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News Release

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TTUHSC Researchers Seek Novel Therapies for Chronic Pain

Ahmed receives NIH grant to study inhibitors that target peripheral neuropathic pain

Chronic pain, a common and debilitating condition, often leads practitioners to prescribe opioids in escalating doses. The prescription of opioids has created a serious nationwide crisis that killed more than 107,000 Americans from December 2020 through December 2021, according to a report by the American Medical Association ("Nation's opioid-related overdose and death epidemic continues to worsen"). Given these realities, an urgent need exists to develop novel non-opioid and non-addicting therapies capable of effectively managing chronic pain.

To help spur the development of these therapies, the National Institute of Neurological Disorders and Stroke at the National Institutes of Health recently awarded a five-year, $1.94 million grant ("Identification of novel lead EphB1/2 tyrosine kinase inhibitors targeting peripheral neuropathic pain') to Mahmoud Salama Ahmed, Ph.D., from the Department of Pharmaceutical Sciences at the Texas Tech University Health Sciences Center (TTUHSC) Jerry H. Hodge School of Pharmacy. The project team includes TTUHSC department colleagues Jenny Wilkerson, Ph.D., (co-investigator) and Heba Ewida, Ph.D., and graduate student Harrison Benson.

In previous behavioral research studies, Ahmed's laboratory demonstrated significant reversal of thermal hyperalgesia (heightened sensitivity to heat or thermal stimuli) and mechanical allodynia (pain from a light touch, pressure or movement) induced by experimental nerve damage and a sciatic nerve constriction injury.
Ahmed's previous research also revealed the synergism of three tetracycline family members: minocycline, chlortetracycline and demeclocycline.

"That study showed the competitive inhibitory profile of chlortetracycline and the catalytic binding domain of EphB1 tyrosine kinase (transmembrane proteins that mediate communication between cells)," Ahmed explained. "It also showed that the tetracycline combination reversed thermal hyperalgesia and mechanical allodynia in various pain models. However, the IC50 (the amount of a drug needed to inhibit a biological process by 50%) for this approach is in the low micromolar range, requiring a near maximal dose of all three antibiotics in combination."

A micromolar is one-millionth (10^-6) of a mole, which is a unit of measurement representing a specific number of molecules or atoms. For some drugs, concentrations this high in humans are difficult to achieve without producing unwanted side effects.

While working at UT-Southwestern, Ahmed published a paper at the proceedings of the National Academy of Sciences resolving the crystal structure of one of the tetracyclines with the EphB1 tyrosine kinase domain. Ahmed said this kinase is integrated into the progression of peripheral neuropathic pain.

“However, it doesn't make sense that when we have a patient that's suffering from a peripheral neuropathic pain, we will give them this combo of the tetracyclines,” Ahmed said. “Because in the long-term, some of the adverse effects the patient might develop include antibiotic resistance. Also, the binding of the tetracyclines to the kinase domain was not optimum. Based on that, I started to look at the structure again, and I came up with new structures to achieve more potency and selectivity.”

Ahmed then began collaborating with Wilkerson at TTUHSC. First, Ahmed’s lab conducted the design phase, synthesized (collected) other evidence and findings from past research and conducted biochemical validation. When the project was set to scale up and conduct in vivo, pre-clinical models, they turned to Wilkerson’s lab.

Wilkerson has 17 years of experience researching the involvement of the immune system in various chronic neuropathic pain models. Using this expertise, Wilkerson’s laboratory will examine the potency of these new compounds to reverse or prevent behaviors associated with chronic neuropathic pain. Her laboratory will also determine if therapeutically relevant doses of these new compounds produce untoward behavioral side effects.

“This project holds a lot of promise because, for so many people, opioids and gabapentinoids are the main options to treat chronic pain, and we know that these drugs often do not work to adequately control pain,” Wilkerson said. “Additionally, this project is very exciting because we might be able to prevent chronic pain from developing.”

As they prepare for this latest study, Ahmed said they have 50 to 60 molecules in hand that exhibit better activity when compared to the tetracyclines used to target the EphB1 tyrosine kinase domain. Two of these molecules are undergoing preclinical evaluation for reversing all the key parameters for peripheral neuropathic pain, such as thermal hyperalgesia and mechanical allodynia.

“The EphB1/2 tyrosine kinase domain inhibitors have the potential to reverse the thermal hyperalgesia and the mechanical allodynia, and those stimuli are interrelated to peripheral neuropathic pain,” Ahmed said. “Our overall goal is to pharmacologically examine whether selective EphB1/2 tyrosine kinase inhibition is necessary and sufficient to reverse and/or block peripheral neuropathic pain development.”

The Ahmed-Wilkerson team hypothesizes that their novel small molecules, which are not related to the tetracycline scaffold, will inhibit EphB1/2 tyrosine kinase signaling.

“These small molecules could prove to be novel tools to investigate the mechanisms that either block or reverse peripheral and central nervous system neuronal activation and nerve damage,” Ahmed said. “This will lead to decreased neuropathic pain-related biomarkers and behaviors associated with peripheral neuropathic pain.”

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