Project Summary/Abstract

Pain is a debilitating and prevalent condition which severely impacts quality of life. Unfortunately, our current treatment options are limited by adverse effects, and the pathways modulating pain signaling are not fully understood. The rostral ventromedial medulla (RVM) is a brainstem site which plays a critical role in pain modulation, primarily by sending descending projections to the spinal cord. While non-specific electrical stimulation of the RVM produces analgesia, RVM neurons can either facilitate or inhibit pain. RVM spinal projections can be characterized as ON-cells, OFF-cells, or NEUTRAL-cells based on their response to, and effect on, nocifensive reflexes, but many details remain unclear. Morphine acts at the mu-opioid receptor (MOR) to inhibit neuronal activity and produces analgesia in part by activating OFF-cells and inhibiting ON-cells. Thus, it follows that ON-cells express MOR. Numerous studies support the assertion that ON-cell circuitry is implicated in chronic pain and opioid-induced hyperalgesia. However, until recently we lacked the genetic tools necessary to dissect the circuitry of MOR-expressing neurons, including ON-cells, in the RVM. With the recent development of the *Oprm1-Cre* knock-in mouse, we now have the genetic tool necessary to study these circuits in better detail. The goal of this proposal is to therefore test the hypothesis that MOR+ RVM neurons facilitate pain by inhibiting interneurons in the superficial dorsal horn. I will test this hypothesis using a combination of genetic, molecular, electrophysiological, and behavioral approaches. **Aim 1** will investigate which cell types in the RVM express MOR through viral tracing, fluorescent in situ hybridization (FISH), and immunohistochemistry (IHC). **Aim 2A** will identify the MOR+ RVM inputs received by interneurons in the dorsal horn through optogenetics and slice electrophysiology. **Aim 2B** will explore the electrophysiological, neurochemical, and morphological phenotype of dorsal horn interneurons receiving input from MOR+ RVM neurons using a combined electrophysiology and anatomical approach. **Aim 3** will test the hypothesis that MOR+ RVM neurons facilitate mechanical, chemical, and thermal pain through the use of chemogenetics and behavioral assays of acute and chronic neuropathic pain. The work detailed in this proposal is critically important because an enhanced understanding of the circuitry underlying the RVM can pave the way for the development of novel pain therapeutics and will advance the field of neuroscience.

Furthermore, this proposal is heavily inspired by my clinical interest in anesthesiology, where I plan to work as a pain specialist and investigate pain signaling mechanisms to minimize patient suffering and improve quality of life. The professional, technical, and intellectual skills which will be developed over the course of this fellowship will position me for success as a physician-scientist in academic anesthesiology.