

Concept Clearance

Branch: ERTB

Council Period: 202101

Concept Title: Chemical Threat Agents-induced Acute Pulmonary and Ocular Pathophysiological Mechanisms

Introduction

The events of September 11, 2001 exposed the vulnerability of the United States to acts of terrorism that could employ unconventional weapons and tactics, such as chemical, biological, radiological, and nuclear (CBRN) agents, against the civilian population. To prepare the country to handle any such potential high consequence public health emergency scenarios, the Department of Health and Human Services (HHS) formed the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) to provide oversight and coordinate medical countermeasure (MCM)-related efforts among federal agencies. The HHS 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 health effects posed by 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 against terrorist threats of 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 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 through the U.S. Department of Homeland Security's Chemical Terrorism Risk Assessment (CTRA) program, which has identified almost 200 chemicals as public health threats to date.

The CCRP developed a robust research infrastructure consisting of 1) A translational research-based extramural grant/cooperative agreement program called "CounterACT" as a Trans-NIH initiative to leverage the scientific expertise across the ICs. 2) Interagency agreements with the Department of Defense's United States Army Medical Research Institute of Chemical Defense (DOD USAMRICD), 3) Research contract resources, such as a preclinical development facility (CPDF); 4) Interagency agreement with HHS Biomedical Advanced Research and Development Authority (BARDA) to coordinate further development of promising products towards FDA licensure and procurement for the Strategic National Stockpile.

Currently, the CounterACT program supports research through four different PARs that fund Centers of Research Excellence (U54), identification and optimization of lead MCMs (U01) that align with the priorities of BARDA/HHS recognized threat agents within CTRA including an exploratory R21 program. Utilizing these existing efforts to date, the pulmonary threats program has been highly successful, and three candidate MCMs (identified for chlorine and sulfur mustard) from the NIEHS-led CounterACT portfolio have already transitioned from the NIH to BARDA for advanced development. Similarly, the ocular threats program has resulted in several funded projects and progress in developing animal models of vesicant exposure especially sulfur mustard.

However, based on the number of CTRA threat agents with potential to cause acute lung and ocular co-injuries and co-morbidities, what we have addressed to date is very limited. For example, BARDA priority currently only includes four such pulmonary and ocular threats, specifically chlorine, phosgene, sulfur mustard and Lewisite, whereas the CTRA includes many more such chemicals of interest where we do not have a clear understanding on physiological mechanisms involved in acute injury and pathogenicity. Some of these understudied CTRA chemicals are produced and transported for diverse industrial and agricultural uses thus making them potential high consequence public health threats. As such, to position our national health

preparedness in the event of mass casualty exposure to these pulmonary and ocular threat agents, it is critical that we have a broader fundamental understanding of the mode of toxicity of these understudied chemicals to inform the development of MCMs with broader applicability across the entire threat spectrum including the HHS-identified higher priority threats.

Research Goals and Scope

Almost a third of the ~200 chemicals on the CTRA list are recognized as pulmonary threat agents and to date the CCRP has supported research on a dozen or so of these chemicals. Some of these chemicals were prioritized by HHS because of their known use as chemical warfare agents in the past and as recently as the Syrian war, such as sulfur mustard, chlorine, and phosgene. Many of these chemicals also induce ocular effects. For the majority of the remaining potential pulmonary threat agents, (for example, ammonia, ethylene oxide, phosphorus trichloride, phosphine, boron trichloride, etc.), what we know is basic toxicology such as LD50 using animal models and in some rare cases for humans.

The major goals of this concept are to support development of a discovery pipeline for understudied chemical threat agents, characterization of fundamental molecular, cellular and physiological pathways involved in acute toxicity by a combination of *in vitro* and *in vivo* approaches that develop of reliable and translatable animal models. These inquiries will provide initial proof of principle biochemical, molecular toxicology and pathological mechanisms as well as identify of potential biomarkers of exposures for their eventual translation to humans. These discoveries will eventually advance to a strategic and focused identification of MCM candidates that will be effective across pulmonary threats.

Given the overlap of the effects of chemicals of interest supported by this program, this FOA is a joint effort in collaboration with the National Eye Institute (NEI) and the NIAID.

Mechanism and Justification

This joint FOA, in collaboration with NEI and NIAID, will solicit research to understand the fundamental mechanisms of pulmonary and ocular toxicity of diverse understudied toxic chemicals in the CTRA list. This FOA will utilize the R01 mechanism. This FOA was developed specifically at the request of the NIAID CCRP and awards will be co-funded by the NIAID under the oversight of the CCRP. The FOA will address the CCRP's mission to advance fundamental chemical toxicology research to inform MCM developments – see DOI: [10.1021/acs.chemrestox.0c00086](https://doi.org/10.1021/acs.chemrestox.0c00086).

This solicitation will stimulate research on understudied toxic chemical agents of CTRA with potential to induce pulmonary and ocular toxicity to gain understanding of acute pathophysiological mechanisms. The proof of principle efforts derived from these research investigations will have potential translational value for identification and optimization of the countermeasures pipeline and advanced development as needed. The immediate outcome of these efforts will be an understanding of acute pathophysiology of CTRA chemicals pulmonary and ocular effects. In addition, this program will also support the NIH strategic plan goal #1.1 Fundamental Science; 4.3 Advance basic science knowledge and conduct applied prevention and treatment research to improve health; as well as the NIEHS 2018-2023 Strategic Plan Theme 1.1 Basic Biological Research.