Credit: Brain light/Alamy Stock Photo

THERAPY

Selective p38α MAPK inhibitor shows promise

CDD-450, a newly developed inhibitor that selectively blocks the mitogen-activated protein kinase p38α (p38α MAPK)–MAPK-activated protein kinase 2 (MK2) axis, is a potential drug candidate for autoimmune and autoinflammatory diseases such as rheumatoid arthritis (RA) and cryopyrinopathies, according to findings published in the *Journal of Experimental Medicine*.

"Global p38α MAPK inhibitors have failed in phase II RA clinical studies owing to transient efficacy. We hypothesize that this transient efficacy is a result of inhibition of multiple downstream pathways, including those with anti-inflammatory functions," remarks corresponding author Gabriel Mbalaviele. "CDD-450 selectively blocks p38α MAPK activation of the pro-inflammatory kinase MK2, while sparing p38α MAPK activation of several other downstream pathways."

MK2 regulates the expression of pro-inflammatory cytokines by phosphorylating downstream effectors that bind to and regulate mRNA stability. In the study by Wang et al., CDD-450 treatment promoted the degradation of mRNA encoding IL-1β and TNF in lipopolysaccharide (LPS)-stimulated bone marrow macrophages.

Oral administration of either CDD-450 or the global p38α MAPK inhibitor CDD-111 inhibited LPS-induced serum expression of TNF in healthy mice. However, unlike CDD-111, the efficacy of CDD-450 persisted for up to 4 weeks.

Mbalaviele and colleagues investigated the therapeutic potential of CDD-450 in two disease models. In a mouse model of neonatal onset multisystem inflammatory disease (NOMID), CDD-450-treated mice lost less weight and produced less IL-1β and IL-18 in their bone marrow compared with untreated mice. CDD-450 treatment also prevented the development of skin lesions, bone destruction and death in these mice. Similarly, in a rat model of streptococcal cell wall-induced arthritis, CDD-450 treatment inhibited paw swelling and preserved bone mineral density.

> "CDD-450 treatment inhibited paw swelling and preserved bone mineral density"

"These findings have clinical translation implications as CDD-450 offers the potential to avoid tachyphylaxis associated with classical p38α MAPK inhibitors," says Mbalaviele "Studies are underway to support the clinical development of CDD-450."

Jessica McHugh

ORIGINAL ARTICLE Wang, C. et al. Selective inhibition of the p38α MAPK–MK2 axis inhibits inflammatory cues including inflammasome priming signals. *J. Exp. Med.* https://doi.org/10.1084/jem.20172063 (2018)

EXPERIMENTAL ARTHRITIS

Drugs deliver themselves during flares

Designing a reliable method of delivering therapeutic agents when and directly to where they are needed has remained an ongoing challenge for arthritis researchers. Now, a new study demonstrates the promise of a drug-loaded hydrogel that releases its cargo in response to enzymes produced during arthritic flares.

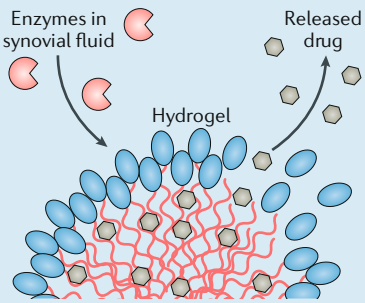
"For inflammatory arthritis, where only one or a few joints are involved, local therapy with intra-articular injections may offer distinct advantages over systemic therapy, by increasing the drug concentration locally and reducing the potential for drug-induced systemic toxicity; however, direct injection into the joint is problematic as drugs are quickly cleared," explains corresponding author Jeffrey Karp.

To address this problem, Karp and colleagues investigated the properties of triglycerol monostearate (TG-18), an amphiphilic molecule that is generally recognized as safe by the FDA and that self-assembles into a hydrogel that can carry several types of therapeutic agent and can disassemble in the presence of certain enzymes.

In vitro, TG-18 created a stable hydrogel that released its cargo of glucocorticoids in response to disease flare-associated enzymes at concentrations similar to those found in the synovial fluid of patients with rheumatoid arthritis (RA). The same response was also observed in response to synovial fluid from patients with RA, but not to synovial fluid from healthy individuals.

The research team then trialled the drug-loaded hydrogel in mice injected with either a medium or a high dose of K/B×N serum to induce moderate or severe inflammatory arthritis, respectively. Drug-loaded TG-18 suppressed disease in mice with moderate arthritis, whereas limited disease suppression was seen when glucocorticoid was administered alone. In addition, a single dose of drug-loaded hydrogel was able to suppress disease in mice with severe arthritis, suggesting that the drug-loaded hydrogel can elicit a long-term therapeutic effect.

> "a single dose of drug-loaded hydrogel was able to suppress disease in mice with severe arthritis"



Credit: Susanne Harris/Macmillan Publishers Limited

"We are interested in validating this approach in large animal models and exploring the potential of this platform to deliver biologics and other disease modifying therapeutics to affected joints," concludes lead author Nitin Joshi.

Joanna Collison

ORIGINAL ARTICLE Joshi, N. et al. Towards an arthritis flare-responsive drug delivery system. *Nat. Commun.* **9**, 1275 (2018)