

## Concept Clearance

Branch: ERTB

Council Period: 202201

Concept Title: CCRP Initiative: Chemical Threat Agent Inhalational Exposure Research Resource

The events of September 11, 2001 exposed the vulnerability of the United States to potential weapon of mass destruction (WMD) terrorism employing unconventional tactics, such as the utilization of chemical, biological, radiological, and nuclear (CBRN) agents against the civilian population. Consequently, to advance the nation's medical and public health preparedness for, response to, and recovery from disasters and public health emergencies, the Department of Health and Human Services (HHS) formed the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) to oversee and coordinate medical countermeasure (MCM)-related needs, research, development, and procurement efforts among federal agencies. The HHS, in turn, directed the National Institutes of Health (NIH) Office of the Director (OD) to initiate a civilian-focused MCMs basic research and early development program to identify therapeutics that may be effective in mitigating the adverse acute and long-term chronic health effects posed by acute exposure to these high consequence threats.

The Director of the National Institute of Allergy and Infectious Diseases (NIAID) was subsequently assigned lead responsibility by HHS and NIH OD in 2003 to develop and oversee a comprehensive biodefense program to discover therapies to address the WMD terrorist threats posed by infectious diseases, radiation, nuclear, and chemical exposure. This program was later expanded to also address public health concerns in the event of inadvertent mass casualty exposure resulting from industrial accidents or natural disaster events. The NIAID Office of Biodefense Research and Surety (OBRS) established the Chemical Countermeasures Research Program ([CCRP](#)) in 2006 to specifically implement and oversee MCM research and early development for chemicals identified as credible public health threats by the U.S. Department of Homeland Security's Probabilistic Analysis for National Threats Hazards and Risks ([PANTHR](#)) program. To date, PANTHR has identified almost 200 chemicals as high consequence public health threats. These chemicals are collectively known as DHS Chemicals of Concern (CoC).

The CCRP developed a robust research infrastructure consisting of 1) A NIH-wide translational research-based extramural grant/cooperative agreement program initiative called "CounterACT"; 2) Interagency agreements with the Department of Defense to leverage the vast expertise of the United States Army Medical Research Institute of Chemical Defense (DoD USAMRICD); 3) Research contract resources, such as a preclinical development facility (CPDF); and 4) Interagency agreements with HHS Biomedical Advanced Research and Development Authority (BARDA) to coordinate screening programs to discover potential therapeutics to repurpose as MCMs and further development of promising products towards FDA licensure and procurement for the Strategic National Stockpile. Importantly, to complement and innovate the translational programs, the CCRP has, in the past year, initiated two basic research mechanisms, specifically planning (R34) and project (R01) grants to stimulate fundamental toxicological understanding of the chemical threats at participating ICs including NIEHS.

The CCRP extramural grant and cooperative agreement program is funded by NIAID but administered by partner ICs across the NIH in recognition of and to leverage the vast expertise available at the participating ICs. The NIEHS is the lead IC overseeing the CounterACT pulmonary threats portfolio. Over the past 15+ years, the CCRP's trans-NIH CounterACT translational portfolio has supported an extramural research programs consisting of three different mechanisms that funded Centers of Research Excellence (U54), identification and optimization of lead MCMs (U01), and exploratory research projects (R21) that aligned with the priorities of BARDA/HHS- and DHS-recognized threat agents. The NIEHS-led translational research pulmonary portfolio has been highly successful overseeing the transition of three candidate MCMs from the CCRP to BARDA for advanced development. For more information, please see [NIEHS CounterACT](#).

### Research Goals and Scope

A recognized critical need of the CCRP chemical MCM discovery and early development initiative is access to facilities with inhalational capabilities that can expose animal models to highly toxic chemicals (including simulating real-world exposure scenarios) and equipped with appropriate strategies for protection and control. There are limited number of facilities capable of inhalational studies mimicking 'real world' exposures for the high threat chemicals of interest to CCRP.

To alleviate this issue and increase access, the major goal of this concept is to support the development of dedicated Inhalational Exposure Core facility(ies) to support the research needs of the CCRP. This Core facility may work with current CCRP-funded investigators to develop standardized protocols to expose diverse animal models to toxic agents of interest to the program. The Exposure Resource and Coordination Core will have three components - (1) Administrative Core, (2) Research Core that develops and standardizes inhalation exposure protocols as well as supports biological sample collection, storage, and transport, and (3) Coordination Core that manages exposures for current and future CounterACT grantees.

The overall goal of this initiative will be to establish a network of exposure resource and coordination cores that will serve as national infrastructures coordinating the discovery and early-stage development of candidate MCMs across the CCRP-supported extramural fundamental and translational research grant and cooperative programs.

### Mechanism and Justification

This joint NIEHS-NIAID FOA will support establishment of dedicated Inhalational Exposure and Coordination Cores to support the overall CCRP initiative. It will support the most critical needs of the program by providing exposure Core resources to study fundamental, systemic mechanisms of toxicity of diverse CoC and coordinate collaborative research efforts across the CCRP. This FOA will utilize the U24 mechanism. This FOA will be co-funded by NIAID (with oversight by the CCRP) and will address the CCRP's mission to advance fundamental chemical toxicology research to inform MCM developments - [doi: 10.1002/ddr.21707](https://doi.org/10.1002/ddr.21707).

This solicitation will provide resources to stimulate research on a diverse list of CoC with potential to develop suitable animal models to gain mechanistic understanding of acute pathophysiology, and assay development for MCM target identification. Anticipated research efforts derived from the Exposure

Cores have the potential to expand the toxicological and pathobiological research database of diverse CoC chemicals. It can position the overall CCRP efforts to promote validation and optimization within the medical countermeasures pipeline for advanced development goals of PHEMCE.

In addition, this program will support NIH Strategic Plan Objective #1.3 Meeting Emerging Public Health Needs, and the NIEHS 2018-2023 Strategic Plan Themes #1.1 Basic Biological Research and #1.6 Predictive Toxicology