

# Leukotriene B4: A Novel Target for Postoperative Pain Control

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Despite the use of multimodal analgesia regimens, many surgical procedures continue to induce acute pain that is severe, difficult to treat, and can persist well beyond the immediate postoperative period, leading to increased opioid use and addiction. Consequently, there is an urgent need to develop non-narcotic analgesics that can effectively supplement opioids and reduce their use. Leukotriene B4 (LTB4) is an eicosanoid that modulates inflammation and promotes the recruitment of neutrophils to sites of inflammation. We have obtained preliminary results demonstrating elevated levels of LTB4 after surgery in mice, suggesting a potential role for this lipid in postoperative pain. Consistent with this premise, our preliminary results reveal that inhibition of LTB4 biosynthesis or signaling suppresses postoperative pain. Mechanistically, we hypothesize that LTB4 signaling enhances pain by potentiating the activation of an ion channel expressed in nociceptive sensory neurons. In parallel, we hypothesize that LTB4 signaling increases the biosynthesis of reactive oxygen species (ROS) that promote pain. **These observations have led to our central hypothesis that LTB4 signaling enhances postoperative pain via two overlapping mechanisms: 1) by sensitizing ion channels in sensory neurons and 2) recruiting leukocytes to the surgical site, which generate ROS that activate this channel.** This hypothesis will be tested in the following aims:

**Aim 1: Test the hypothesis that LTB4 enhances postoperative pain.** We will employ complementary pharmacological and genetic approaches to test the hypothesis that LTB4 signaling promotes postsurgical pain. Specifically, we will inhibit the LTB4 biosynthetic enzymes 5-lipoxygenase and leukotriene A4 hydrolase, as well as LTB4 receptors.

**Aim 2: Test the hypothesis that LTB4 sensitizes ion channels in nociceptive sensory neurons.** In this aim, we will test the hypothesis that LTB4 sensitizes and enhances the activation of a key ion channel in nociceptive neurons that promotes postsurgical pain. First, we will employ immunohistochemistry to assess the co-localization between key ion channels and leukotriene receptors in dorsal root ganglia, the cell bodies of sensory neurons. We will then employ calcium imaging of dorsal root ganglia neurons to test the hypothesis that LTB4 sensitizes key ion channels in nociceptive neurons to exacerbate postsurgical pain.

**Aim 3: Test the hypothesis that LTB4 promotes leukocyte recruitment and ROS biosynthesis at the surgical site to enhance postoperative pain.** LTB4 serves as a chemoattractant for leukocytes, which release ROS into neighboring tissues. In this aim we will test the hypothesis that postsurgical LTB4 promotes the recruitment of leukocytes into the surgical site, which subsequently generate ROS that enhance pain. First, we will assess whether inhibition of LTB4 signaling reduces leukocyte recruitment and ROS biosynthesis after incision. We will then employ complementary leukocyte depletion and ROS inhibition approaches to determine whether leukocytes serve as a major source of postsurgical ROS, which we hypothesize contribute to ongoing postsurgical pain.