

# **Inhibition of the JAK/STAT pathway and granulocyte macrophage colony stimulating factor: emerging therapeutic approaches in pain modulation in patients with rheumatoid arthritis**

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We read with interest the review by Nijs and colleagues<sup>1</sup> describing central sensitisation in chronic pain conditions and latest discoveries. We agree with the authors that pain represents a significant unmet need. Here we describe the emerging nociceptive therapeutic potential of immunomodulatory strategies.

The aetiology of primary chronic pain syndromes (e.g. fibromyalgia) is poorly understood and the significance of peripheral blood cytokine signatures remains unclear<sup>2</sup>. Many patients with rheumatoid arthritis (RA) continue to experience pain, despite adequate control of inflammation. Pathomechanisms underlying this 'residual pain' in RA may be attributable to a complex interaction of subclinical synovitis, structural damage and peripheral and central sensitisation. The development of widespread pain and central sensitisation in RA may be due to sustained inflammatory input on peripheral nerves, as well as a decreased threshold (allodynia) and increased responsiveness (hyperalgesia) to noxious stimuli. It is unclear when central sensitisation patterns are established in the disease course of RA, if they are reversible or amenable to targeted therapies.

The Janus kinase/signal transducer and activator of the transcription (JAK-STAT) is a complex intracellular cascade involving both pro- and anti-inflammatory cytokines. The precise role of the JAK-STAT pathway in nociception is yet to be fully elucidated, but several cytokine receptors associated with pain are expressed on afferent nerves. There is accumulating evidence to suggest that targeting the JAK-STAT pathway may improve pain outcomes in RA<sup>3</sup>. A recent post-hoc analysis of the RA-BEAM phase III clinical trial, found that patients with RA treated with baricitinib (JAK1/2 inhibitor) achieved greater and more rapid improvements in patient-reported pain than patients treated with adalimumab (tumour necrosis factor  $\alpha$  inhibitor), despite similar improvements in swollen joint counts<sup>4</sup>. These findings suggest that JAK inhibition may modulate both inflammatory and non-inflammatory pain pathways, and that simultaneous suppression of multiple cytokines that amplify pain may be more effective than selective cytokine blockade<sup>3</sup>.

Granulocyte macrophage colony stimulating factor (GM-CSF) is a pro-inflammatory cytokine, signalling through JAK2 homodimers, implicated in the pathogenesis of RA, as well as pain modulation pathways, thought mainly to be driven via the chemokine CCL17 axis. Data from experimental arthritis models suggest that GM-CSF may contribute to mechanical hyperalgesia in RA. Recent results from clinical trials targeting GM-CSF in patients with RA show significant analgesic efficacy, supporting its role as a nociceptive cytokine<sup>5</sup>.

Further research is warranted to better understand whether these findings from rheumatoid arthritis can be extrapolated to chronic pain syndromes.

#### **Author Contribution:**

PM and PCT drafted the manuscript. All authors contributed to discussions, revised and approved the manuscript.

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