MEDICAL PROPHYLAXIS TO MITIGATE CHEMICAL THREATS

Development Of Vaccines And Antibody-based Countermeasures To Prevent And Treat Exposure To Ultra Potent Synthetic Opioids

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The number of fatal drug overdoses has dramatically increased in recent years, with >100,000 deaths due to overdose occurring in the United States in 2021. This has been thought to be, in part, driven by the exponential increase in the number of ultra-potent synthetic opioids (UPSO) being synthesized and infiltrating the drug market (e.g., fentanyl(s), carfentanil, nitazenes). The relative widespread availability of novel UPSO has resulted in increased concern regarding the use of these compounds to incapacitate individuals in both civilian and defense scenarios. Selected synthetic opioids such as fentanyl and carfentanil are listed as chemicals of concern by the Department of Homeland Security. Mixtures of carfentanil and remifentanil have been used by Russian Special Forces to resolve the 2002 Moscow Theather hostage situation resulting in a significant civilian death toll of ~130 people. Current medications and countermeasures may be insufficient to treat and/or reverse incapacitation via UPSO, particularly those that may have unexpected pharmacological effects due to their unique structures and pharmacology. To provide a complementary countermeasure strategy, our team has developed a series of vaccines and monoclonal antibodies (mAb) highly specific for fentanyl, carfentanil, and other relevant UPSO. Vaccine-elicited anti-fentanyl antibodies selectively sequester the target drug from circulation, thus preventing opioid-induced respiratory depression and bradycardia in a number of different species. Bivalent vaccines targeting fentanyl and carfentanil offer protection from both opioids when administered in a drug mixture, akin to how they may be encountered by an individual. Further, highly specific anti-fentanyl mAb isolated using such vaccines are able to reverse the effects of UPSO post-exposure, and synergize with naloxone in reversing fentanyl overdose. Due to their selectivity for the target(s), these mAbs do not interfere with endogenous ligands, FDA-approved medications for treating opioid use disorders (OUD) and overdose, and other critical medications. Hence, mAbs can be co-administered with “standard-of-care” treatments for OUD, overdose, and poisoning in both civilian and defense scenarios. Relative to opioid receptor antagonists, mAbs may offer longer-lasting protection against toxicity. Lastly, our laboratory has begun using ML/AI technology to aid in the development of more effective immunotherapeutics. These interventions have been tested in mice, rats, and larger animal models in support of clinical trials. Together, these data demonstrate the utility of the development of vaccines and mAbs to benefit those individuals at a high risk of fatal overdose, poisoning, and mass casualty incidents (MCI) involving UPSO. Vaccines and mAbs can be deployed in both civilian populations and military personnel.

The work was supported by NIH-funded awards UG3/UH3DA048386, U01DA051658, and UG3DA057850 to Marco Pravetoni and collaborators. The vaccines and mAb have disclosed through patents.