National Institutes of Health (NIH) Executive Meeting Summary: Developing Medical Countermeasures to Rescue Opioid-Induced Respiratory Depression (a Trans-Agency Scientific Meeting)—August 6/7, 2019

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Abstract

On August 6th, 2019, a two-day trans-agency scientific meeting was convened by the United States (U.S.) National Institute of Allergy and Infectious Diseases (NIAID/NIH) on the research and development of medical countermeasures (MCMs) and treatment strategies to mitigate synthetic opioid-induced toxicities. This trans-agency meeting was an initiative of the Chemical Countermeasures Research Program (CCRP) and organized by the NIAID in collaboration with the National Institute of Drug Abuse (NIDA), the Biomedical Advanced Research and Development Authority (BARDA), the Food and Drug Administration (FDA), and the Defense Threat Reduction Agency (DTRA). The CCRP is part of the larger NIH biodefense research program coordinated by NIAID, which also includes MCM research and development programs against biological, radiological, and nuclear threats. Its overarching goal is to integrate cutting-edge research and technological advances in science and medicine to enhance the nation's medical response capabilities during and after a public health emergency involving the deliberate or accidental release of toxic chemicals. The potential of a mass casualty public health event involving synthetic opioids is a rapidly growing concern. As such, the overall goals of this trans-agency meeting are to better understand opioid-induced toxicities and advance the development of MCMs to mitigate and reverse opioid-induced respiratory depression (OIRD) to prevent consequential mortality. The primary objectives of the meeting were (1) highlight the latest research on mechanisms of OIRD and related toxicities, animal models, diagnostics, delivery technologies, and emerging new treatment options to prevent lethality; (2) identify current knowledge gaps to advance medical countermeasure development; (3) hear from the U.S. FDA on regulatory considerations to support new technology and treatment approaches; and (4) provide a forum for networking and collaborative partnerships. To accomplish this, a diverse group of almost 200 US domestic and international subject matter experts spanning fundamental and translational research from academia, industry, and government came together in-person to share their collective expertise and experience in this important field. This report briefly summarizes the information presented throughout the meeting, which was also webcast live in its entirety to registered remote attendees.

Keywords Opioids · Medical countermeasures · Respiratory depression · NIAID

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Synthetic opioids such as fentanyl, carfentanil, and their congeners are currently of the utmost public health concern to the US government. This concern stems from multiple factors to include their extremely high potency, wide pharmaceutical and illicit availability, and the potential of large-scale intentional as well as accidental release that could result in mass poisonings and casualties. Consequently, these compounds are not only considered public health risks under the ongoing “opioid epidemic,” but also chemical threats by both civilian and military agencies. Despite the effectiveness of naloxone to

reverse opioid overdose, limitations such as its short circulatory half-life and mode of action necessitate an urgent need for novel therapeutic strategies that can more effectively treat and prevent opioid-induced toxicities including respiratory depression. As such, a trans-agency scientific meeting was sponsored and convened by the NIH, in collaboration with HHS and DOD agencies, to discuss the research priorities and state-of-knowledge concerning the mode of opioid-induced toxicities to better understand and uncover new therapeutic targets and medical countermeasure (MCM) approaches to explore.

Over two hundred domestic and international representatives from academia, industry, and government laboratories attended the meeting in-person or online and heard from forty-three experts in the field over the course of the two-day meeting. This report briefly summarizes each of the scientific presentations that occurred, which were divided among the below sessions (and corresponding sections within this summary):

- Keynote: Overview Perspective on Synthetic Opioids—Overdose/Chemical Terrorism Threats (Section 2)
- Session 1: Government Stakeholder Perspectives (Section 3)
- Session 2: Mechanistic Underpinnings of Opioid-Induced Respiratory Depression (Section 4)
- Session 3: Pharmacotherapeutic Rescue Strategies (Section 5)
- Session 4: Non-Pharmacotherapeutic Rescue Strategies (Section 6)
- Session 5: Drug Development Tools: Biomarkers & Animal Models (Section 7)
- Session 6: Delivery & Diagnostic Strategies (Section 8)
- Session 7: FDA Perspectives and Resources for Researchers (Section 9)

By the conclusion of the meeting, it was readily apparent that improved MCMs and therapeutic strategies are urgently needed to better prepare and protect the civilian and military populations against the toxic effects of synthetic opioids (described in the Opening Keynote; see Section 2). Fortunately, the groundwork for the research and development of novel MCMs against opioid-induced toxicities has already been laid by government stakeholders across the HHS and DOD. While the actual product characteristics desired may differ slightly across federal partners, e.g., BARDA and DTRA are primarily only interested in rapidly effective post-exposure MCMs that do not competitively antagonize the mu-opioid receptors, the various agencies and departments are collaborating closely with one another to harmonize the government's overall MCM development effort (see Section 3). The meeting successfully brought together an expansive group of fundamental and translational researchers who described potential therapeutic targets in the preBöttinger complex (PreBötC or PBC), the

post-inspiratory complex (PiCo), and Kölliker-Fuse (KF) nucleus for MCM development (see Section 4). This was followed by a series of talks highlighting various therapeutic strategies already in development by experts in the field. For example, pharmacotherapeutic approaches in development include intranasal nalmefene, Methocinnamox (MCAM), D-cysteine ethyl ester (D-CYSee), and serotonin-based agonists (see Section 5). Similarly, non-pharmacotherapeutic strategies that were presented included biologic-based approaches such as immunotherapies using opioid-specific antibodies, thyrotropin releasing hormone (TRH), biohybrid nanoparticles-encapsulated naloxone, cyclodextrins, and cucurbituril (CB)-based scrubber molecules (see Section 6). The therapeutics-focused sessions were immediately followed by presentations of development tools such as biomarkers and available animal models. The focus of those talks included (1) phenotypic neuron-in-a-dish platform to identify potential markers of neurotoxicity and MCM screening, (2) restructuring of the prefrontal cortex neurotransmitter network as indicators of opioid-induced toxicity, and (3) animal models currently in use by DOD researchers for MCM development, to include mice, ferrets, and nonhuman primates (see Section 7). Session 6 of the meeting encompassed both delivery (intranasal and a combined bolus and sustained/controlled release system) as well as diagnostic strategies (see Section 8). Speakers of the latter topic focused on diagnostic strategies utilizing either physiological responses, e.g., respiratory depression and cardiac activity, or electrochemical signatures of the opioid compounds to identify/treat potential victims. In the final scientific session of the meeting, the FDA presented on regulatory priorities and considerations critical for seeking approval of novel anti-opioid MCMs before elaborating on publicly available agency resources that developers could leverage to facilitate their MCM development efforts (Section 9).

The purpose of this trans-agency meeting was to better understand the potential mechanism(s) of opioid-induced toxicities and advance the development of novel therapeutic strategies and MCMs to prevent or reverse opioid-induced respiratory depression (OIRD) and consequential mortality. The therapeutic discovery and development process is a long and difficult journey. The process requires close collaborations amongst subject matter experts with diverse background ranging from initial target identification and validation all the way to regulatory and commercial expertise. As such, the NIH convened this trans-agency meeting not only to provide in-depth insights on the potential mechanistic underpinnings of OIRD, current knowledge gaps, new therapeutic strategies, existing drug development tools such as animal models and biomarkers, regulatory considerations, and practical tools of engagement with the U.S. FDA., but also a forum for networking and collaborative partnerships among the experts in attendance. It is hoped that this executive summary could be used to further support the intent of the meeting and help to

guide and advance the development of MCMs against opioid-induced toxicities.

Day One

Meeting Opening Remarks—6 August 2019

Kristopher J. Bough, PhD (NIDA/NIH/HHS), meeting co-organizer, welcomed participants and introduced fellow members of the organizing committee—*David T. Yeung, PhD* (NIAID/NIH/HHS), *Judith W. Laney, PhD* (BARDA/ASPR/OS/HHS), *Shashi Amur, PhD* (FDA/HHS), and *Kensey Amaya, PhD* (DTRA/DOD).

Dr. Bough commenced the meeting by first describing its purpose and explained why beyond the ongoing opioid epidemic, synthetic opioids such as fentanyl and carfentanil are of tremendous interest to the CCRP, NIH, BARDA, and DTRA [1, 2]. More specifically, he mentioned that the number of overdose deaths involving fentanyl-based opioids increased by more than 15-fold between 2011 and 2017 and this increase was likely due in part to the growing availability of these drugs. As an example, he mentioned that in 2016, Canadian border officials intercepted a package originally listed as printer accessories contained 1 kg of illicit carfentanil; an amount estimated to be enough to kill an estimated 50 million people. While the opioids seized in such instances were likely intended for use by individual substance abusers, the potential of a large-scale (either intentional or accidental) release of these chemicals represents a significant mass casualty threat to the general public and on the battlefield for the military. As such, a broadly effective, rapidly and easily deployable, post-exposure anti-opioid therapy would have utility across all three emergency scenarios.

Day one of the trans-agency scientific meeting featured a Keynote presentation by the Department of Homeland Security (DHS) introducing the potential mass casualty public health threat posed by pharmaceutical-based agents, specifically synthetic opioids. Following this, stakeholders from the Department of Health and Human Services (HHS) and the Department of Defense (DOD) provided overviews of ongoing programs and resources available to support the research and development of medical countermeasures (MCMs) against synthetic opioid-induced morbidity and mortality (Session 1). Session 2 offered brief insights into the potential mechanistic underpinnings of OIRD. Speakers in Sessions 3 and 4 introduced some of the novel and innovative pharmacotherapeutics and non-pharmacotherapeutic rescue strategies currently in development.

Day two began with a focus towards new and important tools for drug development, e.g., animal models (Session 5) as well as delivery and diagnostic strategies (Session 6). Finally, in Session 7, the FDA presented on available resources that

product developers could leverage to facilitate MCM development and regulatory approval.

Dr. Bough concluded his opening remarks by reiterating the overall goals of the meeting—(1) To understand the fundamental basis of OIRD, explore current and emerging therapeutic, delivery, and detection technologies and (2) provide a forum for subject matter experts to interact and spur the development of MCMs to address this critical need.

Keynote Presentation

Considerations for Medical Countermeasure Development in Mass Chemical Exposures

Mark A. Kirk, MD & Mark E. Sutter, MD (Chemical Defense Program, Countering Weapons of Mass Destruction, U.S. Department of Homeland Security), jointly presented the keynote talk providing an overview of mass casualty care response from the perspectives of civilian first responders. Dr. Kirk began by highlighting the critical characteristics of “ideal” medical countermeasures (MCMs), e.g., pharmacology, effectiveness, safety, application, and feasibility, before explaining how/where the first response system can improve medical outcomes during and/or after a chemical-based mass casualty incident [3]. More specifically, the first response system can be best optimized if the time between an incident [exposure] to recognition of the toxic effect (e.g., toxidrome recognition) and subsequent administration of the ideal MCM is reduced, i.e., “rapid recognition leads to urgent intervention.” To illustrate this point, Dr. Kirk very briefly summarized the sequence of events and outcomes associated with the 1995 Tokyo sarin attack [4, 5] and the 2002 Moscow theater hostage siege, where synthetic opioids were deployed against civilians [6–8]. Dr. Sutter then provided a first-hand case series report of a 2016 opioid-based mass casualty incident that occurred in Sacramento, California involving fentanyl-adulterated tablets presented as hydrocodone/acetaminophen [9]. This mass casualty public health emergency of exaggerated fentanyl opioid toxicity provided a real-life illustration of where improvements in the current medical response system could be beneficial. More specifically, while naloxone was effective as an MCM in this instance, the mass casualty event rapidly depleted the local supply of the drug due to the need for prolonged and higher dosing to treat the initial toxicity and prevent subsequent renarcotization. As such, a faster epidemiologic confirmation together with identification of the emergent threat and more immediate dissemination of the public health outbreak to regional, state, and federal entities could have enhanced preparedness and response by ensuring adequate availability of an effective therapy [9]. Dr. Kirk concluded the keynote presentation by emphasizing that the medical response system can be best optimized when “sufficient

quantities of the appropriate MCM are available and providers are administering the right drug by the right route in the right dose to the right patient at the right time.”

Session 1: Government Stakeholder Perspectives

Moderated by *Jill R. Harper, PhD* (NIAID/NIH/HHS)—Director of the Office of Biodefense Research & Surety and Associate Director for Science Management at the NIAID

NIAID’s Goal: “The NIH Medical Research Program Directed Against Chemical Threats”

Gennady E. Platoff Jr., PhD (NIAID/NIH/HHS), Director of the NIH Chemical Countermeasures Research Program (CCRP) and Chief of the Biodefense Research and Countermeasures Branch, presented an overview of the CCRP and how it aims to address the NIAID’s goal to support the research and development of MCMs against chemical threats. Dr. Platoff’s presentation highlighted the following:

- 1) The research mission of the CCRP is to accelerate development of novel MCMs for the Strategic National Stockpile (SNS) and/or clinical approaches to reduce mortality or serious morbidity during or after an intended or accidental public health mass casualty chemical emergency.
- 2) Basic and applied/translational research priorities, such as to understand the immediate- and/or long-term pathophysiology associated with acute exposure to chemical threat agents and proof-of-principle demonstration of post-exposure MCM efficacy.
- 3) Elements of the CCRP infrastructure include research support mechanisms such as individual grants (R21s), cooperative agreements (U01s), Research Centers of Excellence (U54), as well as Product Development Support Services, and intra-/interagency collaboration research agreements with other HHS and DOD agencies.
- 4) Chemical threat agents of interest to the CCRP is based on the DHS Chemical Terrorism Risk Assessment (CTRA), which currently includes over 185 compounds. These compounds can be broadly defined as threats targeting (a) the neurological system, (b) cellular respiration, (c) pulmonary system, (d) skin, eyes, and mucous membrane, and (e) others, to include pharmaceutical-based agents such as synthetic opioids.
- 5) Operating under the oversight of the NIAID (Gennady Platoff, PhD and Dave Yeung, PhD), the trans-NIH components of the CCRP include partnerships and collaborations with the National Eye Institute (NEI; Houmam Araj, PhD), National Institute on Drug Abuse (NIDA;

Kristopher Bough, PhD), National Institute of Neurological Disorders and Stroke (NINDS; David Jett, PhD), National Institute of Environmental Health Sciences (NIEHS; Srikanth Nadadur, PhD), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS; Hung Tseng, PhD), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD; Robert Tamburro, MD), and the National Library of Medicine (NLM; Pertti Hakkinen, PhD).

- 6) Currently active CCRP solicitations and/or funding opportunity announcements for extramural collaboration designed to advance the discovery and development of novel MCMs include:
 - a. PAR-18-721 (R21): Exploratory/Developmental Projects in Translational Research
 - b. PAR-19-039 (U01): Identification of Therapeutic Lead Compounds
 - c. PAR-19-040 (U01): Optimization of Therapeutic Lead Compounds
 - d. PAR-18-657 (U54): Research Centers of Excellence

To learn more about the CCRP, see <https://www.niaid.nih.gov/research/chemical-countermeasures-program> and “An Overview of the NIAID/NIH Chemical Medical Countermeasures Product Research and Development Program” in Chemical Warfare Agents: Biomedical and Psychological Effects, Medical Countermeasures, and Emergency Response [10].

NIDA’s Goal: “Expanded Therapeutic Options to Prevent Opioid Overdose”

Kurt Rasmussen, PhD (NIDA/NIH/HHS), Director of the Division of Therapeutics and Medical Consequences (DTMC), began his presentation by reviewing the 1999–2017 evolution of the opioid crisis and corresponding sources of overdose that include fatalities attributable to prescription opioids, heroin, and synthetic opioids (other than methadone). Dr. Rasmussen then highlighted some of the past and ongoing efforts at NIDA such as:

- 1) Research and development of medications for Opioid Use Disorder (MOUD), i.e., full (methadone) and partial agonists (buprenorphine) and antagonist (naltrexone).
- 2) Novel approaches to preventing individual overdose, e.g., novel and/or more efficacious formulation of current FDA-approved drugs, stimulation devices to prevent respiratory depression, real-time detection/alert technologies, improved and/or more user-friendly delivery approaches (autoinjector), and post-overdose intervention.

To learn more about NIDA, its research portfolio, and funding opportunities, see <https://www.drugabuse.gov/>.

Roles of the Investigator, Industry, and BARDA in Countermeasure Development for Chemical Threats

Judith Laney, PhD (BARDA/ASPR/OS/HHS), Chief of the Chemical Medical Countermeasures branch, presented an introductory overview of the Biomedical Advanced Research and Development Authority (BARDA) and how it supports the Assistant Secretary for Preparedness and Response (ASPR) Priorities for Building Readiness for 21st Century Threats, including emerging infectious diseases that could lead to pandemic and the potential for chemical, biological, radiological, and nuclear (CBRN) emergencies. More specifically, in partnership with federal and nonfederal stakeholders, BARDA supports the transition of MCMs, such as vaccines, drugs, and diagnostics from research through advanced development towards consideration for approval by the FDA and inclusion into the SNS. BARDA's support includes funding, technical assistance, and core services, ranging from a clinical research organization network to Centers for Innovation in Advanced Development and Manufacturing, and a fill-finish manufacturing network. In short, BARDA develops and makes available MCMs by driving innovation off the bench to the patient to save lives. Dr. Laney then explained that in response to the current epidemic and potential mass casualty public health threat posed by synthetic opioids, the BARDA Opioid MCM program is currently focused on developing therapeutics that could be utilized for both community use and incident response. BARDA's Opioid MCM program is currently most interested in supporting the development of non- μ -opioid receptor (MOR)-based therapies to mitigate OIRD. The ideal MCMs should be fast- and long-acting, be broadly effective against a variety of opioids, and be amenable for use in a mass casualty setting.

To learn more about BARDA, see <https://www.phe.gov/about/BARDA/Pages/default.aspx> and <https://www.medicalcountermeasures.gov/>.

DOD DTRA S&T—Chemical Medical Countermeasure (cMCM) Development Opportunities

Kensley Amaya, PhD (DTRA/DOD), Science and Technology Manager within the Joint Science & Technology (JSTO) Office for Chemical & Biological Defense (CBD), introduced the audience to DTRA and how its mission enables DOD and the U.S. Government to prepare for and combat weapons of mass destruction and improvised threats and to ensure nuclear deterrence.

More specifically, DTRA seeks to discover, develop, and/or repurpose FDA-licensable MCMs that are effective against chemical threats to protect the warfighter. Within the DOD opioid MCM effort, the goal is to develop rapidly acting, more effective, and long-duration pre- and post-exposure MCMs to protect and prevent renarcotization on the battlefield when access to clinical care locations are not readily available. The ideal anti-opioid MCMs would be broadly effective across the class and centrally active to preserve cognitive functions. Similar to BARDA, traditional MOR antagonist approach, such as naloxone, naltrexone, and nalmefene, is of little interest to DTRA since the utilization of those compounds would subsequently prevent the utility of pain managing opioids on the battlefield. DTRA's opioid MCM program's specific areas of interest include (1) long-duration opioid therapeutics, (2) non-antagonists and opioid scavengers, (3) respiratory recovery and pain management, and (4) novel targets and therapeutics.

To learn more about DTRA and open funding opportunities, see www.dtra.mil and <http://www.dtra.mil/Contracts/Business-Opportunities/Current-Solicitations/>, respectively.

DOD MCS—Rapid Opioid Countermeasures Systems (ROCS) Program

Mr. Saumil Shah, AA (JPEO-MCS/DOD), Assistant Product Manager, spoke about the position/role of the Joint Program Executive Office—Chemical, Biological, Radiological, and Nuclear Defense within the DOD Chemical Biological Defense (CBD) program and how the office collaborates with DTRA to develop MCMs. More specifically, JPEO-CBD is the U.S. DoD point for research, development, acquisition, fielding and life-cycle support of biological, chemical and nuclear defense equipment and medical countermeasures to the Army, Navy, Air Force, Marine Corps, and Special Operations Command. The Rapid Opioid Countermeasure System (ROCS) is an example of a JPEO/MCS-DTRA collaboration to develop an anti-opioid MCM to specifically support DoD missions. Relevant to this meeting, ROCS is supporting the DoD effort to develop, manufacture, evaluate, and field an autoinjector-delivered, rapidly bioavailable high dose (10 mg) naloxone system as a rescue therapeutic to treat toxic symptoms associated with exposure to ultra-potent opioids [11]. Mr. Shah reported that the ROCS program has selected Kaleo, Inc. as the developer and sponsor for a 10-mg naloxone autoinjector and expects FDA approval in 2022.

To learn about Medical Countermeasure Systems (MCS)—Chemical Defense Pharmaceuticals (CDP), see <https://asc.army.mil/web/portfolio-item/cbd-medical-countermeasure-systems-cdp/>

Session 2: Mechanistic Underpinnings of Opioid-Induced Respiratory Depression

Moderated by *Roger Little, PhD* (NIDA/NIH/HHS)—Deputy Director of the Division of Basic Neuroscience and Behavioral Research.

Overdosing on Opioids: How Opioids Take Away Our Breath

Jan-Marino Ramirez, PhD (Department of Neurological Surgery, Center for Integrative Brain Research, Seattle Children's Research Institute, University of Washington) began by highlighting that overdose deaths is mainly due to OIRD. OIRD has been shown to be a highly unpredictable and complex process that involves the dynamic and state-dependent interactions of the respiratory network, i.e., the three phases of breathing—inspiration, post-inspiration, and active expiration. These interactions are driven by the preBötzinger complex (PreBötC or PBC) and the post-inspiratory complex (PiCo) and both complexes have been shown to be exquisitely sensitive to the effects of opioids, e.g., the administration of DAMGO (a highly selective MOR agonist) into the PiCo can abolish post-inspiration activity [12]. The coordination of both the inspiration and post-inspiration phases of breathing is significantly weakened by opioids, and that it is not just the dynamic coordination of these networks but also the state-dependent interactions of the respiratory network that ultimately contribute to OIRD. Dr. Ramirez further described how the respiratory network is also highly modulated by multiple endogenous neuromodulators such as neuropeptides and biogenic amines acting in concert to influence the frequency, regularity, and amplitude of respiratory activity [13, 14]. As such, neuromodulators may present an interesting MCM approach to rescue opioid-induced dysfunction of the respiratory network, which if untreated would likely lead to OIRD. However, Dr. Ramirez cautioned that since normal respiratory network operation involves the interplay of multiple neuromodulators, it is unlikely an MCM composed of only one neuromodulator type would be reliably effective [15]. Dr. Ramirez then concluded his talk with the hypothesis that OIRD may actually be a result of failures in normal glutamatergic signaling within the respiratory network and further understanding of these dysfunctions would aid future MCM efforts.

Genetic Variation in Opioid-Induced Respiratory Depression in Mice

Jason Bubier, PhD (Chesler Lab, Center for Systems Neurogenetics of Addiction, The Jackson Laboratory) described some of the research challenges associated with

animal overdose studies in this field, specifically with regard to observed differences in toxicity response. Dr. Bubier proposed that these differences may be due to genetic variabilities. As such, Dr. Bubier's presentation focused on the evaluation of OIRD in different mouse populations since previous studies have shown strain-specific differences in opioid-induced lethality. Using Advanced Mouse Populations (via Collaborative Cross and Diversity Outbred [16]) for precision systems genetics and an automated piezoelectric detection of respiratory rate, Dr. Bubier presented results showing both strain- and sex-specific differences in lethality (including precise time to death) and morbidity (physiological response such as breath rate and depth of respiratory depression) after morphine exposure. Dr. Bubier reported that on average, both sexes of the A/J strain were most sensitive to the toxic effect of morphine whereas 129S1/SvImJ animals were least susceptible. Interestingly, male animals from most of the inbred strains evaluated were found to tolerate higher levels of morphine than females. These differences in responses were then correlated to genetic variabilities across the various strains by high precision QTL mapping during OIRD. Candidate gene analysis identified fifteen protein coding genes in a region on chromosome 5 that regulated the degree of respiratory depression in response to morphine; six of the fifteen genes are expressed in the PreBötC. Dr. Bubier concluded his talk stating that those identified genetic differences in OIRD traits were both mappable and heritable.

Pontine Mechanisms of Opioid-Induced Respiratory Depression

Adrienn Varga, PhD (Department of Pharmacology & Therapeutics, Center for Respiratory Research and Rehabilitation, University of Florida) began by describing the various respiratory effects mediated by opioids, e.g., decreased respiratory rate, irregular breathing pattern, and loss of upper airway patency/aspiration and difficulty swallowing. Airway patency, in particular, is likely attributable to the action of opioids on the Kölliker-Fuse (KF) nucleus within the dorsal lateral pons [17]. Dr. Varga then focused the rest of the talk on her ongoing research to demonstrate how KF neurons in the pons contribute to breathing control in the presence and absence of opioids. To explore this premise, Dr. Varga presented whole-cell recordings from pontine slices in the presence of a MOR selective antagonist. The presence of the antagonist hyperpolarized ~60% of KF neurons thus demonstrating that opioids can directly act on MORs on neurons in the pons. She then showed in vivo results where MOR-flox mice were infected with the AAV-Cre virus (locally injected into the KF to directly target and inactivate MORs in those neurons) and exposed to varying levels of morphine. Dr. Varga found that the specific inactivation of MORs in KF neurons attenuated not only the resulting morphine-induced

respiratory rate depression, but also reduced the frequency of opioid-induced apneas. Dr. Varga concluded that together, the results support that the KF is indeed highly sensitive to opioids and could play an important role in OIRD.

Identification of Therapeutic Strategies to Prevent Respiratory Depression by Opioids

Gaspard Montandon, PhD (Keenan Research Centre for Biomedical Science, St. Michael's Hospital, Department of Medicine, University of Toronto) started his presentation illustrating the multi-faceted process of opioid overdose, beginning with sedation, which occurs almost immediately after an acute toxic exposure. Sedation is then followed by respiratory depression and brain hypoxemia, which is likely still ongoing when an overdose reversal drug such as naloxone available to be administered (usually prior to hospitalization). Dr. Montandon then discussed the general goal of his research is to better understand the mechanism of opioid toxicity within various neural sites to identify potential molecular targets that can mediate respiratory depression but not analgesia [18]. Dr. Montandon then presented previous results showing the PreBötC is highly sensitive to opioids and that activation of substance P-expressing preBötC neurons in rodents can reverse fentanyl-induced respiratory depression thus demonstrating that these neurons may possess potential therapeutic targets [19]. Additionally, he also presented evidences that secondary messengers such as G-proteins with various roles in the regulation of opioid inhibition within the PreBötC could also be potential therapeutic targets [20, 21]. Dr. Montandon then described some of his laboratory's ongoing larval zebrafish-based high-throughput phenotypic drug screening efforts to discover novel therapeutics to block the toxic effects of opioids. In those studies, the presence of fentanyl in the wells decreased zebrafish respiratory depression (as gauged by buccal movements), which can then be reversed upon the addition of naloxone, ampakine, or serotonergic drugs. As such, larval zebrafish represents a viable screening tool to discover novel MCMs to specifically mitigate OIRD. Dr. Montandon concluded that his laboratory and larval zebrafish model are available to collaborate with anyone wishing to screen their compound library for efficacy against OIRD (<http://www.gasplab.com>).

preBötzinger Complex: Critical Site for Opioid-Induced Respiratory Depression

Jack L. Feldman, PhD (Department of Neurobiology, University of California, Los Angeles) opened his talk describing some of the seminal brainstem work from his laboratory that initially identified the preBötC to be critical for breathing, specifically for rhythmic inspiratory activity [22]. His more recent efforts showed that drug-induced silencing of

only ~10% preBötC neurons, including by DAMGO (a highly selective MOR agonist), can result in a cessation of breathing activity both *ex vivo* and *in vivo* (awake rats). These studies further support the importance of the preBötC in respiration [23]. Focusing on the preBötC, Dr. Feldman then presented previously published results by Manzke et al. that showed colocalization of serotonin (5-HT₄) receptors with MORs within those neurons and that selective activation of these receptors can protect against fentanyl-induced respiratory depression [24]. However, this protection against OIRD was not observed in a clinical trial involving the 5-HT₄ receptor agonist mosapride after the administration of morphine for reasons that are still unclear [25]. Dr. Feldman directed the remainder of his talk towards a more detailed mechanistic description of how PreBötC-produced breathing pattern is actually a rhythmogenic process consisting of (1) low amplitude burstlets and preinspiratory activity that determine timing [26], and (2) a pattern-generating process producing suprathreshold inspiratory-bursts essential for motor output. These represent potential processes that may be directly acted upon by MOR activation to produce respiratory depression [27, 28]. Dr. Feldman concluded by briefly describing his laboratory's ongoing efforts to identify compounds that can act specifically as agonists of G-protein coupled receptors within the PreBötC to stimulate respiration.

Session 3: Pharmacotherapeutic Rescue Strategies

Moderated by *Judith Laney, PhD* (BARDA/ASPR/OS/HHS)—Chief of the Chemical MCMs Branch, Chemical Biological Radiological, and Nuclear (CBRN) Division.

Development of Intranasal Nalmefene: a High-Potency, Long-Duration Opioid Antagonist

Phil Skolnick, PhD, DSc (hon.) (Opiant Pharmaceuticals) presented on Opiant's ongoing BARDA and NIDA-supported projects to develop intranasal nalmefene as a novel MCM product against synthetic opioid poisoning. While naloxone is effective against all opioids, fentanyl is 50x more potent than heroin and has a duration of action that is approximately three times as long as naloxone. As such, rescuing a fentanyl-based overdose with naloxone would more than likely require multiple administrations of the drug to mitigate both the initial toxicity and to prevent subsequent re-narcotization. Therefore, "stronger, longer-acting formulations of opioid antagonists" would likely be beneficial in counteracting the toxic effects of these high potency synthetic opioids [29]. Dr. Skolnick then explained why nalmefene represents one such potentially "stronger, longer-acting, higher potency" option. Specifically, when compared against naloxone, nalmefene

has been shown to have five-fold higher affinity at MORs and is ten times more potent [30, 31]. Additionally, since rapid onset of activity can enhance the efficacy of a drug product, Dr. Skolnick discussed ongoing efforts to incorporate Intravail® as an adjunct nalmefene to expedite its intranasal uptake [32, 33]. Lastly, while no longer commercially available in the USA, nalmefene injection (REVEX) was previously approved by the FDA for the management of known/suspected opioid overdose. As such, Dr. Skolnick proposed that the FDA's familiarity with nalmefene and an identical proposed indication would benefit the development of an intranasal nalmefene anti-opioid MCM product.

Methocinnamox (MCAM): Reversal of and Long-Term Protection from Opioid-Induced Respiratory Depression in Nonhuman Primates

Charles France, PhD (Department of Pharmacology, University of Texas Health Science Center at San Antonio) began by presenting a brief perspective on the discovery and early development of MCAM as a potent, long-lasting, and selective antagonist of MORs [34, 35]. Dr. France then described ongoing work in his laboratory to develop MCAM for opioid use disorder using an NHP freely self-administering i.v. opioid model of drug abuse (heroin and remifentanyl) [36]. Compared against naltrexone, a single MCAM treatment was found to successfully antagonize the reinforcing effects of heroin for ≥ 1 week. Similarly, when compared to naloxone, a single treatment of both compounds successfully reversed heroin-induced respiratory depression (measured by dose-dependent decreases in minute volume) within 30 minutes, but again, only MCAM continued to antagonize the toxic effect on subsequent days [37]. Dr. France then presented unpublished data showing MCAM was similarly effective in reversing fentanyl-induced respiratory depression. Dr. France concluded by briefly summarizing ongoing efforts to identify possible mechanisms behind the long-acting duration of MCAM protection that can explain the pseudoirreversible nature of the drug.

Novel Thioester Compounds for Reversal of Opioid-Induced Respiratory Depression

Stephen Lewis, PhD (Department of Pediatrics & Pharmacology, School of Medicine, Functional Electrical Stimulation Center, Case Western Reserve University) described some of the attributes necessary for novel anti-OIRD therapies in this area, e.g., (1) does not block opioid analgesia, (2) can reverse OIRD, (3) can overcome impaired gas exchange in the lungs and skeletal muscle rigidity elicited by opioids, and (4) does not include opioid withdrawal symptoms. Dr. Lewis then provided an

overview of work done by his laboratory to identify cysteine-based compounds, e.g., L-NAC methyl ester (L-NACme), L-cysteine ethyl ester (L-CYSee), L-cysteine methyl ester (L-CYSme), and D-cysteine ethyl ester (D-CYSee), that could address those attributes. Using freely moving morphine-exposed rats, Dr. Lewis's laboratory showed that morphine-induced changes in respiratory parameters such as tidal volume, minute ventilation, pO₂, pCO₂, peak inspiratory flow and drive, and alveolar-arterial gradient can be successfully reversed with cysteine-based compounds [38]. Of the cysteine compounds evaluated, D-CYSee was the most efficacious with only a slight attenuation of the analgesic effect. Importantly, Dr. Lewis then showed D-CYSee was also therapeutically efficacious in reversing the ventilatory depressant effects of fentanyl also in freely moving rats. Dr. Lewis concluded his talk describing current efforts to further develop D-CYSee to improve upon its potency and stability. These efforts include chemically modifying D-CYSee into S-nitroso-D-cysteine ethyl ester (SNO-D-CYSee), which initial tests show may be $\sim 1000\times$ more potent than D-CYSee at reversing respiratory depression.

Serotonin Agonists as a Treatment for Opioid Intoxication

Gerard Ahern, PhD (Department of Pharmacology & Physiology, Georgetown University Medical Center) presented on noncompetitive strategies to stimulate respiration after OIRD. He highlighted that the high potency and rapid onset of toxicity of synthetic opioids, such as fentanyl, sufentanil, and carfentanil are the biggest challenges against the antagonist-based effectiveness of naloxone. As such, Dr. Ahern's research is focused on noncompetitive therapeutic approaches, specifically with serotonin receptor (5-HT) agonists. He postulated that the noncompetitive 5-HT MCM approach may be more effective than MOR antagonists to prevent OIRD because (1) 5-HT neurons have already been demonstrated to provide an excitatory drive to the respiratory network, (2) 5-HT_{1A} receptor agonists have been shown to normalize dysregulated breathing induced by morphine [39], and (3) 5-HT_{1A} receptor agonists can provide generalized protection against other respiratory toxins such as GABAR agonists and glutamate receptor antagonists. As such, Dr. Ahern concluded that 5-HT_{1A} receptor agonists such as Buspirone, Repinotan, Befiradol, and Flesinoxan are potential candidate MCMs to reverse opioid/sedative respiratory toxicity. However, various challenges to develop 5-HT agonists as a viable therapeutic product currently include poor bioavailability and slow onset of action though both of which could possibly be improved via intranasal delivery technology.

Opioid Antidote Strategies: Target Product Profiles and Chemical Modalities

Pierre Rivière, PhD (Peptide Logic, LLC) provided details from some of his company's NIDA-funded projects such as the design and development of monoclonal antibodies (mAbs) against fentanyl and carfentanil. The overall goal of Peptide Logic's opioid-mAbs program is to identify antibodies that (1) have immediate onset of action to rapidly reverse OIRD, which would be suitable for mass casualty care, (2) possess long- to ultra-long acting profile suitable for use in by individuals with substance abuse disorder to prevent relapse and overdose. The aim of the mAb approach is to reduce circulatory opioid levels to minimize the duration of toxicity. In essence, mAbs would sequester and neutralize long-lasting synthetic opioids from plasma while endogenous clearance is ongoing to mitigate toxicities such as loss of consciousness, respiratory depression, and death. The mAb development process typically begins with identifying the relevant immunogens/screening probes to develop and screening the initial mouse hybridomas and mAbs against the antigen of interest before those lead/hit candidate(s) is then humanized and produced for additional more advanced efficacy and pre-clinical characterizations. Dr. Rivière concluded by presenting an envisioned TPP for carfentanil-mAb, which includes (1) immediate/sustained reversal of respiratory depression after a single dose, (2) $K_d \leq 300$ pM, (3) dose ≤ 200 mg, and (4) cross reactive against both carfentanil and fentanyl.

Session 4: Non-pharmacotherapeutic Rescue Strategies

Moderated by *Kensy Amaya, PhD* (JSTO/CBD/DTRA/DOD)—Science and Technology Manager

Biopharmacologic Strategies to Reverse Opioid-Induced Respiratory Depression

Joseph Cotten, MD, PhD (Department of Anesthesia, Critical Care, & Pain Medicine, Massachusetts General Hospital) presented primarily on the use of thyrotropin releasing hormone (TRH), a broadly expressed, water-soluble tripeptide, as an MCM to reverse OIRD. TRH has been previously shown to stimulate breathing, blood pressure, locomotion, and decrease anesthesia and hypothermia [40, 41]. Although no longer marketed in the USA, TRH is an FDA-approved product, which combined with its activity profile makes it a promising therapeutic candidate. Dr. Cotten then presented data from his laboratory demonstrating intravenously administered TRH (and/or Taltirelin, a long-acting TRH analog) to intact, spontaneously breathing isoflurane-anesthetized and conscious rats can successfully reverse morphine-induced respiratory

depression (as measured by breathing rate, minute ventilation, tidal volume, arterial blood gas analysis). Additionally, post-exposure administration of TRH can rescue apneic rats exposed to an otherwise lethal level of morphine [42]. Dr. Cotten then presented results from a small pilot NHPs study that showed neither TRH nor Taltirelin were effective in reversing remifentanyl-induced respiratory depression (quantified by helmet-plethysmography and blood gas analysis). Dr. Cotten concluded that the conflicting efficacy results observed in the rats versus NHPs studies may suggest that rodents may not be an appropriate animal model of OIRD in higher mammals.

Biohybrid Materials to Reverse Synthetic Opioid Poisoning

Saadyah Averick, PhD (Neuroscience Disruptive Research Lab, Allegheny Health Network Neuroscience Institute) began by reiterating the problem and major risk presented by synthetic MOR agonists, i.e., opioids like fentanyl and carfentanil have increased toxicity and resulting lethality because of their long circulatory half-life, are readily permeable via inhalation, and easily manufactured as a commodity chemical. The main disadvantage of the three currently available anti-opioid antidotes is that they function solely as MOR antagonists with less than ideal circulatory half-life to overcome the immediate poisoning and subsequent renarcotization. They also all possess the potential to precipitate withdrawal syndromes. As such, Dr. Averick's research focus is to develop novel MCMs such as (1) longer-acting polymer-based antagonists (up to 24 hours) and (2) absorption/sequestration agents targeting synthetic opioids in circulation. Under the first focus, Dr. Averick presented data showing that covalent nanoparticle-linked naloxone can completely block acute morphine-induced analgesia in vivo for 26+ hours and it was still partially effective for up to 96 hours. This data demonstrated that naloxone could be successfully reformulated to extend its duration of action and overall efficacy [43]. In support of the second approach, the Averick laboratory has started to develop synthetic DNA/RNA aptamers as well as mAbs/Fabs to bind and sequester circulating synthetic opioids.

Cyclodextrins as Versatile Scaffolds for Medical Countermeasure Development Against Opioid Poisoning

Carlos Valdez, PhD (Nuclear and Chemical Sciences, Lawrence Livermore National Laboratory) provided an overview of the potential utilization of cyclodextrins as an MCM to capture circulating fentanyl and related analogs. Cyclodextrins are cyclic oligosaccharide structures composed of glucose units joined together via α -1,4-glycosidic linkages that holds the glucose molecules together giving rise to their

well-defined, rigid, three-dimensional truncated cone structure with a hydrophobic interior and a hydrophilic exterior [44]. According to Dr. Valdez, the physical and chemical properties of the cyclodextrin scaffold allow for the use of NMR to easily elucidate its structure. Structural information would then allow for the understanding of how the compound interacts with and binds fentanyl. This knowledge would then aid in identifying potential ligand sites that could be modified to improve binding properties. Dr. Valdez then presented data from molecular dynamics simulations and NMR-based titration measurements showing the β -cyclodextrin scaffold bound fentanyl (and related analogs) with higher affinity than the other scaffolds tested [45]. The β -cyclodextrin scaffold also had the right cavity size to accommodate fentanyl molecules. As such, this scaffold was selected as a lead for further chemical modifications to produce both anionic and neutral analogs with the hope of improving its fentanyl-binding properties. One of the lead candidate analogs that has been identified thus far was found to bind fentanyl with a $K_a = 6.6 \times 10^4 \text{ M}^{-1}$, which is the most promising for any of the β -cyclodextrin screened to date. Dr. Valdez concluded by highlighting ongoing efforts to incorporate isothermal titration calorimetry into his studies to more accurately measure binding affinities and inform future chemical modification and therapeutic development efforts.

Broad-Spectrum Medical Countermeasures Against Pharmaceutical-Based Agents

Xinhua Li, PhD (Clear Scientific, Inc.) began by highlighting the overall mission of his company which is to develop new technologies and products for detection, decontamination, and medical countermeasures against threat agents. Dr. Li focused his talk on a new class of scrubbers or sequestrant molecules (originally invented by Dr. Lyle Isaacs and licensed from the University of Maryland) to treat opioid intoxication. These synthetic scrubbers function via high affinity, irreversible binding of free opioids in blood. Once bound, the scrubber-opioid complexes are then excreted via renal elimination which prevents the potential of renarcotization. Dr. Li next presented various examples of orally available and injectable scrubber/sequestrant-based drugs that have been approved by the FDA such as activated charcoals, Welchol, Deferoxamine, and Sugammadex to support the developmental prospect of scrubbers as potential antidotes against opioid intoxication. Dr. Li then described their lead cucurbituril (CB)-based scrubber molecules currently under development, i.e., CS-1103. This lead binds specifically to the phenylethylpiperidine moiety of fentanyl with a $K_a \sim 10^7 \text{ M}^{-1}$. Based on binding mechanisms and chemical properties, CS-1103 is expected to bind the same moiety on related -tanil compounds and thus is expected to be broadly effective against the range of synthetic opioids. Dr. Li also presented efficacy data showing that CS-

1103 can (1) dose-dependently reverse the respiratory depressive effects of fentanyl (based on minute ventilation) in less than 10 minutes after treatment, (2) reverse fentanyl-induced respiratory acidosis and hypercapnia, and (3) overcome opioid-induced muscle rigidity based on intramuscular electromyography (EMG) of gastrocnemius muscle activity. Dr. Li concluded by detailing future development efforts, such as structure optimization, determining efficacy against additional highly potent synthetic opioids, and formulation/delivery studies.

Antibody-Based Countermeasures to Opioid Toxicity

Marco Pravetoni, PhD (Department of Medicine and Pharmacology, Center for Immunology, University of Minnesota Medical School) presented various NIDA and NIAID-funded immunological-based MCMs under development in his laboratory, such as vaccines and mAbs-focused approaches, to counteract opioid use disorders and OIRD. The original aim of Dr. Pravetoni's research had been focused on mitigating the toxic effects of oxycodone, hydrocodone, and heroin, but more recent efforts have concentrated on fentanyl and fentanyl-like compounds. He then explained that immunological-based approaches are highly promising MCM options because antibodies are highly selective for their target molecule and once the antibody-opioid complexes are formed, the opioids are immediately inactivated, would not cross the blood brain barrier thus blocking any opioid-induced reward and central toxicities. Other clinical benefits include modular platforms allowing for the design and development of a diverse array of mAbs selectivity, long-lasting circulatory half-life, generally safe, cost-effective, and because of high specificity, would not interfere with endogenous opioids or other pain/addiction medications [46]. Dr. Pravetoni then elaborated on the general blueprint that his laboratory utilizes to develop vaccines and mAbs against opioids that may also be amenable towards other chemical threat agents. In brief, the process begins with the generation of an immunogen composed of a hapten derived from the chemical threat of interest that is chemically conjugated via covalent amide bonds to an immunogenic carrier protein. The conjugated immunogen is then injected with along with an adjuvant to stimulate T cell-dependent B cell activation-based mAb production [47]. Using this approach, Dr. Pravetoni's laboratory has already developed various vaccine and mAb candidates that could sequester opioids from serum to reduce their distribution into the brain. These candidate MCMs has been shown to protect against opioid-induced analgesia, respiratory depression, and bradycardia, without interfering with the protective effect of a MOR antagonist such as naloxone and naltrexone [48, 49]. Dr. Pravetoni concluded his talk by briefly presenting data generated from his current NIH grants showing the promising development of prophylactic anti-fentanyl

vaccines (to prevent relapse and overdose due to accidental or deliberate exposure) [48] and mAb that can be acutely administered pre- and post-exposure to opioids.

Peripheral and Central Influences of Opioids on the Regulation of Respiratory Motor Drive During Breathing and Airway Protective Behaviors

Donald Bolser, PhD (Department of Physiological Sciences, College of Veterinary Medicine, University of Florida) presented on (1) evidence that systemic administration of centrally-acting opioids can influence peripheral sensory receptors that then impacted swallowing and breathing behaviors normally modulated by vagal sensory feedback and (2) an airway protective behavior, specifically the laryngeal adductor reflex, that can be depressed by opioids. Under the first topic, Dr. Bolser cited previously published data from a double-blind, randomized, cross-over study in healthy volunteers showing that systemically administered remifentanyl and morphine affected aspiration and pharyngeal swallowing in humans [50, 51]. He then corroborated those observations with results from his laboratory where intravenously administered codeine affected diaphragm EMG in an anesthetized, spontaneously breathing feline model. In those studies, the systemically administered opioid reduced the number and expiratory efforts of mechanically induced coughing. Additionally, the opioid also produced dose-dependent increases in spontaneous swallowing and affected the upper airway motor drive which resulted in transient disrupted breathing. Intravenously delivered codeine effectively decreased respiratory frequency while eliciting multiple spontaneous swallows [52, 53]. He then presented data showing that codeine also reduced the activity of the thyroarytenoid- and posterior cricoarytenoid- adductors in a dose-dependent manner in those studies [54]. Based on the presented data, Dr. Bolser concluded that in addition to the central effects exerted by opioids, peripheral effects such as the dysregulation of swallowing may need to be better understood to support the development of anti-opioid MCMs.

Day Two—7 August 2019

Session 5: Drug Development Tools: Biomarkers & Animal Models

Moderated by Dave Yeung, PhD (NIAID/NIH/HHS)—Deputy Director of the NIH Chemical Countermeasures Research Program (CCRP) within the Biodefense Research Countermeasures Branch (BRCB), Office of Biodefense Research & Surety (OBRS)

Directly Converted Human “Neurons in a Dish” for Phenotypic Screening and Medical Countermeasures to Opioid Toxicity

Babak Esmaeli-Azad, PhD (CiBots, Inc.) presented on two topics in his talk: (1) Neurotoxicity profiling of toxins and (2) narcobond: biomimetic nanosponge countermeasure for opioids. The primary goal behind CiBots’s NIDA-supported “neurons in a dish” effort is to develop a methodology that allows for “personalized” drug screening specifically to identify potential therapies against the neurotoxic effects of opioid addiction and/or overdose. Dr. Esmaeli-Azad presented an example of one such methodology that could produce personalized dopaminergic, cholinergic, GABAergic, and glutamatergic neurons for neurotoxicity profiling and drug screening use within just 30 days of a blood draw. The rest of the talk was then focused on the discovery, production, and early development of Narcobond, a human opioid receptor encapsulated by a liposome [55]. NarcoBond can be administered by IV or injection and functions as a “decoy receptor” for circulating opioid compounds. Since Narcobond acts as a circulating human opioid receptor, Dr. Esmaeli-Azad postulated that as an MCM, this compound would be broadly effective as a sequestrant agent against all synthetic opioids. This premise was supported by unpublished rodent efficacy data demonstrating Narcobond can successfully reverse fentanyl-, oxycodone-, and heroin- induced antinociception and respiratory and heart rate depression when administered after opioid exposure. Additional data were presented showing Narcobond does not cross the blood brain barrier and accumulates mainly in the liver before it is digested and excreted.

Opiates Reconfigure Cortical Neurochemical Networks

Helen Baghdoyan, PhD (Departments of Anesthesiology and Psychology, University of Tennessee Knoxville, Joint Faculty, Oak Ridge National Laboratory) spoke about how the prefrontal cortex contributes to OIRD based on its interaction with brain stem respiratory nuclei, such as those within the Böttinger complex (BötC). This premise is supported by previous publications demonstrating that the MOR-containing prefrontal cortex modulates cardiovascular and respiratory functions in rodents and humans via respiratory-entrained rhythmic oscillations [56–61]. Dr. Baghdoyan then presented data demonstrating that microdialysis injection of an opioid, either fentanyl or morphine, directly to the prefrontal cortex can acutely depress respiration (as measured by frequency of breaths, tidal volume, and minute ventilation in an awake, unanesthetized mouse model). This microdialysis approach also allowed for real-time collection and liquid chromatography with tandem mass spectrometry (LC-MS/MS) quantification of various metabolites and neurotransmitters, e.g.,

acetylcholine, adenosine, glycine, glutamate, from the prefrontal cortex. The collected data suggest that the administration of an opioid, specifically morphine, resulted in quantifiable differences in the level of metabolites and neurotransmitters present in the prefrontal cortex. Dr. Baghdoyan concluded that these observed changes indicate morphine has effectively restructured the neurotransmitter networks in the prefrontal cortex by reconfiguring the otherwise predictive and directional relationships of the neurochemicals [62].

Assessing Medical Countermeasures Against Opioid Exposure in Multiple Animal Models

Benjamin Wong, PhD (U.S. Army Medical Research Institute of Chemical Defense) started his presentation discussing the general approach in defining an experimental model, i.e., the delicate balance between the “realism” of an exposure (e.g., dose and route) and the “quantifiability” of the measures of interest. A balanced approach between the two factors is necessary to improve technology and methods. Dr. Wong’s research in opioid toxicity is focused primarily on whole body inhalation exposure using either the mouse or ferret as the preferred animal models. Experimental parameters of interest include: physiological, histopathological, biochemical, observational, computational, and toxicological responses. Dr. Wong then presented data describing differences in the timeline and intensity of carfentanil-induced respiratory effects between mice and ferrets, specifically looking at two key respiratory parameters: minute volume (respiratory frequency + tidal volume) and duty cycle (a temporal quantification of average respiratory function). He presented evidence that the mouse was able to survive a carfentanil exposure (low and high dose) for > 24 hours, whereas this was not true for the ferret. Dr. Wong then showed the MOR antagonist, naloxone, displayed partial, dose-dependent efficacy in both animal models with different times for behavioral and physiological recovery [63]. He also presented histopathological data showing pancreatic and kidney necrosis. Dr. Wong concluded that there are now established and well-characterized models for carfentanil inhalation and injection in both mice and ferrets.

The Ferret as an Animal Model for Opioid Intoxication

Michael G. Feasel, PhD (U.S. Army Combat Capabilities Development Command—Chemical Biological Center) highlighted the ultimate goal of his carfentanil-focused research program is to “establish a test model for opioid intoxication that takes into account major opioid toxidromic features, such as respiratory depression, apnea, and hypoxic injury” to support risk assessment studies to better protect the warfighters. Dr. Feasel then briefly described previous in silico physiologically based pharmacokinetic (PBPK) modeling efforts that utilized information derived from rabbit

toxicity studies to predict the estimated human intravenous toxic dose of carfentanil was $\sim 0.34 \mu\text{g/kg}$, which was later corroborated in a report by Casale et al. [64]. More current efforts in the laboratory are to translate the intravenous model into a more relevant route of exposure, i.e., inhalation. Dr. Feasel next described his laboratory’s attempt to develop a rabbit carfentanil inhalation toxicity model and some of the issues that were encountered, such as variabilities in progression of toxic symptoms and dose-response probit, physical attributes of the animals were not conducive to the exposure and physiological response measurement systems, etc. It was subsequently determined that the ferret is a more appropriate model of opioid toxicity (for multiple routes of exposure) and it compares more favorably to historical NHPs data than rabbits did. Additionally, it was found that severe apnea as endpoint in ferrets is likely more representative of lethality in humans and that death should be considered an adverse outcome of opioid agonism rather than a direct effect.

The African Green Monkey (AGM) as a Laboratory Model for Pharmaceutical-Based Agent Characterization and Medical Countermeasures Evaluation

Todd Myers, PhD (U.S. Army Medical Research Institute of Chemical Defense) began by explaining how the African Green Monkey (AGM) is a good model for opioid toxicity research, e.g., similarity to man allows for more predictive intoxicant and MCM responses, availability of well-established behavioral apparatus and methods, and larger size for better PK characterizations. From the DOD perspective, performance-based metrics are the key indicators of MCM efficacy, i.e., allowing the warfighters to “complete the mission” after exposure and, just as importantly, treatment. As such, the goal of Dr. Myer’s laboratory is to first define the progression of opioid (carfentanil) intoxication, which would then inform the selection of a ‘trigger’ treat and finally evaluation of dose-specific MCM (naloxone) efficacy and safety. Based on subcutaneously-administered carfentanil studies, where bradypnea was used as the primary endpoint, the probability of incapacitation (ED_{50} values) at 1x and 1.6x were determined to be 0.71 and 1.15 $\mu\text{g/kg}$, respectively [65]. The clinical signs of intoxication were found to be reliable, though the time to onset of symptoms was variable. When treated with varying doses of naloxone, respiration was the first sign of recovery followed by postural changes and movements. Recovery to “normal functioning” occurred between ~ 10 and 40 minutes after treatment. Lower naloxone doses often produced only transient recovery, necessitating readministration of the MCM [65]. Dr. Myers then discussed redirection of the project to quantify toxicity, MCM efficacy and safety via an automated operant behavioral testing approach instead. This automated approach included assays such

as visual discrimination and choice reaction time tests. At the 1.6x ED₅₀ carfentanil level, Dr. Myers showed that a single post-exposure treatment of 10 mg naloxone human-equivalent dose (HED) was the most efficacious over the entire course of the operant testing period. While this 10 mg naloxone HED dose was also acutely effectiveness against an even higher level of carfentanil (4.89 µg/kg), its efficacy rapidly decreased as the operant testing period progressed, which is likely indicative of re-narcotization. Utilizing the same automated operant testing approach, data were then presented demonstrating intramuscular (i.m.) bolus doses of naloxone from 2 to 80 mg HED (in the absence of carfentanil) produced no to mild behavioral toxicity. Additionally, these high i.m. HEDs produced PK profiles similar to the 2 mg Evzio naloxone autoinjector. Dr. Myers concluded by reporting on ongoing studies from physiological toxicity and efficacy assessment (ECG, blood pressure, body temperature, activity, and respiration) after exposure to a range of carfentanil challenge doses with and without 10 mg HED naloxone treatment administered upon bradypnea. These efforts have led to the identification of (1) dose-dependent physiological changes, (2) time course of toxicity onset, treatment window, duration of treatment effect, etc., and (3) differences between physiological and behavioral/functional recovery.

Session 6: Delivery & Diagnostic Strategies

Moderated by *Kristopher Bough, PhD* (NIDA/NIH/HHS)—Program Director within the Division of Neuroscience and Behavior and NIDA Coordinator to the trans-NIH CounterACT extramural grant program

Nasal Drug Delivery & the Treatment of Opioid-Induced Respiratory Depression

Andrew Walker, PhD (Emergent BioSolutions) presented on the general benefits and challenges of nasal drug delivery systems. While Emergent Biosolutions/Adapt Pharma is the commercial manufacturer and vendor of NARCAN® (naloxone HCl) nasal spray, this talk was not specific to that product rather the focus was on nasal drug delivery. Advantages of nasal drug delivery include: highly vascular, easily accessible, non-invasive, and readily permeable site of delivery that allow for direct access to both the central nervous (bypassing the blood brain barrier) and circulatory systems which circumvents the hepatic first-pass metabolism thus allowing for higher bioavailability. Challenges include (1) limited delivery volume, (2) not suitable for high molecular weight compounds (> 1kDa) and high doses of poorly water-soluble drugs, (3) can be adversely affected by pathological conditions and defense mechanisms (i.e., ciliary action, mucociliary clearance, enzymatic barriers), (4) large interspecies

variability, and (5) lack of in vitro models. As such, physico-chemical properties, i.e., molecular weight, lipophilicity, osmolality, enhancers, particle size of droplet/powder, site and pattern of disposition, are some of the critical formulation considerations that must be addressed to safely and effectively deliver an MCM. Dr. Walker then highlighted several FDA, EU, and USP-issued regulatory guidance documents applicable to nasal spray/inhalation product development before briefly describing the developmental background of NARCAN®, which was first approved by the FDA in 1971 as an i.v. or i.m. administered opioid overdose reversal product before it was later approved for intranasal delivery in 2015 (as a pre-filled 4 mg naloxone in 0.1 ml single-use, inhalational needle-free system). He concluded his talk by indicating that ~76% of opioid poisoning deaths occur in the community and >90% of the general population can quickly and safely administer NARCAN® without reviewing the included instructions.

Nanoengineered Long-Acting Naloxone

Manijeh Goldberg, PhD (Privo Technologies) started her talk describing Privo's vision to build a nanotechnology-enabled customizable drug delivery platform to deliver potent drugs in challenging environments more effectively while minimizing side effects. Dr. Goldberg then explained that (1) the nanoengineered delivery platform developed by Privo consists of all FDA-defined generally recognized as safe (GRAS) material which should allow for expedited FDA approval, (2) is highly adaptable for use across therapeutic classes, i.e., drug (small molecules) and biologics (immunotherapies and proteins), and (3) amenable for use via different routes of administration (dermal patches/films, oral pills/capsules, and injections). Importantly, using this delivery platform, Privo's lead product (PRV111) is currently in clinical stage Phase I and II for oral squamous cell carcinoma (<https://clinicaltrials.gov/ct2/show/NCT03502148>). Her laboratory is now focused on adapting this same delivery platform to develop safer and more effective MCMs for opioid intoxication, e.g., bolus and sustained/controlled release within a single treatment system. Dr. Goldberg concluded by stating that her laboratory is available and interested in collaborating with anyone wishing to license, co-develop and/or commercialize their lead MCM compound with this platform delivery technology.

Medical Device-Based Interventions for Opioid Poisoning

Roger Narayan, PhD (Joint Department of Biomedical Engineering, University of North Carolina Chapel Hill & North Carolina State University) described the 3-D printing, stereolithography apparatus (SLA)-based approach that his

laboratory is currently utilizing to develop an easy-to-use, victim/patient-wearable, hollow microneedle-based biosensor array device for the emergent treatment of opioid poisoning. Treatment would be informed by autonomous microneedle-based detection of physiological responses, e.g., depression of heart rate to under 30 beats per minutes and saturated oxygen level of 70% or lower, changes in pH, glucose, and lactate levels [66]. The putative sensor array would collect, process, and wirelessly transmit data to a smart device platform enabling immediate alerts to inform therapeutic interventions, i.e., monitoring via vital signs. Dr. Narayan then described the various ongoing engineering and analytical testing/validation studies underway in his research program to quantitatively detect the different analytes within clinical ranges.

Automated Diagnosis and Therapy of Opioid-Induced Respiratory Depression—Potential Application to Mass Casualty Chemical Warfare/Terrorism/Public Preparedness

Howard Levin, MD (Coridea LLC) presented on a simple to use (by both first responders and bystanders) external automated external defibrillator (AED)-like device that can automatically detect respiratory depression caused by opioid intoxication in the absence of medical personnel and self-activate to physically maintain normal respiration. He first explained that OIRD is an unmet clinical need and while the research and development of drug- and biologic-based MCMs is progressing, it would also be beneficial to rescue and maintain respiration without a pharmacological therapy, e.g., using a device-based maintenance of ventilation via phrenic nerve stimulation (PNS) [29]. According to Dr. Levin, PNS has been used effectively in the clinical in different forms over the past 50 years for acute and chronic respiratory support in patients with Polio and Ondine's Curse (or central hypoventilation syndrome). As such, phrenic nerve or respiratory muscle stimulation to rescue OIRD is a promising and viable non-pharmacological rescue approach. Advantages of an external AED-like, PNS-focused approach include (1) it can be easily and widely distributed in public spaces, (2) can support respiration until definitive MCM treatment and/or overdose recovery, (3) would allow one person the capacity to treat many victims at the same time, and (4) it has the potential to provide respiratory support in the setting of other types of chemical agent attacks, traumatic brain injury, or other etiology that results in inadequate ventilation.

Using Smart Devices to Detect Opioid Intoxication

Jacob Sunshine, MD (Department of Anesthesiology and Pain Medicine, University of Washington) emphasized that the takeaway from his talk is that by taking advantage of already built-in inaudible sonar and audible sound technologies in

commodity electronic devices, e.g., smart phones and speakers, they can be successfully utilized to accurately classify breathing patterns associated with opioid toxicity and cardiac arrest to inform medical response. Some of the primary advantages of using modern commodity smart devices are that they are ubiquitous, require no additional hardware (software based only), and technologically capable in terms of storage and processing capacities. As such, one focus of Dr. Sunshine's laboratory is to utilize the native microphone and speaker of these devices to monitor respiration by converting them into portable, contactless, short-range active sonar so that frequency shifts can be detected to identify respiratory depression, apnea, and gross motor movements associated with acute opioid toxicity to reduce the time to resuscitative treatment [67]. Dr. Sunshine then described the development, field-testing, and validation of the active sonar algorithms in an approved supervised injection facility (i.e., illicit opioid self-injection setting) and an operating room, i.e., (using routine general anesthesia to simulate OIRD). The results are further described by Nandakumar et al. [67]. Since cardiac arrest is a terminal pathway of opioid toxicity, Dr. Sunshine concluded by highlighting another ongoing effort that is focused on using similar smart devices-based contactless technology to monitor agonal breathing as a potential biomarker of opioid-induced cardiotoxicity [68].

Lab-on-a-Glove for Rapid On-Site Opioid Detection

Drew Hall, PhD (Biosensors and Bioelectronics Lab, Jacobs School of Engineering, University of California, San Diego) focused his talk on developing (miniaturized) technology to detect opioids, specifically point-of-care (POC) testing to enable personalized/precision medicine and alert law enforcement and emergency responders to the presence of synthetic opioids. Dr. Hall then explained that his laboratory's opioid sensing technology can differentiate compounds based on their oxidation/reduction potentials. Therefore, even though opioids may be structurally similar, it is still possible to identify specific compounds based on distinct electrochemical signatures. Dr Hall then elaborated on potential platform approach applications of rapid POC testing, which include:

- 1) Quantitative, accountable treatment monitoring (e.g., substance use disorder)
- An envisioned "Fitbit" approach where a self-contained, injectable, wirelessly powered sensor capable of multi-parameter biochemical measurements is implanted below the skin and a wearable transceiver, e.g., a smart watch, is then placed over the site to receive and process the collected information [69].

- 2) Harm reduction (for users of illicit opioids)
 - An electrochemical biosensor platform approach that incorporates screen-printed electrodes attached peripherally to smartphones to allow “illicit drug” users to detect (and quantitatively assess) for the presence of various compounds/contaminants before administration [70].
- 3) First responder safety and (4) border crossing/airport drug screening
 - Flexible electrochemical sensors pre-integrated into nitrile gloves, i.e., “lab-on-a-glove,” worn as part of a personal protective equipment (PPE) protocol [71].

Session 7: FDA Perspectives and Resources for Researchers

Moderated by *Shashi Amur, PhD* (OTS/CDER/FDA/HHS)—Senior Scientific Advisor in the Office of Translational Science

Regulatory Priorities and Approval Considerations in Developing Medical Countermeasures for Opioid Intoxication

Sharon Hertz, MD (Director, Division of Anesthesia, Analgesia, and Addiction Products, Office of Drug Evaluation II, Office of New Drugs, CDER, FDA) centered her presentation primarily on the regulatory history of naloxone. Dr. Hertz began by highlighting key differences and challenges in the management of opioid overdose in the inpatient vs. outpatient setting, e.g., availability of ventilatory or circulatory support, known versus suspected intoxication, before focusing the remainder of her talk on naloxone. Dr. Hertz then compared the original and current indication and labeling of naloxone products, and then elaborated on its use in the community for medical and harm-reduction purposes, public meetings to identify which populations are most at risk for opioid overdose and discuss the value of wider availability of naloxone in support of developing new formulations, routes of administration, acceptable studies and endpoints, etc. Dr. Hertz concluded by very briefly touching on the background of nalmefene, naltrexone, and other peripherally active MOR antagonists before discussing future directions envisioned to improve access to anti-opioid therapies, such as additional and novel products for outpatient use, reduced costs, and over-the-counter opioid antagonist treatment.

Clinical Pharmacology Perspective and Considerations in Developing Products for Emergency Treatment of Known or Suspected Opioid Intoxication

Yun Xu, PhD (Office of Clinical Pharmacology, Office of Translational Sciences, CDER, FDA) directed his talk specifically on the pharmacology of naloxone-based products recently approved by the FDA, such as the 0.4 and 2.0 mg Evzio autoinjectors (NDA205787 and NDA209862) and 4 mg Narcan nasal spray (NDA208411). Since it is not possible to conduct efficacy studies in humans to identify minimally effective dosing for new naloxone products, the primary development pathway for new/test products is by relative bioavailability (BA) bridging studies using the already approved injection product (NDA16636) as a reference or standard, i.e., the comparator. For an accurate comparison, the proposed new product and the reference comparator would, respectively, need to be administered at the envisioned and approved method, route, and dose. To demonstrate putative efficacy, the new product must meet or exceed the systemic naloxone exposure (PK/PD) of the reference comparator. Additional systemic safety studies may also be necessary if the new product demonstrates substantially higher exposure level than the comparator. Dr. Xu ended his presentation by referencing several publicly accessible FDA Guidance for Industry documents, e.g., Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs - General Considerations, Statistical Approaches to Establishing Bioequivalence, and Bioanalytical Method Validation, that would be relevant to developing bioequivalent products.

Assessing the Structural and Pharmacological Similarity of Newly Identified Drugs of Abuse to Controlled Substances using PHASE

Chris Ellis, PhD (Division of Applied Regulatory Science, Office of Clinical Pharmacology, Office of Translational Sciences, CDER, FDA) described how the Public Health Assessment via Structural Evaluation (PHASE) provides a systematic and reproducible approach to determine the potential public safety risk of newly identified drug compounds that lack in vitro and/or in vivo data. PHASE consists of three steps: (1) a chemical structure-activity similarity assessment with respect to all currently controlled substances, (2) computational biological target prediction, and (3) molecular docking simulation studies to predict binding affinity. Dr. Ellis presented a case study that evaluated the potential public safety risk of para-fluoroisobutyl fentanyl (FIBF) [72]. Based on structural similarity assessment, p-fluorofentanyl, acetylfentanyl, acetyl- α -methylfentanyl, p-chloroisobutylfentanyl, p-fluorobutylfentanyl, o-fluorofentanyl, and fentanyl were identified as the most similar from the controlled substance

databases. Using the chemical structure of FIBF and information from the structure similarity assessment, *in silico* biological profiles of FIBF were then undertaken to identify potential binding targets. The results indicated that FIBF was most likely to bind opioid receptors, specifically MORs, as well as serotonin receptors and transporter, dopamine receptors, and the human ether-a-go-go potassium channel [72]. Finally, molecular docking studies using the solved MOR crystal structure predicted the binding affinity of FIBF to be between 0.5 and 160 nM which is roughly equivalent to fentanyl [73]. Based on PHASE evaluation, FIBF was determined likely to be a public safety risk. Dr. Ellis concluded that various refinement efforts to PHASE are currently ongoing, such as including “Off Rate” kinetics to more accurately predict toxicity.

Development of Mechanistic Pharmacodynamic Models to Predict Adequate Naloxone Doses to Reverse Opioid Intoxication

Zhihua Li, PhD (Division of Applied Regulatory Science, Office of Clinical Pharmacology, Office of Translational Sciences, CDER, FDA) presented on the FDA’s *in vitro* receptor binding assays and *in silico* mechanistic pharmacokinetic/pharmacodynamic (PK/PD) modeling efforts to identify the optimal dose of naloxone necessary to counter the toxicity of emerging synthetic fentanyl derivatives in the community setting. This effort was undertaken due to questions surrounding whether the current dosing standards of 0.4 mg *i.v.*, *i.m.*, or *s.c.* or 2.0 mg *IN* naloxone should be increased. The *in vitro-in silico* strategy sought to quantify the degree/severity of OIRD as a function of MOR occupancy kinetics and PK/PD endpoints (of synthetic opioids and naloxone). The preliminary simulations modeled “worst case scenario,” where the synthetic opioids exhibit extremely slow clearance, full agonist activity, and no saturating effects. Results from these pilot efforts suggest that under this scenario, a single dose (4 mg *IN*) naloxone would take about 5 minutes to sufficiently reverse respiratory depression, but absent any additional MOR antagonist treatment, OIRD is predicted to recur as soon as ninety minutes later. Dr. Li concluded that efforts are ongoing at the FDA to better understand the receptor occupancy and PK/PD information of emerging synthetic opioids. This information would then inform the development of more realistic prediction models.

Advancing Drug Development Through Public-Private Partnerships

Chekesha Clingman, PhD (Office of Translational Sciences, CDER, FDA) discussed ways that CDER can partner with stakeholders to advance innovation and streamline the drug development pipeline. Dr. Clingman began by briefly discussing some of the challenges in drug development and

the results of some of these partnerships could include new clinical endpoints, novel trial designs, response predictors, and biomarkers for safety and efficacy. The remainder of her talk focused on the Public Private Partnership/Consortium (PPPs) as a model for collaboration. A PPP/consortium is a collaborative group managed by a convening or coordinating organization involving multiple stakeholder organizations including at least one non-profit or 501(c)(3) organization and at least one for profit organization. The role of the PPP includes (1) providing a neutral collaborative environment for partnering, sharing, and leveraging the resources in the precompetitive domain to generate scientific knowledge, standards, methods, and tools, (2) facilitating workshops, scientific discussions, gather input from scientific community, and streamline advances in regulatory science, and (3) providing an opportunity for scientific staff engagement to discuss current thinking on drug development tools and other regulatory science efforts. CDER viewed its role as a potential catalyst to bring stakeholders (e.g., universities, drug manufacturers, patient groups) together to translate findings and update policies and standards. Some examples of successful PPP-driven collaboration she highlighted included the Critical Path for Alzheimer’s Disease (CPAD), the Biomarkers Consortium (BC), and the Predictive Safety Testing Consortium (PSTC). Dr. Clingman then spoke about other opportunities to engage with CDER, which include the FDA Technology Transfer Program and Critical Path Innovation Meetings (CPIMs) which provide an opportunity for stakeholders to communicate directly with FDA subject matter experts. To learn more about Scientific Public Private Partnerships and Consortia, see <https://www.fda.gov/drugs/science-research-drugs/scientific-public-private-partnerships-and-consortia>.

Opportunities for FDA-Stakeholder Interactions

Shashi Amur, PhD (Office of Translational Sciences, CDER, FDA) presented an overview of science and research at CDER/FDA in addition to various opportunities and examples of CDER/FDA external stakeholder interactions. Science and research programs at CDER are under the stewardship of the Research Governance Council (RGC), which is responsible for establishing the broad goals and objectives based on inputs from Office leadership. The RGC also provides oversight, advices, and recommendations regarding CDER’s research investment portfolio. FDA primarily supports regulatory science, which is the science of developing new tools, standards, and approaches to assess the safety, effectiveness, quality, toxicity, public health impact, or performance of FDA-regulated products. Dr. Amur then highlighted various opportunities for external stakeholders to engage with CDER/FDA, to include:

- 1) Training and fellowship opportunities at the FDA, e.g., paid and volunteer student training and post-graduate internship, clerkship, and fellowships programs.
- 2) Extramural funding support, such as (1) Broad Agency Announcements (BAAs) to solicit innovative ideas and approaches to developing and evaluating FDA-regulated products by tapping into external knowledge and infrastructure in areas where FDA has limited expertise or capacities and (2) Centers of Excellence in Regulatory Science and Innovation (CERSI), which are collaborations between FDA and academic institutions to advance regulatory science.
- 3) CDER's regulatory science initiatives, e.g., the Critical Path Initiative to modernize the process through which FDA-regulated products are developed, evaluated, and manufactured, and the Sentinel Initiative to proactively monitor the safety of medical products after they have reached the market.

Dr. Amur concluded her presentation by providing evidence that FDA external collaborations are paying dividends. The number of FDA-NIH co-authors publications has increased steadily for the past 10 years as have the number of ongoing collaborative projects with academia, for-profits, NIH and non-profit organizations since 2015.

Meeting Wrap Up

Moderated by *Kristopher Bough, PhD* (NIDA/NIH/HHS)—Program Director within the Division of Neuroscience and Behavior and NIDA Coordinator to the trans-NIH CounterACT extramural grant program

The meeting concluded with two brief HHS-led presentations by *Jeremy Brown, MD* (Office of Emergency Care Research, NIH) and *Michael Schwartz, MD* (BARDA/ASPR/OS/HHS) that focused primarily on “real world” perspectives. Dr. Brown presented on “Oh Yeah, I Forgot. What About the Patients?” which emphasized upon currently available treatment approaches and doctrines. Dr. Schwartz's talk concentrated on “The Bottom Line for Opioid MCM Development,” which centered on the perceived, i.e., media-portrayed, versus actual toxicity and public threat of synthetic opioids.

Concluding Remarks

Kristopher Bough, PhD noted the trans-agency meeting brought together, as intended, experts from academia, industry and government to discuss the development of new medical countermeasures for OIRD. Presenters shared their expertise relating to (1) underlying mechanisms of OIRD, (2) new treatment opportunities, (3) tools to facilitate therapeutic

development, and (4) governmental resources for R&D and regulatory support. Attendees from very diverse backgrounds provided a unique forum for networking and partnerships and led to a useful cross-fertilization of ideas, experience, needs, and techniques that may one day lead to the development of MCMs to rescue opioid-induced toxicity as expressed in Session 1.

Finally, on behalf of all the organizers, Dr. Bough formally adjourned the meeting after thanking everyone's attendance and generous contributions.

Acknowledgements On behalf of the meeting organizers, we want to thank all the presenters and attendees for their participation. The purpose of the trans-agency meeting was to better understand the potential mechanism(s) of opioid-induced toxicities and advance the development of MCMs to prevent or reverse OIRD and consequential mortality. 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. 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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Compliance with Ethical Standards

Conflicts of Interest None

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