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Pipeline for Evaluating Efficacy of Novel Non-opioid Compounds for Battlefield Injury-induced Pain

Dr. Clifford is the Branch Chief and PI in the Battlefield Pain Branch of the Pain and Sensory Trauma Management Combat Casualty Care Research Team (CRT), at the US Army Institute of Surgical Research (USAISR) at Joint Base San Antonio, TX. He received his Ph.D. in Cancer Biology from the University of Texas Health Sciences Center Graduate School of Biomedical Science – MD Anderson Cancer Center - Houston, in 1992. He did his postdoctoral research at the INSERM (Institute of Genetics and Molecular and Cellular Biology) in Strasbourg, France. His independent research career followed in 1997 at MD Anderson in the Department of Clinical Cancer Prevention. In 2003 he took a position as Associate Professor at the Louisiana State University Health Sciences Center in Shreveport School of Medicine, in the Department of Biochemistry and Molecular Biology, where he was joint appointed at the Feist-Weiller Cancer Center. In 2011 he moved to the USAISR, where he is currently conducting translational research using animal models, in-vitro laboratory technologies, and systems biology (omics) approaches. Their projects are aimed at preclinical screening of non-opioid analgesics and analgesic devices (non-pharmacologic), as well as understanding pain signaling in chronic neuropathic pain and burn pain models.

Abstract: Recent advances in combat casualty care have resulted in an unprecedented survival rate for battlefield injuries of over 90%, and these injuries typically involve severe acute pain. Currently the standard of treatment for acute pain in the battlefield is opioid drugs, which can cause loss of consciousness, immobility, and inability to remain in the fight. Opioids also produce other negative effects such as dependence, tolerance, hyperalgesia, and cognitive and psychological impairment, that further reduce unit effectiveness. We are therefore testing a range of novel, non-opioid compounds with analgesic potential in battlefield-relevant models of pain and hemorrhage. These analyses combine three established pain models, two of which have been developed at our institution: 1) the full thickness thermal injury (FTTI) pain model, 2) a model for acute extremity trauma that includes hemorrhage (ET+HEM), and 3) the spinal nerve ligation (SNL) model. The FTTI and SNL models provide precise analgesic efficacy characteristics for the novel compounds, such as optimal

dosing, timing and routes of administration. The ET+HEM model determines effects of analgesics on the compensatory hemodynamic and respiratory responses to moderate and severe hemorrhage, and survival to severe hemorrhage.

We have previously used the FTTI model to study the effects of morphine and other standard of care opioids as follows: 1.) to assess tolerance and hyperalgesia (Cheppudira et al, BMC Anesthesiology, 16:73, 2016), 2.) to determine efficacy of topical application, in an effort to reduce the overall opioid requirements (Clifford et al., Burns, 43:1709-1716, 2017) and 3.) as a standard for comparison for testing the analgesic efficacy of the novel non-opioid candidate drugs. We have shown that morphine is highly effective in suppressing both thermal hyperalgesia (TH) and mechanical allodynia (MA) at several times post thermal injury (Days 3,4,5,6,7), at a range of doses when administered intraperitoneally (2,5, and 10 mg/kg IP), and that the analgesic effects lasted for up to 2 hr post administration. In addition, topical administration of morphine to the burn wound site (0.1ml, 5mg/ml) in the FTTI model, produced comparable suppression of TH, with a lesser effect on MA. We have used the SNL model at very early time points post ligation to test the plasma secretome's ability to reduce nerve-injury induced nociceptive behavior and found that bath application of the ligated nerve with a secretome derived product reduces MA at 1 and 2 hours post SNL. With the ET model (without hemorrhage), behavioral responses to trauma were characterized and effects of intravenous (iv) opioid analgesics (morphine, fentanyl, sufentanil) and ketamine were assessed (Xiang et al., J Trauma Acute Care Surg, 85:S49-S56, 2018). Compared with the saline vehicle (VEH) group, opioid analgesics reduced MA for at least 80 minutes post injury. Opioids and ketamine were tested further in the complete ET+HEM model. When the volume loss of 40% was analyzed, opioids caused an increase in blood pressure and decrease in respiration, while ketamine had no effect on compensatory responses. Interestingly, i.v. administration of opioids given immediately after severe hemorrhage (55% blood volume loss) did not affect survival ($P = .55$).

Combining the use of these three distinct pre-clinical models in a 'pipeline' provides optimal candidate analgesics for clinical testing. This is a unique platform for determining both the precise analgesic effectiveness and the suitability for use in a severe polytrauma setting, for novel, non-opioid analgesics.

Disclaimers: Research was conducted in compliance with the Animal Welfare Act, the implementing Animal Welfare regulations, and the principles of the Guide for the Care and Use of Laboratory Animals, National Research Council. The facility's Institutional Animal Care and Use Committee approved all research conducted in this study. The facility where this research was conducted is fully accredited by the AAALAC.

The views expressed in this abstract are those of the author(s) and do not reflect the official policy or position of the U.S. Army Medical Department, Department of the Army, DoD, or the U.S. Government.

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