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Considerations in developing medical countermeasures against chemical ocular toxicity

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Abstract

The Chemical Countermeasures Research Program (CCRP) was established in 2006 by the National Institute of Allergy and Infectious Diseases (NIAID/NIH) on behalf of the National Institutes of Health Office of the Director (NIH OD). It is a trans-NIH initiative to expedite the discovery and early development of medical countermeasures (MCMs) that can reduce mortality and serious morbidity during and after large consequence public health emergency involving the deliberate or accidental large-scale release of highly toxic chemicals (HTCs).

Keywords

Ocular toxicity; Medical countermeasures; Chemical threats; CCRP; Vesicants

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Disclosure statement

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Declaration of Competing Interest

The authors report no declarations of interest.

HTCs of interest to the CCRP are those compounds that have been specifically identified by the United States Department of Homeland Security (U.S. DHS) as national security threats to public health (Good et al., 2013). These HTCs of interest are broadly categorized as (U.S. Department of Health and Human Services and National Institutes of Health, 2018):

- Vesicating agents that may cause ocular and/or dermal pathologies (e.g., sulfur mustard, nitrogen mustard, and Lewisite)
- Pulmonary, irritant, and corrosive agents that target the respiratory system (e.g., chlorine and phosgene)
- Pharmaceutical-based agents and incapacitating compounds (e.g., synthetic opioids)
- 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 (e.g., organophosphate nerve agents)

The CCRP complements the emerging/re-emerging infectious diseases and pandemic influenza as well as the radiological and nuclear threats MCM research and early development programs at NIAID to comprise the broader NIH chemical, biological, radiological, and nuclear agents (CBRN) civilian biodefense research portfolio. In particular, CCRP research priorities include basic research to expand fundamental knowledge of HTC toxicology, such as understanding molecular and systemic mechanisms of toxicity, and translational research to identify and validate potential targets for therapeutic intervention to develop candidate MCMs. Promising MCM products may then be transitioned from the NIH to an advanced biomedical product developer, specifically the Biomedical Advanced Research and Development Authority within the Department of Health and Human Services (HHS BARDA), for further development activities, e.g., Good practice (GxP) quality studies to support FDA 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 HTCs and easy to administer in a mass casualty situation (Office of the Assistant Secretary for Preparedness and Response and Department of Health and Human Services, 2007).

Often overlooked, the eyes are usually the first and most frequent route of HTC exposure thus making them especially vulnerable to chemically induced injuries. While chemical toxicity to the eyes is typically non-fatal, injury to one of the most biologically complex and important sensory organs can result in immediate and/or chronic incapacitation due to vision loss and overall changes in the quality of life; very serious morbidities. With little to no effective therapeutic options currently available, developing effective MCMs to treat ocular injuries induced by HTCs is a major focus of the CCRP. The optimal MCM must ameliorate the ocular insult enabling rapid return of normal visual function and performance. Furthermore, while counteracting the acute effects of ocular chemical injury is critical, mitigating the chronic effects that often occur is equally vital.

Therapeutic drug or biologic product development is often a long and difficult process that typically begins with a clear understanding of the molecular mechanisms that underlie disease progression, something that is largely unknown for ocular toxicity induced by HTC's such as the vesicating chemicals sulfur mustard, nitrogen mustard, and Lewisite as well as some toxic industrial chemicals and materials of interest to the CCRP. Consequently, the CCRP is keenly interested in improving upon this fundamental biological knowledge gap that includes exploring possible mechanisms of acute chemical toxicity, biological markers of exposure, and relevant physiological targets of ocular toxicity to unravel the progression of the disease state after the insult. It is hoped that an in-depth understanding of the "natural history" of the toxic injury will be predictive of the outcomes in humans and drive the discovery and early development of candidate MCMs.

Acutely, vesicating chemicals can cause moderate to debilitating injuries and pain to the eyes. Symptoms of vesicant-induced injuries include photophobia, uveitis, corneal lesions, edema, ulceration, and neovascularization (Goswami et al., 2016). Chronic or delayed onset toxicity includes limbal stem cell deficiency, irreversible, idiopathic keratitis with associated secondary pathologies. These are collectively referred to as mustard gas keratopathy (MGK), and may lead to loss of vision (McNutt et al., 2012; Dachir et al., 2017). Therefore, the immediate and long-term health burden associated with a mass casualty public emergency involving these chemicals are highly consequential. Under the leadership of the National Eye Institute (NEI/NIH), the CCRP ocular portfolio has supported (and continues to support) a number of promising projects that have developed various *in vivo* and *ex vivo* models of vesicant toxicity (U.S. Department of Health and Human Services and National Institutes of Health, 2018; Araj et al., 2020). These ocular models include Lewisite, nitrogen mustard, as well as sulfur mustard induced acute and long-term eye injury and their utilization have subsequently led to the discovery of several very early but promising MCM candidates, such as an engineered human fibroblast growth factor-1 derivative (TTHX1114) (Eveleth et al., 2018), ADAM17 inhibitors (DeSantis-Rodrigues et al., 2016), silibinin, doxycycline, and dexamethasone (U.S. Department of Health and Human Services and National Institutes of Health, 2018; Tewari-Singh et al., 2012).

Even with these preliminary successes, much more remains to be done. For example, most of the CCRP-supported ocular toxicity MCM discovery efforts to date have primarily focused on addressing injuries only to the ocular surface, specifically the cornea (Araj et al., 2020). However, as one of the most complex and intricate organs in the body, it is imperative that other anatomical features within the anterior and posterior segments not to mention the innervation of the eyes must also be addressed and understood in the context of possible ocular toxicity pathogenesis and resulting visual impairment. Fortunately, the ophthalmic research community is ripe with expertise in various aspects and targets of mechanical and nonspecific chemical eye injury as well as acquired and degenerative ocular diseases and disorders that could potentially be recruited to address the currently unmet biosecurity and health preparedness need for effective MCMs. In fact, this was a stated goal of a recent trans-agency scientific meeting convened in February 2020 by the NIH in collaboration with the U.S. Army Medical Research Institute of Chemical Defense of the Department of Defense (Yeung et al., 2020a). Briefly, the meeting offered a venue for basic and applied scientists from academic, industry, and government laboratories with expertise in corneal

and retinal injuries, such as alkali burn injuries, ocular complications associated with diabetes, and limbal stem cell deficiency, to identify potentially common pathologies and models that could be utilized to inform therapeutics and MCM development.

Recognizing the pressing need for MCMs against HTC, the CCRP employs a wide array of mechanisms and resources to fund and support research institutions and sister federal agencies to address the stated research priorities. These mechanisms and resources include funding opportunities, product development support services, as well as NIH and government-wide expertise to foster a vibrant chemical MCM research and development community. More specifically, the CCRP leverages upon the vast and varied subject matter expertise that already exists across the NIH by partnering with specific Institutes and Centers (ICs) to administer a portfolio of extramural research programs called “Countermeasures Against Chemical Threats (CounterACT),” which consist of various R21 grants, U01 cooperative agreements and U54 Centers of Excellence. CCRP IC partners include the NEI/NIH, which as described earlier, oversees the ocular toxicity portfolio, the National Institute of Environmental Health Sciences (NIEHS/NIH) for pulmonary toxicity research, the Eunice Kennedy Shriver National Institute of Child Health and Development (NICHD/NIH) for projects focused on protecting pregnant and pediatric populations against HTC toxicity, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS/NIH) for dermal injury projects, the National Institute of Drug Abuse (NIDA/NIH) for efforts to develop MCMs against pharmaceutical-based agents (Yeung et al., 2020b), and the National Institute of Neurological Disorders and Stroke (NINDS/NIH) for neurological injury efforts (Jett et al., 2020). This NIH-wide approach ensures CCRP-supported efforts are guided by the most relevant and knowledgeable expertise.

Lastly, a unique CCRP resource that is available to the research community is the CounterACT Ocular Therapeutics Screening (COTS) program. The COTS program offers an in vivo screening model to accelerate the discovery of novel MCMs to treat sulfur mustard-induced ocular injuries. Studies are conducted through a NIAID/NIH-supported research facility with the primary purpose of providing investigators with pre-application, pilot proof-of-principle efficacy data in support of potential follow-on research and development efforts. In general, the COTS program is available to all investigators with promising MCMs responsive to the mission of the CCRP. NIH will accept applications from individual principal investigators (PIs) from academic institutions, government laboratories, and companies. If accepted after a competitive review, studies are executed and completed at no cost to the applicant. If interested, prospective applicants should consult with the authors (H.A. and D.T.Y.) of this editorial for more information and/or to determine eligibility. Other elements of the CCRP, such as preclinical product development support services and specific NIH funding opportunity announcements, are described in detail elsewhere (Yeung et al., 2020c, d).

In conclusion, corneal toxicity, ocular surface toxicity, and anterior segment toxicity represent a progression of escalating challenges that are ripe for discovery and advancement. Accessibility of the cornea, which makes it particularly vulnerable to injury, also makes it particularly amenable to scientific investigation. The same applies to the ocular surface which more broadly includes the conjunctiva and the lacrimal and meibomian glands. This

accessibility, albeit to a lesser degree, also applies to the other anterior segment structures of the eye like the lens, iris and ciliary body. The eye represents a powerful model for understanding chemical injury in general, and vesicant injury in particular. For example, a hallmark of many pathologies is inflammation. Ocular chemical injury is no exception. Following vesicant injury, conjunctivitis, corneal edema, ulceration, scarring, wounding, and corneal neovascularization are typically seen. Consequently, this led to the testing of anti-inflammatory (e.g., corticosteroid) and anti-angiogenesis (e.g., anti-VEGF) agents to counteract such sequelae. While good efficacy was observed – these benefits unfortunately were not permanent, and the pathology tended to rebound in the long term. This raises the need to potentially move beyond monotherapy and consider combinations of counteract measures. And it is not just in modulating or attenuating the inflammatory or vascular response. Oxidative damage and fibrosis are also known outcomes in chemical injury. This in turn opens the possibility of including antioxidants and anti-fibrotic candidates in the treatment regimen. In closing, the tension between splitting and lumping in science is enduring (Berg, 2018). Reductionist approaches have clearly led to major breakthroughs in multiple areas of eye biology and pathobiology. However, to develop broadly effective MCMs to enhance civilian medical response capabilities against HTC ocular toxicity, the time is opportune to restore some balance and do a bit less splitting and a bit more lumping.

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