No Pain, No Gain
Current pain management therapies, commonly opioids and anti-inflammatory drugs, are not sufficient long-term solutions to pain management. Cell specific approaches to pain management therapies may be the answer. The signal cascade involved in pain transmission is a process that researchers have been trying to unlock for a long time. Recent research into the inflammasome NLRP3 (Nucleotide-binding Domain and Leucine-rich Repeat Containing Family Pyrin Domain Containing 3) has begun to open new possibilities for the development of novel pain therapies. NLRP3 is a protein of the innate immune system and produces the inflammatory cytokine IL-1β. NLRP3 is found in the trigeminal ganglia and is activated in a model of migraine. The activation of NLRP3 during migraine may result in pain due to IL-1β activation of its receptor on trigeminal sensory neurons. Therefore, NLRP3 may be a novel target for migraine pain therapeutics. The innate immune system (also known as the non-specific immune system) is triggered by an outside irritation or chemical signal that results in an inflammatory cascade that helps to contain the infection. NLRP3 is commonly found in macrophages (phagocytes).

Molecular Structure of 2NAQ
Injured cells begin releasing molecular patterns that are recognized by toll-like receptors (TLR) which induces inflammation and leads to pain. TLR4 and P2X7 receptor stimulation on the cell membrane of undamaged cells, such as the trigeminal ganglion neurons are upstream of NLRP3 activation (Figure 2). Activation of NLRP3 (Figure 1) causes oligomerization of seven NLRP3 subunits with ASC (apoptosis-associated speck-like protein containing a carboxy-terminal CARD) and caspase-1. Amino acids Lys24, Asp29, and Arg41 of NLRP3 allow the molecule to bind to the ASC. This leads to the production and release of IL-1β which directly causes pain. Researchers are working to further understand the role of NLRP3 in pain, which could lead to more safe and effective methods to eliminate pain.

IL-1β Concentration after Inflammatory Soup Injection
A Western blot analysis (Figure 4) demonstrates the production of IL-1β in treatment-naive (N) and treated animals 3 h, 6 h, 1 d, 2 d, 3 d after injection of an inflammatory soup. Trigeminal ganglion lysates were immunoblotted, showing that processing of IL-1β is caused by dural inflammation (Figure 3 & 4). β-actin was used as a control group.

Summary
Further research into NLRP3 could lead to a deeper understanding of its role in inflammation and cell damage. Understanding these roles could increase development of more effective -- and possibly cell specific -- treatments for pain caused by inflammation-driven diseases. Ideally, more addictive opiates and anti-inflammatory drugs would be replaced with more effective and safe long term solutions to pain management.