Strengthening Warfighter Resiliency Using Broad-Spectrum or Host-Directed Therapies within the Rapid Acquisition and Investigation of Drugs for Repurposing (RAIDR) Program

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Abstract

To maintain cadence with looming threats in a prolonged field-care environment, the broader medical countermeasure (MCM) enterprise must adopt new strategies for CBRN-addressing drug development. The Countering Emerging Threats - Rapid Acquisition and Investigation of Drugs for Repurposing (CET RAIDR) program within the JPM CBRN Medical is designed to rapidly tackle known, unknown, and emerging threats by utilizing late-stage or licensed therapeutics. The focus of the CET RAIDR effort is to bridge treatment gaps between threat identification and the implementation of licensed targeted MCMs, thereby strengthening warfighter resiliency. The repurposing approach conserves both time-to-market and funds by leveraging previous conventional development work as a launch point for repurposing efforts. The CET RAIDR program minimizes development and procurement costs by supplementing the military medical providers’ toolbox with post-Phase II therapies that demonstrate established safety and manufacturing processes, leading to a cost-sparing model for niche medicines (i.e., CBRN MCMs).

Significance Statement:

CET RAIDR program candidates are selected based on several pillars: a proven human safety profile, the availability of tools and validated literature on the drug’s mechanism of action (MOA), well-defined assays and/or animal models to demonstrate efficacy, as well as collaborations with willing and trusted industry partners. This broader repurposing approach to address the growing CBRN threat landscape will better safeguard the warfighter against well-documented or unpredictable threats when a direct-acting MCM is unavailable, or not-yet conceived.
Introduction: Expanding the Medical Toolbox

There are over 20,000 prescription drug products approved for marketing in the U.S. (Food and Drug Administration, 2023; Food and Drug Administration, 2018 B). Each drug takes, on average, between 12-15 years from bench to bedside, and costs anywhere from $100 million to $2.8 billion dollars to gain licensure (Congressional Budget Office, 2021; Wouters, 2020). While this paradigm may be a necessary and warranted approach to conventional drug development, it struggles to address the rapid response and innovation required for dual trauma and CBRN casualties in prolonged field-care environments. Medical staff in military operational environments need reliable, predictable, fast-acting, environment-agnostic prophylactics and treatment options to address a broad range of threats against the warfighter. CBRN exposure is a higher risk in the military setting, so it is only fitting that the warfighter requires a bespoke solution to optimize gap-filling treatments in care, starting with broad spectrum treatments that increase the decision space for operators and clinicians alike (see Figure 1).

The military medical community has adopted a new strategy for MCM development, whereby new CBRN-related products are pushed through the conventional drug development pipeline in parallel to driving repurposing of the repository of over 20,000 (and growing) licensed drugs (Food and Drug Administration, 2023; Food and Drug Administration, 2018 B).

The Dilemma: Reinventing Rapid Treatments Against CBRN Threats

U.S. military forces conduct missions worldwide, in hostile environmental conditions that may include exposure to novel agents and emerging threats. Numerous countries, with mature or developing chemical or biological weapons programs, have developed, produced, and subsequently weaponized numerous lethal or incapacitating agents (Congressional Budget Office, 2021). The threat of CBRN agents and emerging infectious diseases of biodefense consequence will continue to become more complex over the next decade, resulting from increased agent variety, demographic and geographic shifts, and engineering sophistication (Vergun, 2023). U.S. forces must maintain the capability to mitigate, prevent, and treat a wide swath of high-priority threats.

Maintaining stockpiles and developing tailored, targeted treatments to the evolving and numerous potential threats is unrealistic and unattainable. However, building an infrastructure whereby drugs with host-driven or broad-spectrum capabilities are applied to meet the immediate need of multiple threats could spare lives and hasten warfighter recovery (see Figure 1). To further shorten the time window between threat exposure and treatment, the CBRN medical community has expanded opportunities by repurposing FDA-licensed drugs with proven safety profiles, well-established manufacturing processes, and commercial viability. These three factors promote treatments that:

- Are readily available with potential for expedited access and scale-up.
- Retain market resiliency by virtue of their current and future commercial earnings.
- Enhance confidence in the predictability a drug’s safety, assuming dosage and formulation remains in an acceptable FDA-approved form.
• Offer reassurance to the care provider that these drugs are well-characterized, well-tolerated, and widely accepted within a broader population setting, thereby minimizing hesitancy expressed toward new entities (Garjón, 2012).

As previously mentioned, the conventional pathway for development of MCMs against CBRN threats, while important for layered defense, is often time-consuming and more costly than a repurposed product. Often, only demonstration of effectiveness is required to repurpose a drug to a new indication. With meticulous research, and sometimes serendipitous findings, the MOA for existing molecules can be leveraged to reposition a known drug against an untested threat. The medical community could pair novel combinations of FDA-approved drugs to known, novel, or emerging threats by cross-walking the patient’s pathophysiology and symptomology to a licensed drug’s MOA. This personalized host-threat approach equips the medical community with potentially new treatment options that are driven by the desired clinical outcome (e.g., bolstering immune cells, suppressing immune activation or cytokine cascades, modulating expression factors, blocking virus entry points across viral families).

A COVID-19 Jumpstart to Repurposing Efforts

In 2019, there were no FDA-approved medicines against the pandemic virus SARS-CoV-2, which elicits the disease COVID-19. With Coronavirus Aid, Relief, and Economic Security (CARES) Act funding, the Defense Department (DOD) sought to rapidly develop MCMs for prophylaxis or treatment against COVID-19 in asymptomatic and symptomatic populations. However, since traditional drug development is costly and time-prohibitive, the DOD initiated a repurposing program, in parallel with conventional efforts, that was called COVID-19 Repurposed Therapeutics (or CRTx). CRTx launched at a pivotal moment to address active and growing concerns over the impact that COVID-19 would have on military readiness and warfighter wellbeing. CRTx was conceived to competitively select and drive studies with the most likely success, to obtain data sets to support potential new applications for FDA-licensed drugs against COVID-19.

Proving the benefit and expediency of repurposing through their COVID-19 work, the DOD’s JPM CBRN Medical team launched a subsequent repurposing program targeting CBRN-specific threats called Countering Emerging Threats - Rapid Acquisition and Investigation of Drugs for Repurposing, or “CET RAIDR.” The CET RAIDR program is positioned to leverage lessons learned from the COVID-19 pandemic to perform advanced development activities that repurpose late-stage and FDA-approved products, in both the host-directed (broad) and direct-acting (targeted) threat categories. Expanding beyond COVID-19, this program aims to adapt existing, safe, and commercially viable treatment options to address threats prevalent within the broader CBRN space as novel MCMs (JPEO-CBRND, 2023).

A Solution to Address the Gap in Available, Safe and Effective Treatments against Dual Trauma and CBRN Exposure
The purpose of the CET RAIDR program is to establish effectiveness against CBRN agents through *in vitro* and *in vivo* testing in a non-clinical setting. Efficacy data are designed to inform the treating medical provider and expand clinical practice guidelines (CPGs) and the level of personalized care (Joint Trauma System, 2023). CPGs serve as a cornerstone of the military medical providers’ toolbox, and it starts at the point of care. Expanding and refining CPGs will be pivotal to maintain the leading edge against emerging CBRN threats.

The CET RAIDR program actively evaluates well-characterized late stage or licensed drugs for rapid repurposing against a new threat, which could span all roles of care: Role 1 - the point of injury (First Responder), Role 2 (Forward Resuscitative), Role 3 (Theater Hospital), and Role 4 (Medical Treatment Facility). Each CET RAIDR program effort has individualized success metrics based on the intended application of the MCM. These metrics are driven by warfighter need, previously conducted non-clinical data, well-characterized animal models or cellular assays, and discussions with the drug manufacturer. While CET RAIDR program products are often already approved, the program is navigating non-traditional label expansion regulatory pathways to encourage adoption of new MCM treatment strategies for the warfighter.

For example, one of CET RAIDR’s portfolio members, Partner Therapeutics, Inc., is seeking FDA-approval for Leukine® under the Animal Rule, as a MCM for sulfur mustard gas exposure (Partner Therapeutics, 2022). Leukine® is currently licensed for hematopoietic acute radiation syndrome (H-ARS) (Food and Drug Administration, 2018 A; Partner Therapeutics, 2018). The success parameter for this effort stems from the drug’s ability to quench myelosuppression and accelerate recovery of platelets, red blood cells and white blood cells (Food and Drug Administration, 2018 A; Partner Therapeutics, 2018). Leukine® treatment may apply across both threat types since both radiation (approved indication) and sulfur mustard exposure (potential new indication) mirror a similar clinical outcome (or syndrome). The success of this program and others within the CET RAIDR program will be driven by the physiological pathways impacted by the drug, the regulatory path, the threat under question, opportunities from current treatment regimens, and/or warfighter need.

This threat-host approach can feed into a clinical syndromic management concept, wherein symptoms of the patient will drive the first-level treatment decisions (see Figure 2). The symptoms of many CBRN threats for different threat agents manifest similarly, and diagnosis can remain obscure or ambiguous during early-stage onset. Hence, host-directed treatments (which are broadly applicable across multiple threats), drugs that bind diverse epitopes, or broad-spectrum antimicrobials, will not only refine the number of drugs required to be on-hand, but also cover a wide swath of possible threats. This approach could provide early treatment and improve patient outcomes, thereby stabilizing a patient’s condition until a definitive treatment can be delivered. In this manner, the CET RAIDR program tactically expands the medicinal toolbox available to early-role medical staff operating within the Continental U.S. or Outside the Continental U.S. (CONUS or OCONUS). Collectively, the CET RAIDR program builds a readily accessible knowledge base for trauma medical staff published within CPGs to accelerate treatment decisions and delivery while greatly expanding opportunities for better care overall.
In addition to tailoring treatment to early symptomatic indicators, the CET RAIDR program could consolidate the number of drugs necessary for early-role care providers or medics to carry as part of their basic combat load. Instead of continuing the “one-drug, one-bug” paradigm, whereby each drug only covers one threat, the broad-spectrum approach of the CET RAIDR program could supply one repurposed therapy that may be efficacious against multiple threats. This multifaceted coverage may enable faster treatment post-exposure in theatre and prolong the treatment window until a higher role of care can be reached. Finally, the CET RAIDR program approach can expand the number of drugs to treat CBRN casualties under prolonged field care conditions or for mass casualty (MASCAL) events. This is accomplished via repurposing multiple commonly available drugs for the same clinical indication. For example, the CET RAIDR program is examining multiple solutions for nerve agent-induced, refractory status epilepticus.

The CET RAIDR program is based on an Office of the Secretary of Defense (OSD)-directed requirement, indicating that repurposing will be an integral pillar for future MCM development. To further advance MCM delivery in the future operating environment, the Office of the Deputy Assistant Secretary of Defense (DASD) for Chemical and Biological Defense (CBD) established four strategic priorities that CET RAIDR program utilizes to extend efforts: Prepare for the Future Fight; Deliver at Speed; Drive Innovation; and Optimize the Enterprise (9. Office of the Under Secretary of Defense for Acquisition & Sustainment, 2022). The CET RAIDR program supports DASD (CBD)’s strategic priorities through enabling efficient delivery of innovative MCMs to existing, emerging, and developing threats of the future CBRN environment. The CET RAIDR program synchronizes other organizations in the CBDP enterprise to support nontraditional DOD partners while ensuring these partnerships result in maximum benefit to the warfighter. From a strategic perspective of national preparedness, enhancing the biodefense toolbox is a pivotal component to realizing the 2021 American Pandemic Preparedness Plan: Transforming Our Capabilities (White House, 2021). Additionally, the 2022 National Biodefense Strategy and Implementation Plan for Countering Biological Threats, Enhancing Pandemic Preparedness, and Achieving Global Health Security clearly calls for repurposed therapeutics within reach, ideally within a period of weeks. This cannot be achieved without considering appropriate, relevant, repurposing of available pharmaceuticals. Under Therapeutic Development and Manufacturing, the Strategy directs stakeholders to “identify, develop, test, authorize, manufacture, and deploy new and repurposed therapeutics” (White House, 2022). This goal synergistically maps to the CET RAIDR program mission space.
CET RAIDR program candidates for viral, bacterial, toxin, and chemical targets are prioritized for development using three key criteria:

1. **Warfighter Impact** – Focus on Service-identified threats impacting the warfighter (Risk to Force).
2. **Strategic Threat Coverage** – Prioritizing broad-spectrum prophylactics or treatments to address anticipated operational threats (Risk to Mission).
3. **Accelerated Delivery** – Repurposing safe and already manufacturable medicines for rapid deployment, as compared to conventional drug development pathways.

Highlighted priority threats and potential CET RAIDR program targets have been aggregated from the National Institute of Allergy and Infectious Diseases (NIAID), the Centers for Disease Control and Prevention (CDC), the Defense Threat Reduction Agency (DTRA), the World Health Organization (WHO), and the Federal Select Agent Program’s (FSAP’s) Biological Select Agents and Toxins (BSAT) list (Centers for Disease Control, 2023). Figure 3 highlights threats of interest to the CET RAIDR program.

**On the Horizon: Expect the Unexpected**

The CET RAIDR program offers a unique opportunity to capitalize on numerous FDA-approved pharmaceuticals for repurposing against CBRN threats. The CET RAIDR program continues to seek partnerships with other government agencies, private industry, academic laboratories, and allied nations in this product development effort (see the Broad Agency Announcement at Sam.gov, 2022). The success of the CET RAIDR program depends on strategic public-private partnerships, with established and sustainable performers, and leveraging flexible contracting vehicles (Joint Trauma System, 2023).

It is imperative that MCM developers continue to adapt their approach to drug development as CBRN threats continue to evolve and become more accessible. Establishment of a strong pipeline of repurposing candidates selected from late-stage or FDA-approved therapies will be essential to replenish, reinvigorate, and improve upon the existing standard of care in theatre to empower a more robust resilient warfighter of the future.

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Dr. Lauren Quattrochi – Wrote the manuscript

Dr. Anthony Cardile – contributed to the writing of the manuscript

LTC Amanda Love – contributed to the writing of the manuscript
Mr. Andrew Glenn - contributed to the writing of the manuscript
Mr. Micah Almas – contributed to the writing of the manuscript
Ms. Alicia Coronado - contributed to the writing of the manuscript
COL Matthew Clark – contributed to the writing of the manuscript
Mr. Charles Paschal – contributed to the writing of the manuscript
Dr. Lucy Ward - contributed to the writing of the manuscript

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For Correspondence:

The Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense (JPEO-CBRND) mission is to provide integrated layered chemical, biological, radiological, and nuclear defense capabilities to the Joint Force across combined Joint All-Domain Operations. The JPEO-CBRND’s goal is to enable the Joint Force to fight and win unencumbered by a CBRN environment.

The Joint Project Manager for Chemical, Biological, Radiological, and Nuclear Medical (JPM CBRN Medical) facilitates the rapid response, advanced development, manufacturing, and acquisition of medical solutions such as vaccines, therapeutics, and diagnostics to combat CBRN and emerging threats. The JPM CBRN Medical’s mission is to deliver quality, safe, and effective integrated medical solutions to counter CBRN threats for the Joint Forces.

To learn more about the JPEO-CBRND, visit: https://www.jpeocbrnd.osd.mil/, or follow JPEO-CBRND on social media @JPEOCBRND.
### Abbreviation List:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ARS</td>
<td>Acute Radiation Syndrome</td>
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<td>BSAT</td>
<td>Biological Select Agents and Toxins</td>
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<td>CARES</td>
<td>Coronavirus Aid, Relief, and Economic Security</td>
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<td>CBD</td>
<td>Chemical and Biological Defense</td>
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<td>CBRN</td>
<td>Chemical, Biological, Radiological &amp; Nuclear</td>
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<td>CET RAIDER</td>
<td>Countering Emerging Threats – Rapid Acquisition and Investigation of Drugs for Repurposing</td>
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<td>CONUS</td>
<td>Continental US</td>
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<td>COVID-19</td>
<td>COronaVIrus Disease of 2019</td>
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<td>CPG</td>
<td>Clinical Practice Guideline</td>
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<td>CRT-x</td>
<td>COVID-19 Repurposed Therapeutics</td>
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<td>DASD</td>
<td>Deputy Assistant Secretary of Defense</td>
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<td>DTRA</td>
<td>Defense Threat Reduction Agency</td>
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<td>FSAP</td>
<td>Federal Select Agent Program</td>
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<td>H-ARS</td>
<td>Hematopoietic acute radiation syndrome</td>
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<td>DOD</td>
<td>Department of Defense</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>JPM</td>
<td>Joint Program Manager</td>
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<td>MASCAL</td>
<td>Mass Casualty</td>
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<td>MCM</td>
<td>Medical Countermeasure</td>
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<td>MERS</td>
<td>Middle East Respiratory Syndrome</td>
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<td>MOA</td>
<td>Mechanism of action</td>
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<td>OCONUS</td>
<td>Outside the Continental US</td>
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<td>OSD</td>
<td>Office of the Secretary of Defense</td>
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<tr>
<td>PBA</td>
<td>Pharmaceutical Based Agents</td>
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<td>PEP</td>
<td>Post-exposure Prophylaxis</td>
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<td>PPE</td>
<td>Personal Protective Equipment</td>
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<td>PrEP</td>
<td>Pre-exposure Prophylaxis</td>
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<td>ROM</td>
<td>Restriction of Movement</td>
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<tr>
<td>SARS</td>
<td>Severe Acute Respiratory Syndrome</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Footnotes:

This work received no external funding.

Figure Captions:

Figure 1. The strategy of MCM designation and approaches taken by JPM Medical.

Figure 2. The threat landscape has evolved, requiring medical responders to address complex threat scenarios. The clinical syndromic management concept capitalizes on the patient’s early symptoms to drive initial treatment actions and decisions. Since many CBRN threats manifest into seemingly similar symptoms soon after exposure, it is imperative that broad-spectrum or host-directed therapies are applied as a first line of treatment, until a threat-tailored remedy is available.

Figure 3. Threat Agents of Interest to the CET RAIDR program as of 01 January 2023
Figure 1.
Figure 2.
Figure 3.

**Chemical Threats of Interest**
- V agents and G agents (e.g., sarin, soman, VX).
- Vesicants and blistering agents (e.g., sulfur mustard).
- Incapacitating agents (e.g., fentanyl, opioids, other pharmaceutical based agents (PBAs)).
- Others.

**Acute Radiation Syndrome (ARS)**

**Biological Threats of Interest**

- **Viral Targets**
  - Crimean-Congo Hemorrhagic Fever (Nairovirus).
  - Nipah and Hendra Virus.
  - Lassa Virus.
  - Coronaviruses, such as SARS-CoV or MERS-CoV, but excluding SARS-CoV-2.
  - Pandemic Influenza (Specifically H5 and H7 hemagglutinin subtypes).
  - Filoviruses (Ebola Zaire, Ebola Sudan, and Marburg virus).

- **Bacterial Targets**
  - Antimicrobial Resistant Bacteria (*E. coli, S. aureus, or P. aeruginosa*).
  - Plague (*Yersinia pestis*).
  - Tularemia (*Francisella tularensis*).
  - Q Fever (*Coxiella burnetii*).
  - Glanders (*Burkholderia mallei*) and Melioidosis (*B. pseudomallei*).

- **Toxin Targets**
  - Botulinum Toxin A-G.
  - Staphylococcal Enterotoxin B (SEB).
  - Ricin.
  - T2 Mycotoxin.
  - Marine Toxins.