REVOLUTIONIZING BIOMEDICAL RESEARCH: INTEGRATING CUTTING-EDGE AI/ML TO UNLEASH INNOVATION IN DRUG DISCOVERY AND THERAPEUTICS DEVELOPMENT

Rational Design Of Antibody-based Countermeasures Against Fentanyl, Carfentanil, And Ultrapotent Synthetic Opioids

Marco Pravetoni University of Washington **Robert Seaman** University of Washington

The United States continues to be in the midst of an overdose epidemic, with >100,000 deaths yearly due to drug overdose, the majority of these involving ultra potent synthetic opioids (e.g., fentanyl, carfentanil). The ease of illicit manufacturing and transportation of highly potent small quantities of synthetic opioids and their widespread availability pose both civilian and defense threats. Although there are medications available to treat opioid overdose and poisoning (e.g., Narcan®, Opvee®), they may not be effective in fully reversing overdose of novel synthetic opioids with unique structures and pharmacology (e.g., non m-opioid receptor-mediated effects).
To provide a complementary countermeasure strategy, our team has developed a series of monoclonal antibodies (mAb) and fragments (e.g., scFvs) that are highly selective for fentanyl and carfentanil. These antibodies rapidly and selectively sequester the target drug from circulation and thereby reverse opioid-induced respiratory depression and bradycardia in small and large animal models. Due to their selectivity for the target(s), antibodies do not interfere with endogenous ligands, FDA-approved medications for treating opioid use disordersand overdose, and other commonly used medications. Hence, mAbs can be co-administered with “standard-of-care” treatments for overdose and poisoning. Relative to opioid receptor antagonists, mAbs may offer longer-lasting protection against toxicity.
To accelerate development, our laboratory employs structure-guided and in silico tools (ML/AI) to aid in the engineering of synthetic opioid targeting immunotherapeutics to provide benefits such as multi-compound specificity, improved affinity, and improved PK/PD profile. In this studies, our team has shown that mAb and scFv can be administered in mice, rats, and larger animal models to reverse the respiratory and cardiovascular depressant effects of fentanyl, carfentanil, and other chemicals of concern. In vivo data are supported by in vitro characterization to determine affinity, selectivity, stability, and other biophysical characteristics of these novel medical countermeasures. Together, these results demonstrate the utility of mAbs in post-exposure treatment of individuals involved in accidental or deliberate exposure to potent opioids.

The work was supported by CounterACT and HEAL NIH awards to Marco Pravetoni, and by a pilot grant from the Washington Research Foundation to Marco Pravetoni. Sequences and structure of the mAb and scFv have been disclosed in patents filed by Marco Pravetoni and his team.