THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

Patrick Dib

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE

GRADUATE COLLEGE

DEPARTMENT OF GRADUATE PHARMACEUTICAL SCIENCES

Thursday, November 17, 2016 2:30 pm
Robert M. Bird Health Sciences Library
Auditorium, Room 299

THE ROLE OF TNF-α IN THE PATHOPHYSIOLOGY OF AN ANIMAL MODEL OF PTSD AND CO-MORBID PAIN

COMMITTEE IN CHARGE:
Kelly S. Standifer, Ph.D., Chair, Randle Gallucci, Ph.D., Michael Ihnat, Ph.D., Michael McShan, Ph.D., Beverley Greenwood-Van Meerveld, Ph.D.

ABSTRACT: Post-Traumatic Stress Disorder (PTSD) is a debilitating mental health disorder that occurs after exposure to a traumatic event. Patients with co-morbid conditions, such as chronic pain, experience affective distress, higher levels of life interference, and greater disability than patients with either condition alone. They also generally respond more poorly to treatments for pain or PTSD than patients with PTSD alone. Only two drugs have been approved by the FDA for PTSD, paroxetine and sertraline, and neither is an effective analgesic. Often additional drugs are necessary to treat co-morbid symptoms. Therefore, a better

understanding of the pathophysiology of PTSD and chronic pain is needed to develop new treatment strategies. The single prolonged stress (SPS) model of PTSD induces the development of persistent mechanical allodynia and thermal hyperalgesia. Accompanying this exaggerated pain response are increased N/OFQ levels in both serum and CSF as well as significant increase in the pro-inflammatory cytokine TNF-α on day 3 post SPS. Therefore, our first objective was to determine the efficacy of paroxetine on SPS-induced anxiety and co-morbid pain symptoms and the second was to determine the role of TNF-α in the development and maintenance of SPS and pain symptoms. Paroxetine offers partial efficacy for co-morbid pain and may exert its therapeutic effect in part due to central modulation of N/OFQ and reversal of protein expression changes in the hypothalamus and hippocampus. Initiating administration of the TNF-α blocker, thalidomide immediately after SPS prevented development of PTSD and co-morbid pain symptoms and prevented increased TNF-α. This anti-nociceptive effect was maintained for up to 21 days; well after thalidomide treatment ended (day 5). Thalidomide also prevented SPS-induced serum increases in N/OFQ and reversed protein expression changes in the hippocampus. The peripherally-restricted TNF-α blocker, enalapril (ENL), prevented SPS-induced anxiety symptoms but only slightly reduced hyperalgesia. This suggests that peripheral TNF-α surge is necessary for the appearance of anxiety, and that pain associated with SPS is likely to be of inflammatory origin. Therefore, targeting inflammatory mediators such as TNF-α provides new therapeutic options for investigation as future PTSD and co-morbid pain treatments.