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Supporting Fundamental Chemical Toxicology Research to Inform Medical Countermeasure Developments - The National Institutes of Health Chemical Countermeasures Research Program (NIH CCRP)

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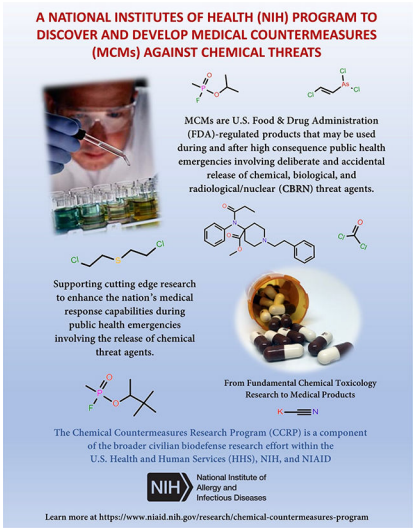
Abstract

High consequence chemical emergency is a major public health concern. In the United States, the National Institute of Allergy and Infectious Diseases within the National Institutes of Health (NIAID/NIH) pioneers discovery and early development of critical medical countermeasures against chemical threats.

Graphical Abstract



Keywords

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Disclosure statement

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The events of September 11, 2001 and the subsequent anthrax mailings in October 2001 exposed the vulnerability of the United States (U.S.) to unconventional terrorism threats. Chemical, biological, radiological, and nuclear (CBRN) agents, traditionally viewed as threats to the military, rapidly became prominent dangers to public health security. Consequently, the U.S. government implemented a national strategy to develop medical countermeasures (MCMs) and plans to support civilian health preparedness and disaster response to CBRN-based emergencies. Civilian-focused biodefense MCMs research and development programs were subsequently established across the federal government. The civilian-led programs largely complemented similar MCM development efforts already in place at Department of Defense (DoD) laboratories where the focus is to protect active duty military populations. Nonetheless, chief among these civilian biodefense MCM programs is that led by the National Institute of Allergy and Infectious Diseases (NIAID) within the National Institutes of Health (NIH). NIAID coordinates and/or leads the research and early development of MCMs across the NIH Institutes and Centers and includes biodefense programs directed against emerging infectious diseases and pandemic influenza, radiation exposure, and chemical threats [1].

In the almost two decades since 2001, the public health and biosecurity spectrums have evolved from focusing only on intentional (terrorism-based) release of CBRN agents to also include inadvertent exposure resulting from industrial accidents and/or natural disasters as well. To address the increasing potential of both deliberate and accidental public health CBRN emergencies, the U.S. Department of Health and Human Services (HHS) established the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) in 2006 to meet the public health emergency needs of the entire civilian population. As such, the PHEMCE must address the needs of both the general population and those that may require unique medical attention, such as children, pregnant women, older adults, those with pre-existing health conditions, as well as first responders, health care personnel, and other critical infrastructure personnel [2].

Under the leadership of the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR), the PHEMCE takes a whole-of-community approach to advance the Nation’s preparedness and medical response options entailing planning, preparing, response, and recovery efforts during and after CBRN events [2]. To execute the various components of the whole-of-community approach, PHEMCE coordinates a federal government-wide “end-to-end” agenda of threat assessments, requirements generation, research, product development, acquisition, storage, maintenance, deployment, and guidance for MCM utilization [3]. As such, interagency partners, including the NIH, Biomedical Advanced Research and Development Authority (BARDA), the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the DoD, the Department of Veterans Affairs (VA), the Department of Homeland Security (DHS), and the U.S. Department of Agriculture (USDA), collaborate closely with each other to maximize national preparedness to respond to CBRN threats.

Owing to the large numbers of manufacturing sites, general commercial availability and utility, and extensive transportation of highly toxic chemicals (HTCs) across the nation, the probability of an unintentional, mass casualty public health event involving this class of

threat agents is high. Compounding the high potential of exposure to HTCs are the devastating health effects that have been observed both in and outside of military conflicts after exposure in recent history and the general lack of effective MCMs. Consequently, the DHS has since identified close to two hundred HTC compounds as credible public health and safety threats [4]. These HTCs are broadly categorized as:

- Pulmonary, irritant, and corrosive agents that target the respiratory tract and may induce edema and/or other long-term pathologies (e.g., chlorine and phosgene)
- Pharmaceutical-based agents, such as incapacitating compounds (e.g., synthetic opioids)
- Vesicating agents that may cause dermal and/or ocular pathologies (e.g., sulfur mustard and Lewisite)
- Cellular respiration inhibitors, such as blood, hemolytic, and metabolic agents (e.g., cyanide)
- Cholinergic, convulsant, encephalopathic, and sympathomimetic/stimulant agents that target the nervous system and/or induce neuropathology (e.g., organophosphate nerve agents and pesticides)

On behalf of HHS, the NIAID/NIH established the Chemical Countermeasures Research Program (CCRP) in 2006 to lead the civilian efforts to discover new and improved MCMs against HTCs. The overall aims of the CCRP are to expand the fundamental knowledge of HTC toxicology and to identify promising MCMs that can be transitioned to an advanced biomedical product developer, specifically HHS BARDA, for further development, studies to support regulatory approval, and potential procurement for the Strategic National Stockpile (SNS). The ideal MCMs must be rapidly effective in treating the acute post-exposure health effects of chemical threats and easy to administer in a mass-casualty situation. As such, the CCRP research priority areas include, but are not limited to:

- Improving basic/fundamental biological knowledge, such as mechanisms of acute chemical toxicity, biological markers of exposure, and relevant physiological targets that may be exploited for medical interventions
- Demonstrating appropriate *in vitro* biological activity, such as target engagement to counteract the effects of HTCs
- Developing novel screening assays to identify candidate MCMs
- Developing natural history models of the disease state/injuries induced by HTCs in human-relevant animal models to fully understand the resulting pathophysiology

Recognizing the diversity of HTCs that have been identified as public threats by the DHS, the CCRP implemented and oversees a highly collaborative NIH-wide extramural MCM discovery and early development program that includes program officials from the NIAID, National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Environmental Health Sciences (NIEHS), National Eye Institute (NEI), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), *Eunice Kennedy Shriver*

National Institute of Child Health and Human Development (NICHD), and National Institute of Drug Abuse (NIDA). This trans-NIH partnership allows the CCRP to capitalize on relevant subject matter expertise in pulmonary, dermal, ocular, and neurological research that already exists at the respective NIH institutes and their extramural communities. Similarly, the CCRP also utilizes both inter- and intra-agency agreement programs to collaborate with various DoD and HHS partners to leverage capabilities and expertise available among PHEMCE partners and to offer resources to the research communities, when appropriate. These interagency resources include not only DoD chemical defense expertise but also preclinical research and development services that could be utilized in fundamental studies to uncover potential biological targets or markers of chemically induced injuries as well as identify MCM candidates [5]. These resources include:

- The **CounterACT Efficacy Research Facility (CERF)**, established in 2010, conducts studies in support of NIH-funded projects, as well as those initiated by the NIH. The facility also increases the capacity for conducting studies with chemical agents that require special surety facilities. The facility has a long-standing partnership with the DoD.
- The **CounterACT Preclinical Development Facility (CPDF)**, established in 2006, enables investigators to conduct preclinical studies needed for drug discovery and development and, ultimately, FDA approval.
- The **CounterACT Neurotherapeutics Screening (CNS)** program, established in 2015, enables investigators to submit compounds to be evaluated for both anti-convulsive and neuroprotective properties against organophosphate-induced seizures.
- The **CounterACT Ocular Therapeutics Screening (COTS)** program, established in 2019, conducts pilot studies to evaluate the efficacy of investigational MCMs against the acute and/or chronic ocular injuries due to sulfur mustard exposure.

To further engage and support the extramural scientific communities at large, the CCRP provides several targeted NIH grant and cooperative agreement funding opportunities (Table 1). The grants, Centers, and cooperative agreements awarded through these funding opportunities are collectively referred to as the “Countermeasures Against Chemical Threats (CounterACT)” program and are administered by NINDS under the oversight of NIAID. Depending on the proposed research topics, “CounterACT” program awards are managed directly by the various trans-NIH CCRP program officials. For example, projects seeking to uncover mechanisms of inhalation chlorine toxicity or to validate potential targets or MCM candidates to treat chemically induced pulmonary injuries are managed by NIEHS/NIH. Similarly, “CounterACT” grants focused on understanding and mitigating ocular chemical toxicity such as corneal neovascularization and fibrosis, are administered by NEI/NIH. In this way, “CounterACT” projects are under the oversight and guidance of the most scientifically relevant and knowledgeable NIH expert(s).

Developing novel medical products for high consequence public health and security emergencies is a daunting challenge made even more difficult when the number of chemicals

identified as threats is high and little may be known about their mechanisms of toxicity. As such, the CCRP recognizes the utmost importance of maintaining a diverse scientific portfolio. This scientific portfolio must be built on a firm foundation of both basic and translational research. Fundamental knowledge of chemical toxicology obtained through basic research is essential in making progress towards the discovery of potential medical interventions to mitigate toxicities. Promisingly, CCRP-supported scientists have already discovered novel therapeutic approaches through fundamental chemical toxicology research. For example, CCRP-supported basic research developed several human-relevant models of sulfur mustard-induced pulmonary toxicities which have led to a better understanding of the pathophysiological responses after exposure [6]. These advancements in inhalation sulfur mustard toxicology knowledge subsequently led to the breakthrough discovery of 'off-the-shelf' fibrinolytics as potential MCMs [7]. Similarly, using real-time positron emission tomography imaging, another CCRP-supported project successfully interrogated the *in vivo* toxicokinetic/pharmacokinetic and toxicodynamic/pharmacodynamic properties of various toxic organophosphorus (OP) compounds and their interactions with acetylcholinesterase (AChE) and AChE oxime reactivators within the central nervous system [8]. It is possible that this advancement in understanding the interplay among the HTC insult (OP), physiological target (AChE), and antidote (oxime reactivator) could inform the future design of more effective MCMs. In any event, these are just two examples from the CCRP portfolio where basic research discoveries have led (or will hopefully lead) to candidate MCMs. Other CCRP-supported early stage research projects have similarly identified first-in-class new molecular entities as potential MCMs in addition to potentially new indications for already FDA-approved drugs [5]. Further highlighting these successes are advanced product development contracts recently awarded by HHS BARDA to further develop some of those candidate MCMs (Table 2).

While some successes have been achieved to date, much more still needs to be accomplished considering the ever-increasing threat of terrorism, warfare, and storage/transportation accidents involving civilians and HTCs. As such, the CCRP has developed a collection of research funding opportunities, preclinical research and development services, and expertise available to prospective partners interested in furthering the current fundamental understanding of acute and long-term chemical toxicology that could inform the discovery and development of MCMs to prevent lethality and/or treat the injuries after a high consequence chemical emergency. In order to sustain a pipeline of promising candidate MCMs against HTCs, the CCRP is committed to support basic chemical research in toxicology that informs the state-of-the-field that may one day drive biomedical advances and enhance national health preparedness and public safety.

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Table 1.

CCRP Extramural Research Funding Opportunities Through the CounterACT Program

Funding Opportunity Announcement (FOA) Number	Title	General Scope of Research
PAR-18–657 (U54)	Research Centers of Excellence (Clinical Trial Optional)	Target and candidate identification and characterization, through candidate optimization and demonstration of in vivo efficacy consistent with the product's intended use in humans
PAR-18–721 (R21)	Exploratory/Developmental Projects (Clinical Trial Not Allowed)	Basic toxicological research on the chemical threat for the purpose of target and therapeutic hit identification, hit validation, lead optimization, and demonstration of in vivo ADME/Tox and efficacy
PAR-19–039 (U01)	Identification of Therapeutic Lead Compounds (Clinical Trial Not Allowed)	Confirmation of molecular targets for therapeutic development, demonstration of in vitro activity of candidate therapeutics, preliminary in vivo proof-of-concept efficacy data, preliminary adsorption, distribution, metabolism, excretion, and toxicity (ADME/Tox) evaluations and pharmacokinetics/pharmacodynamics (PK/PD) data
PAR-19–040 (U01)	Optimization of Therapeutic Lead Compounds (Clinical Trial Optional)	Development of appropriate human-relevant animal models and generation of in vivo efficacy data consistent with the intended use of the product in humans. It also includes bioanalytical assay development and validation, laboratory-scale and scalable manufacturing of the product, and non- GLP toxicity and pharmacology studies
NOT-NS-20–030 (Administrative Supplements through PA-18–591)	Notice of Special Interest (NOSI): Administrative Supplements to Promote and Expand into the Research and Development of Medical Countermeasures Against Chemical Threats	Consistent with PAR-18–721, PAR-19–030, and PAR-19–040

Table 2.

Notable Products Transitioned from the NIH to BARDA for Advanced Development[5]

Drug	Putative Mechanism(s) of Action	Awardee	Proposed MCM Indication
Galantamine	Reversible Acetylcholinesterase (AChE) inhibitor and potentiating ligand of nicotinic Acetylcholine receptors (nAChRs)	CounterVail Corporation	Nerve agent-induced seizures and neuronal degeneration
Midazolam (Seizalam®)	Allosteric potentiation of synaptic Gamma aminobutyric acid (GABA)-A receptors	Meridian Medical Technologies, a Pfizer subsidiary	Status epilepticus in adults (including seizure induced by nerve agents)
Alteplase (Activase®)	Fibrinolytic agent	Genentech	Sulfur mustard-induced pulmonary injuries
R-107	Bifunctional nitric oxide donor and redox degradation catalyst	Radikal Therapeutics, Inc.	Chlorine (Cl_2)-induced inhalational lung injury (CILI)
GSK2798745	Transient Receptor Potential cation channel V4 (TRPV4) Antagonist	GSK	Acute Respiratory Distress Syndrome (ARDS) due to chlorine gas inhalation
Tezampanel	Glutamate Kainate Receptors (GluR5) Antagonist	Proniras Corporation	Treatment of benzodiazepine-refractory seizures induced by nerve agents