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SAT0051 BARICITINIB IMPROVES JOINT MOBILITY AFTER INJURY IN A RODENT FORCED-AMBULATION MODEL

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Background: Movement-evoked pain and impaired joint mobility are common comorbidities in inflammatory diseases such as Rheumatoid Arthritis (RA) and Osteoarthritis. The Janus kinase (JAK) pathway has been implicated in both inflammation and chronic pain. Clinical data suggests that baricitinib, a selective JAK 1/2 inhibitor, can robustly and rapidly alleviate pain in RA.¹ Utilizing a rodent forced-ambulation model, we have previously shown attenuation of gait deficits with analgesics such as opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and an anti-NGF (Nerve Growth Factor) antibody.² However, in this same model a fusion protein blocker of TNF α (tumor necrosis factor alpha) signaling failed to demonstrate efficacy though inflammation was decreased. The present work investigated the potential of baricitinib, recently approved for treatment of RA, to reduce inflammation-induced joint pain and gait impairment in this model of joint inflammation mediated pain.

Objectives: To determine if JAK 1/2 pathway inhibition is effective in treating inflammation-induced joint pain and gait impairment.

Methods: Unilateral joint injury was induced in female Sprague Dawley rats (Harlan, Indianapolis, IN, USA) by unilateral intra-articular injection of 20 μ g Complete Freund's Adjuvant (CFA). Using the GaitScan (CleverSys Inc., Reston, VA) treadmill system, a composite gait score comprising of range of motion, normalized stance distance, stance/swing ratio, and paw print size was evaluated over 3 days post-injection.² Rats were treated with vehicle, positive control (40 mg/kg Tramadol), or clinically relevant (based on plasma levels) increasing doses of baricitinib (1, 3, or 10 mg/kg p.o., 2-hrs prior to each test, q.d.). Dorsal root ganglion (DRG) were harvested post-gait evaluation and Total STAT3 (Cell Signaling, #4904) and phospho-STAT3 (Y705) (Cell Signaling, #9131) protein levels were examined via immunoblotting. The p-values were derived from repeated measures ANOVAs.

Results: In rat DRG homogenates, baricitinib significantly decreased phospho-STAT3 (Y705) protein levels in a dose-dependent manner ($p < 0.01$) with a significant effect after a 3 mg/kg dose and a maximal response after a 10 mg/kg in both the ipsilateral (right) and contralateral (left) sides. Total STAT3 protein levels remained unchanged. Similarly, treatment with baricitinib significantly improved composite gait score at the 10 mg/kg dose ($p < 0.05$) by Day 3.

Conclusion: These data indicate that treatment with baricitinib attenuates CFA-induced joint deficits, a surrogate measure of joint pain. This effect correlated with the pharmacodynamic inhibition of JAK-STAT signaling in DRGs. These data support a role for JAK-STAT signaling in pain

signaling and provide an opportunity to investigate the potential mechanism of action of baricitinib in joint pain.

Figure 1. Representative still images from video recordings of animals during gait analysis at baseline (Top Panel), 3 Days post-CFA and vehicle treatment (Middle Panel) and 3 Days post-CFA with 10 mg/kg daily baricitinib treatment (Bottom panel). The ventral image of the rat illustrates the same part of the gait cycle (ipsilateral stance phase initiation) across treatment groups to highlight impairment in the CFA-injected limb (Red Box) vs Baseline and apparent improvement following 10 mg/kg baricitinib treatment. The panels on the left provide examples of software-detected paw prints for each treatment group which show that CFA + vehicle treatment produced a small, closed-toed paw print (Middle) which appears restored to near baseline levels following baricitinib treatment (Bottom).

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SAT0052 PHOTODYNAMIC THERAPY TARGETING ACTIVATED FIBROBLASTS INDUCES SYNOVIAL CELL DEATH IN EXPERIMENTAL ARTHRITIS

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Background: Activated synovial fibroblasts (SF) contribute to rheumatoid arthritis (RA) by producing a multitude of cytokines, chemokines and proteases thus aggravating disease. Activated SF can be distinguished from quiescent fibroblasts by their expression of fibroblast activation protein (FAP). Selective depletion of FAP+ SF in inflamed joints could decrease their contribution to the arthritis process and thus constitute a viable treatment option. Further focussing of the treatment to only those areas affected by the disease can be accomplished by applying targeted photodynamic therapy (tPDT). In tPDT a light sensitive molecule, a photosensitizer (PS), is conjugated to a targeting moiety. Upon activation by light this construct produces reactive oxygen species, killing the targeted cells.

Objectives: To this end we developed and tested a therapy that selectively depletes activated SF by targeting FAP on these cells with an