OFFICE OF THE UNDER SECRETARY OF DEFENSE
4000 DEFENSE PENTAGON
WASHINGTON, D.C. 20301-4000

PERSONNEL AND
READINESS

The Honorable Jon Tester
Chairman
Subcommittee on Defense
Committee on Appropriations
United States Senate
Washington, DC 20510

OCT - 9 2024

Dear Mr. Chairman:

The Department's response to the Joint Explanatory Statement, page 112, accompanying H.R. 2882, the Further Consolidated Appropriations Act, 2024 (Public Law 118–47), "Non-Opioid Drug Research," is enclosed.

The report summarizes current collaborative research efforts and provides an overview of plans to develop capabilities, including research spanning the assessment, monitoring, and control of pain in both the prehospital and definitive care environments. The Department of Defense works closely with Federal, academic, and industry partners to ensure research investments for pain control are well integrated into the broader military medical development environment to deliver impactful capabilities for Service members.

Thank you for your continued strong support for the health and well-being of our Service members. I am sending similar letters to the other congressional defense committees.

Sincerely,

Ashish S. Vazirani
Performing the Duties of the Under Secretary of
Defense for Personnel and Readiness

Enclosure:
As stated

cc:
The Honorable Susan Collins
Ranking Member

[redacted]

OFFICE OF THE UNDER SECRETARY OF DEFENSE
4000 DEFENSE PENTAGON
WASHINGTON, D.C. 20301-4000

PERSONNEL AND READINESS

The Honorable Ken Calvert
Chairman
Subcommittee on Defense
Committee on Appropriations
U.S. House of Representatives
Washington, DC 20515

OCT - 9 2024

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Sincerely,

Ashish S. Vazirani
Performing the Duties of the Under Secretary of Defense for Personnel and Readiness

Enclosure:
As stated

cc:
The Honorable Betty McCollum
Ranking Member

[redacted]

OFFICE OF THE UNDER SECRETARY OF DEFENSE
4000 DEFENSE PENTAGON
WASHINGTON, D.C. 20301-4000

PERSONNEL AND
READINESS

OCT - 9 2024

The Honorable Jack Reed
Chairman
Committee on Armed Services
United States Senate
Washington, DC 20510

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Sincerely,

Ashish S. Vazirani
Performing the Duties of the Under Secretary of
Defense for Personnel and Readiness

Enclosure:
As stated

cc:
The Honorable Roger F. Wicker
Ranking Member

[redacted]

OFFICE OF THE UNDER SECRETARY OF DEFENSE
4000 DEFENSE PENTAGON
WASHINGTON, D.C. 20301-4000

PERSONNEL AND READINESS

The Honorable Mike D. Rogers
Chairman
Committee on Armed Services
U.S. House of Representatives
Washington, DC 20515

OCT - 9 2024

Dear Mr. Chairman:

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Sincerely,

Ashish S. Vazirani
Performing the Duties of the Under Secretary of Defense for Personnel and Readiness

Enclosure:
As stated

cc:
The Honorable Adam Smith
Ranking Member

[redacted]

Report to the Congressional Defense Committees

Non-Opioid Drug Research

October 2024

The estimated cost of this report for the Department of Defense (DoD) is approximately $9,000.00 for Fiscal Year 2024. This includes $2,100.00 in expenses and $6,900.00 in DoD labor.

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PURPOSE

This report is in response to the Joint Explanatory Statement, page 112, accompanying H.R. 2882, the Further Consolidated Appropriations Act, 2024 (Public Law 118–47), which requests that the Assistant Secretary of Defense for Health Affairs provide a report to the congressional defense committees on the Department's plans to conduct collaborative research on development of non-opioid drugs for acute pain control on the battlefield.

OVERVIEW

As directed by the Office of the Assistant Secretary of Defense for Health Affairs, the Defense Health Agency (DHA) manages the Defense Health Program (DHP) Research, Development, Test, and Evaluation (RDT&E) appropriation with the objective to develop capabilities for current and future medical and operational needs of the military community. This includes research aimed at both furthering the understanding of and developing treatments for acute pain. Battlefield pain management focuses on safely and effectively treating pain at, or very close to, the point-of-injury (POI). Pain treatments must work quickly, be safe, easy to use, and lightweight to allow medics to carry sufficient doses for the planned operation. As part of DHA's strategic planning, the development of prehospital pain control products for military operational needs, such as maintaining operational effectiveness after application of pain control products and addressing pain control products for use in an operational environment, are priorities for DHA.[1]

DHA invests in non-opioid acute pain research across numerous DHA organizations (Research and Engineering, Acquisition and Sustainment, and Research and Development), and in efforts with external partners (other Department of Defense (DoD) laboratories, academia, and industry). Current research and development efforts include activities funded by DHP Guidance for the Development of the Force, Congressional Special Interest, and Advanced Development. The efforts align to the three research capability areas within the DHA sensory system portfolio: 1) Characterize; 2) Assess, Diagnose, and Monitor; and 3) Treat. Table 1 describes these capability areas.

Table 1. Overview of Capability Areas for Acute Pain

Capability Area	Capability Area Description
Characterize	Characterize mechanisms and risk factors for sensory injury or illness.
Assess, Diagnose, and Monitor	Develop practices or tools that aid diagnosis of sensory injury or illness, assess the health of sensory systems, and develop fitness standards.
Treat	Provide treatment for sensory injury or illness at/near POI, in-transit, and acute care.

[1] Defense Health Agency Strategic Research Plan: Sensory Systems. February 2024. Available at: https://www.health.mil/Reference-Center/Publications/2024/04/25/DHA_Sensory_Systems_SRP_508_Compliant.

Table 2 provides an overview of current DHP RDT&E funded projects related to non-opioid drugs for acute pain control on the battlefield. Current efforts related to non-opioid acute care pain management may be organized into two main themes: (1) repurposing of existing Food and Drug Administration (FDA)-approved treatments and/or combination therapies; and (2) development of novel compounds and/or delivery methods.

Table 2. Current DHP-Funded Non-Opioid Acute Pain Projects

Capability Area	Project Title	Summary	Performer
Characterize	Mechanisms of Acute Pain Generation and its Transition into Chronic Pain	The project aims to identify the mechanisms by which an acute pain signal is initiated in sensory neurons and elucidate how alterations in neuronal signaling cause acute pain to transition into chronic pain.	U.S. Army Telemedicine and Advanced Technology Research Center
	Preventing the Development of Chronic Pain: Treating PTSD (Post-Traumatic Stress Disorder) at Acute Pain Onset	This project will evaluate if the treatment of PTSD symptoms using focused Cognitive Processing Therapy or Stellate Ganglion Block at acute pain onset may reduce the occurrence of chronic pain following trauma and decrease the burden of chronic pain on military personnel. Preventing the transition from acute to chronic pain may directly translate to improved troop readiness.	Rush University Medical Center
Assess, Diagnose, and Monitor	Evaluation of Modern Analgesics and Pain Effects on Warfighter Function	The project aims to evaluate the effects of analgesics and pain with and without pharmacologic relief on warfighter function.	U.S. Army Institute of Surgical Research (USAISR)
	Impact of Analgesics on Cardiovascular and Respiratory Responses After Trauma and Hemorrhage	The project aims to evaluate the effects of modern analgesic approaches to identify alternatives for battlefield pain management. The novel analgesic treatments evaluated in this protocol will be selected based on their non-addictive properties with the purpose of mitigating the crises of opioid tolerance and addiction.	USAISR
Treat	Assessing the Efficacy of Novel	The project aims to assess analgesics/ anesthetics in battlefield-relevant	USAISR

Capability Area	Project Title	Summary	Performer
Treat (Continued)	Compounds on Pain (Includes Model of Development)	models: laceration trauma and extremity fracture.	
	Battlefield Pain Management	The project aims to deliver a rapid-acting analgesic treatment for combat battlefield pain during tactical field care and casualty evacuation.	U.S. Army Medical Materiel Development Activity
	Cardiovascular and Respiratory Effects of Multiple Dose Analgesia	The project aims to use a unique platform for assessing the effects of three novel analgesics (CYT1010, crocetin, and SBS1000) on cardiovascular and respiratory responses after trauma, with and without hemorrhage.	USAISR
	Developing Non-Opiate GPCR (G Protein-Coupled Receptor) Signaling-Biased Agents for Pain Management	The project aims to develop a novel therapeutic based on the biased signaling of neurotensin receptor 1 for treating acute and chronic pain.	Duke University
	Development of a Highly Selective mPGES-1 (Microsomal Prostaglandin E Synthase-1) Inhibitor as an Effective Non-Opioid Treatment of Chronic Pain	The project aims to identify a mPGES-1 inhibitor compound that can effectively relieve both nociceptive and neuropathic pain without addiction potential of opioids or adverse effects of cyclooxygenase (COX)-1/2 inhibition.	University of Kentucky
	Development of Combination Therapy for Battlefield Pain in Conjunction with Battlefield Opioid	This project aims to provide evidence-based guidance on administering battlefield analgesia and concurrent pulmonary/cardiac support to casualties exposed to an opioid-contaminated environment.	U.S. Army Research Institute of Chemical Defense

Capability Area	Project Title	Summary	Performer
Treat (Continued)	Low-Dose Short-Term Ketorolac to Reduce Opioid Use and Pain Scores on Orthopedic Polytrauma Patients	The project aims to examine whether an early scheduled short-term course of ketorolac treatment has a sustained impact by decreasing chronic opioid use. Military personnel are at elevated risk for extremity battle wounds that cause post-traumatic pain, placing them at high risk of chronic opioid use that can limit and/or delay return to duty.	University of Kentucky
	Nanoparticle Based Therapeutics (NPBTs) for Reduction of Inflammatory Pain	The project aims to identify and assess novel NPBTs that reduce the inflammatory pain phenotype and can be applied in a prolonged field care scenario. Novel non-opioid NPBT treatments may alleviate the need for high-dose opioid treatment for wounded Service members on the battlefield and during the continuum of care.	USAISR
	Novel Analgesics and Anesthetics for Acute Incisional Pain	The project aims to investigate a multimodal analgesic approach with components of long-acting local anesthetics and non-opioid analgesics to provide pain relief with minimal side effects in a battlefield-relevant model of incisional pain that mimics a laceration injury on the battlefield. Two novel therapeutics, Probudur (a liposomal bupivacaine long-acting local anesthetic) and Bitopertin (a glycine transporter inhibitor), will undergo evaluation when used alone and in combination.	USAISR
	Novel Non-Opioid Analgesic for Acute and Chronic Pain	The project aims to demonstrate the capacity of the ketamine metabolite (2R,6R)-hydroxynorketamine ((2R,6R)-HNK) to produce opioid sparing effects using models of pain.	Uniformed Services University of the Health Sciences (USUHS)

Capability Area	Project Title	Summary	Performer
Treat (Continued)	Pain Management in Critical Combat Casualty Environments Using Resorbable Polyester Urea Films for Sustained Delivery of Meloxicam and Bupivacaine	The project aims to develop a therapeutic strategy to co-deliver bupivacaine and meloxicam, an FDA-approved non-steroidal anti-inflammatory drug, from degradable amino acid-based polyester urea films. These films could be carried in critical combat casualty environments by combat medics and deployed at the site of injury. Addressing inflammation and nerve conduction simultaneously at the site of injury may result in more effective pain relief by targeting different pain mechanisms.	Duke University
	Phases 1 Design and Testing of a Photobiomodulation Therapy Mobile Device for Pain Control	The project aims to assess a non-invasive, light based, non-opioid photobiomodulation therapy (PBMT) device. The PBMT devices will be light, wearable, and battery-operated for use in military missions within austere medical environments.	USUHS
	Prolonged Intranasal Delivery of Ketamine Using Mucoadhesive Particles	The project aims to evaluate the effectiveness of an intranasal formulation for mucoadhesive ketamine nanoparticles for sustained delivery of the drug to enhance treatment for pain and PTSD models. This will enable medics and healthcare professionals to provide controllable sustained drug delivery of ketamine in resource-limited environments (e.g., the battlefield).	USUHS and Boston University
	Refinement of a Portable AI (Artificial Intelligence)-Assisted Ultrasound-Guided Device for Regional Anesthesia	This project aims to refine an AI-guided vascular access device for development of regional analgesic indication and use.	USAISR and Metis Foundation

Capability Area	Project Title	Summary	Performer
Treat (Continued)	Sustained Release of 2R,6R-Hydroxy-norketamine (HNK) by MacroPoSH Microneedle Patch for the Treatment of Post-Traumatic Stress Disorder and Pain	The project aims to demonstrate the utility of grooved microneedle arrays for sustained and repeated drug delivery for pain. Crossover-lines technology will be used to fabricate a wearable microneedle delivery device that will provide user-defined and accurate (2R,6R)-HNK release to facilitate repeated or prolonged treatments in clinical, home, and battlefield settings.	USUHS and Tufts University
	Topical Novel Nonopioid Pain Relief for Eye Injury	The project aims to develop IC800, a novel non-opioid therapy for the topical treatment of ocular pain resulting from trauma. Researchers hypothesize that IC800 will be safe and well-tolerated when administered topically to the eye and an effective stabilizing treatment for acute eye injuries in the austere environment.	IACTA Pharmaceuticals, Inc

CONCLUSION

The plan for pain science and technology investments includes research to characterize basic mechanisms of pain; assess and monitor pain; and control pain in both the prehospital and definitive care environments. DHA will focus on capabilities related to the development of novel compounds and/or techniques that provide effective acute pain relief while not degrading physiologic state and/or increasing support care demand. DHA recognizes the importance of addressing acute pain, which may prevent transition to future chronic pain. DHA works closely with the Services, other DoD Components, and Federal, academic, and industry partners to ensure research investments for pain control are well integrated into the broader military medical development ecosystem to deliver impactful capabilities for Service members.