Targeting Local B Cells to Prevent Chronification of Neuropathic Pain

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Background/Rationale: Current therapeutics for chronic pain conditions like neuropathic pain have poor efficacy with Numbers Needed to Treat > 6, and are frequently accompanied by unwanted effects, including abuse liability. Critically, these treatments simply mask the symptoms without resolving the underlying mechanisms. Our preliminary data suggest that a B cell-immunoglobulin G (IgG) axis promotes neuropathic pain, and that immunotherapies to disrupt this cascade are a revolutionary approach to prevent and treat neuropathic pain. Our innovative proposal builds on this strong foundation to rigorously test whether and how B cells and secreted IgG initiate and maintain neuropathic pain in mice and non-human primates. Specific Aims and Study Design: Our long-term objective is to harness the disease-modifying potential of neuroimmune signaling to treat neuropathic pain. Our central hypothesis is that B cell-IgG signaling around the lumbar spinal cord and dorsal root ganglia (DRG) initiates and maintains neuropathic pain resulting from nerve trauma. We predict that such signaling can be locally silenced without impairing systemic adaptive immune responses. The rationale for testing our hypothesis is that we will identify completely new, safe, and pragmatic approaches to preventing and treating neuropathic pain after Service Members sustain traumatic nerve injuries in the theater of war. To accomplish the overall objective of this application, our qualified and multidisciplinary team will test the central hypothesis across the following specific aims: 1. Determine whether local depletion of B cells prevents and treats neuropathic pain. We will test the pronociceptive role of B cells residing around the lumbar spinal cord and DRG in mice and in non-human primates. Mice will receive a single intrathecal injection of an anti-CD20 mAb at the time of CCI (prevention) or on day 14 post injury (treatment). A comprehensive battery of tests will be used to assess evoked and ongoing/spontaneous pain behaviors. CCI will also be performed in rhesus macaques, and a single anti-CD20 mAb intrathecally administered at day 0 or 14 post CCI. Hypersensitivity to evoked stimuli will be quantified, as well as homecage behavior (measuring ongoing pain and function). The effects of anti-CD20 mAb treatment on immune cell recruitment to the DRG and spinal cord meninges of both species will be quantified via flow cytometry and immunohistochemistry. All experiments will employ sham and IgG isotype controls. 2. Reveal how locally reducing IgG half-life alleviates neuropathic pain. IgG half-life is extended by recycling through neonatal Fc receptors (FcRn). Consequently, FcRn blockade has proven effective for treatment of IgG-mediated disorders, without leading to general immunosuppression. We will test whether biologic or genetic disruption of FcRn prevents and treats neuropathic pain. Mice will receive repeated intrathecal injections of the FcRn blocker efgartigimod beginning at the time of CCI (prevention) or on day 14 post injury (treatment). As an orthogonal approach, genetically mutated mice deficient in FcRn will also undergo CCI. Evoked and ongoing/spontaneous pain behaviors will be assessed. IgG deposition in the spinal cord and DRG will be quantified by immunohistochemistry. All experiments will employ sham, isotype, and/or wild-type controls. 3. Establish whether systemic antigen-specific B cell

responses are retained with intrathecal anti-CD20 or FcRn blocking antibody treatments. To test whether intrathecal safely leaves systemic adaptive immune responses intact, mice will receive a single intrathecal dose of anti-CD20 or FcRn blocking antibodies (or isotype controls), followed by vaccination and boosts with tetanus toxoid. Serum IgM and IgG antibody titers will be quantified over time. Successful completion of this project will have major short- and long-term impact through application of completely new and safe immunotherapies to prevent and treat neuropathic pain. As these treatments (e.g., rituximab, ocrelizumab, efgartigimod) are already FDA-approved for other diseases, they could be rapidly repurposed. This research is conceptually innovative, because it will shift our paradigm of neuroimmune regulation of peripheral nerve injury by identifying a local B cell-IgG axis as a therapeutic target to prevent and treat neuropathic pain. Future studies will investigate other strategies to target B cell inhibitors to the central nervous system and to selectively degrade pathogenic autoantibodies.