HD and CI studies to JPM CBRN Medical to support CPG submission.

Obtain FDA Approvals to Expand Leukine Label
- Conduct adequate and well-controlled (AWC) studies after FDA consultation.
- Add treatment of HD-induced myelosuppression and combined injury to label.

Results

Establish Ability for Initial Deployment and Use to Protect the Warfighter

FDA approval, SNS acquisition, and DoD CPGs for H-ARS were achieved based upon data from three Good Laboratory Practice (GLP) studies conducted in non-human primates. In these studies, Leukine accelerated recovery of suppressed lymphocytes, monocytes, neutrophils, eosinophils, platelets, reticulocytes, and erythrocytes after lethal total body irradiation, and reduced the incidence and severity of infection, sepsis, and hemorrhage. Benefits were observed in male and female subjects managed with minimal supportive care (e.g., absence of whole blood transfusions) when Leukine treatment was initiated up to 96 hours after radiation exposure, mimicking operational complexities expected in a radiation event.

Generate Data to Expand Use to Treat Warfighter Complex Injuries

HD Exposure: There are presently no FDA-approved MCMs to treat HD-induced myelosuppression, which is the primary driver of morbidity and mortality in human exposures. HD is a radio-mimetic and myelosuppression after exposure resembles radiation-induced myelosuppression, as described by Meisenberg and Anderson at United States Army Medical Research Institute of Chemical Defense. This was confirmed in the CET RAIDR program under a Leukine HD development contract initiated in 2022. A Proof-of-Concept (POC) study evaluating Leukine will be completed in April 2023.

CI: There are presently 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 infection risk. AFRRI evaluated GM-CSF in a murine CI model funded by NIH-NIAID RNCP and found that GM-CSF improved survival and accelerated wound healing.

Results from HD and CI studies will be provided to DoD for review and submission to support CPGs. Data will also be shared with FDA at Type C meetings to obtain concurrence on designs of AWC studies 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.

Applicability to Medical Roles of Care

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 (i.e., radiation contamination, infrastructure damage). Efficacy without blood transfusions simplifies response and is critical 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 hospitalization and mortality for a threat for which there are no currently approved treatments. 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.

Impact to the Warfighter/Significance

Expanding Leukine as a host-directed therapy to address multiple threats provides enhanced warfighter protection against known chemical, biological, radiological, and 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.

Development Status of the Technology

Leukine is FDA approved for treatment of H-ARS. For HD, Leukine is Technology Readiness Level (TRL) 7B, and submission of a supplemental Biological License Application is planned in 2024. Leukine is at TRL 6C for CI. Confirmation of efficacy in a large animal model will be required to complete TRL 7 and inform an AWC study to complete TRL 8.

Disclaimer

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Learning Objectives

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.

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.

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.