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Abstracts of Presentations from the 2020 Trans-Agency Scientific Meeting on Developing Medical Countermeasures to Treat the Acute and Chronic Effects of Ocular Chemical Toxicity, 25–26 February, Bethesda, Maryland

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1. Introduction

In response to the high consequence terrorism events of 2001, the United States (U.S.) Government tasked several agencies with the critical mission to research and develop medical countermeasures (MCMs) that can save lives and/or treat injuries resulting from exposure to chemical, biological, and radiological nuclear (CBRN) threat agents during a mass casualty public health emergency. Included among these organizations is the National Institutes of Health (NIH), which has the primary responsibility for the discovery and early development of promising therapeutic approaches. More specifically, the National Institute of Allergy and Infectious Diseases (NIAID) was assigned to coordinate, implement, and lead this biodefense initiative across the various NIH Institutes and Centers. The overall goal of the program is to integrate cutting-edge research with the latest technological advances in science and medicine for a more rapid and effective national medical response during and after large scale public health CBRN emergencies (Office of the Assistant Secretary for Preparedness and Response; Department of Health and Human Services, 2007).

The public health risk posed specifically by chemical agents is perhaps more challenging than that of biological and radiological nuclear threats. Unlike exposures to infectious

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Disclosure statement

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diseases and radiological and nuclear threats, where a latent period may allow for prophylactic and/or post-exposure pre-symptomatic treatments to be instituted, injuries from chemical exposures can occur rapidly with immediate casualties and fatalities. Additionally, many highly toxic chemical (HTC) agents may be easily procured or manufactured undetected. As such, the probability of an unintentional, mass casualty public health event involving chemical threat agents is high (Yeung et al., 2020). Consequently, the U.S. Department of Homeland Security has identified close to two hundred HTC compounds as credible public health and safety threats. Directly relevant to the aim of this trans-agency meeting are those HTCs broadly categorized as “vesicating agents” or “vesicants.” This category of HTCs includes sulfur mustard, nitrogen mustard, Lewisite, phosgene oxime, and various arsenicals, which can cause moderate to debilitating short-and long-term injuries and pain to the mucous membranes, skin, and eyes. While exposure to vesicants is not often lethal, the U.S. government is nonetheless extremely interested in developing MCMs effective against their chronic toxic effects, particularly those affecting the eyes (U.S. Department of Health and Human Services; National Institutes of Health, 2018).

The development of MCMs and therapeutics rely critically on the availability of well-characterized animal models with defined pathophysiology that allows for effective bridging to humans. There are significant gaps in the understanding of the disease processes and progression after vesicant exposure to the eyes, as well as the optimum approaches to develop MCMs to mitigate the resultant ocular injury. To address this, the Chemical Countermeasures Research Program (CCRP) at the NIAID/NIH convened this trans-agency meeting to examine the current state-of-the-field and available well-characterized experimental models of acute and chronic corneal injuries and recovery. It is hoped that the biological/physiological responses of the eyes to chemical toxicity, particularly those induced by vesicating chemicals, may be similar to those observed from other ocular insults and resultant injuries. As such, we sought to bring together a diverse cadre of 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, among others.

Given the high costs associated with bringing promising new molecular entities from the bench through advanced product development activities, and ultimately, to regulatory approval - the ideal candidate MCM may be one that is already U.S. FDA-approved for a commercial clinical indication that can be repurposed for vesicant-induced ocular injuries. Repurposing product(s) for which there already exists relevant safety, efficacy, and other important information concerning their use in humans would reduce not only the cost but time necessary to bring a new MCM onto the market. As such, the meeting also included experts knowledgeable in therapeutic development for commercial/clinical ocular pathology indications, such as corneal neovascularization, edema, fibrosis, and endothelial cell dystrophy regardless of etiology.

This trans-agency meeting was convened to: 1) Further our understanding of pathologies and models available for studying toxic ocular injuries and how they could be utilized in the research and development of therapeutics and MCMs, 2) Provide a forum for networking and collaborative partnerships among the experts in attendance, and 3) Familiarize

researchers to NIH resources available to support ocular chemical injury research. Consequently, the meeting was designed with the following keynote and five session focuses:

- **Keynote Presentation**: Ocular Toxicity Testing and the Development of Medical Countermeasures (James Jester, PhD - University of California, Irvine)
- Session 1: Acute and Chronic Responses to Corneal Toxicity
    1. Regulatory Roles for Collagen XII in Re-establishment of Stromal Structure and Function After Injury (Edgar Espana, MD - University of South Florida)
    2. Delayed Development of Limbal Stem Cell Deficiency Following Sulfur Mustard Exposure - Pathogenesis and Potential Therapy in the Mouse, Rat and Rabbit Models (Tamar Kadar, PhD - Israel Institute for Biological Research)
    3. Topically Applied Neurokinin-1 Receptor Antagonists to Treat Ocular Surface Inflammation (Giulio Ferrari, MD, PhD - San Raffaele Hospital)
    4. How Mustard Gas Broke the Blind Watchmaker (Patrick McNutt, PhD - U.S. Army Medical Research Institute of Chemical Defense)
- Session 2: Mechanistic Basis of Corneal Pathophysiologies and Wound Healing
    1. Corneal Epithelial Exosomes in Transmitting Pathogenic Factors Causing Neuropathy and in Treating Hyperglycemia-Induced Delay of Epithelial Wound Healing and Sensory Nerve Regeneration (Fu-Shin Yu, PhD - Wayne State University School of Medicine)
    2. Dynasore and Analogues Protect the Ocular Surface against Damaging Oxidative Stress (Elizabeth Fini, PhD - Tufts University School of Medicine)
    3. Novel Therapeutic Strategies for Sulfur Mustard-Induced Ocular Injury Using the Rabbit Model (Vered Horwitz, PhD - Israel Institute for Biological Research)
    4. Biomechanical Modulation Therapy: Stem Cell Therapy Without the Stem Cells for the Treatment of Severe Ocular Burns (Che Connon, PhD - Newcastle University)
- Session 3: Therapeutically Accessible Models of Corneal Toxic Injury
    1. Corneal Injuries of Different Origin: Predictive Performance of the 3D Human Corneal Epithelial Tissue Models (Yulia Kaluzhny, PhD - MatTek Corporation)
    2. Treatment of Corneal Infections Utilizing an Ocular Wound Chamber (Gina Griffith, PhD, CPT - U.S. Army 20th CBRNE)

3. The Beneficial Effects of Aflibercept (VEGF-Trap) in Treating the Late Sulfur Mustard-Induced Corneal Pathology in the Rabbit Model (Ariel Gore, PhD - Israel Institute for Biological Research)
4. The Novel Role of Kallistatin in Wound Healing and Diabetes (Dimitrios Karamichos, PhD - University of Oklahoma Health Sciences Center)
5. Development of Stem Cell-Based Therapies for Corneal Diseases (Sophie Deng, MD, PhD - University of California, Los Angeles)

- Session 4: Therapeutic Approaches to Mitigate Corneal Pathophysiologies
  1. Subconjunctival Nanoparticle as a Long-Lasting Therapy for Corneal Diseases (Qingguo Xu, PhD - Virginia Commonwealth University)
  2. INvV-102 Significantly Reduces Long Term Injury After Ocular Sulfur Mustard Exposure in Rabbits (Robert Shalwitz, MD - Invirsa, Inc)
  3. Early Interventions for Toxicant Ocular Injury May Need to be Toxicant-Specific (Albert Ruff, PhD - U.S. Army Medical Research Institute of Chemical Defense)
  4. A One-Two Punch to Corneal Fibrosis and Retinal Gliosis in Alkali Injury (Royce Mohan - University of Connecticut Health Center)
- Session 5: Current Research/Development Perspectives and Resources for Researchers
  1. 3D-Printed ABCB5-Positive Stem Cells for the Treatment of Corneal Blindness (Catherine Lee, PhD - Brigham & Women's Hospital)
  2. Bio-Electrical Signaling in Epithelial Biology and Corneal Wound Healing (Min Zhao, MD, PhD - University of California at Davis)
  3. Biological Variance in Corneal Stromal Wound Healing: A Hurdle to Translation and Tool for Discovery (Daniel Gibson, PhD - University of Florida)
  4. CALEC: New Frontier in the Treatment of Limbal Stem Cell Deficiency (Lynette Johns, OD - Schepens Eye Research Institute)
  5. Tried and True as Well as New Approaches to Drug Development (Christine Colvis, PhD - National Center for Advancing Translational Sciences [NCATS/NIH])

It is hoped that this report could be used to further support the intent of the meeting and help to guide and advance the development of MCMs against chemical toxicity to the eyes to enhance public health preparedness and national security.

Acknowledgements

On behalf of the meeting organizers, we want to thank all the presenters and attendees for their participation. We strived to recruit the participation of a diverse and dynamic group of presenters and subject matter experts spanning

both fundamental and translational research to highlight this critical R&D area of need. The selection of persons to present at the workshop was made by the meeting organizers from NIAID, NEI, and USAMRICD from among those with subject-matter expertise relevant to the purpose of the meeting.

Everyone's time and valuable contributions directly led to the overall success of the meeting. We hope that everyone found the meeting of value and the interactions that occurred throughout might lead to new collaborative partnerships and advance the field.

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