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Development and evaluation of a theranostic nanomedicine platform for targeted drug delivery in rheumatoid arthritis

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Background: Many rheumatoid arthritis (RA) patients fail to respond satisfactorily to frequently given anti-arthritic drugs or experience side effects. The main reason for non-ideal treatment is that insufficient drug doses reach the joints, therefore higher and more frequent doses needed.

Objectives: To improve the drug pharmacological profile and direct the anti-inflammatory activity to the inflamed joints, the purpose of our study was developing a pro-drug with increased circulation time resulting in sustained release when it reaches the microenvironment of the inflamed joints.

Methods: Our methods encompass the chemical syntheses of the polymeric prodrugs and the investigation of their stability and release kinetics. The pharmacokinetics of the prodrug was established after radiolabeling with In-111, and preclinical SPECT/CT imaging in an RA mouse model. The efficacy of the prodrugs is also established in the same RA model and compared to the free drug given in the same form/ timing as it is currently administered to patients. In vitro stability measurements of the prodrugs in human synovial fluid from rheumatoid arthritis patients is ongoing to better understand the impact of the local environment of an inflamed joint and how that influences drug release.

Results: Delivering methotrexate (MTX) bound to a carrier polymer produces a significant increase in drug uptake in the inflamed joints. When MTX was delivered as a prodrug, a 2 to 4 times lower dose given every two weeks was just as effective as two standard dosages per week of free MTX. In addition, attaching folic acid (a targeting ligand that selectively binds to folate receptors) to the polymeric carrier helped to keep the active drug longer in the targeted lesion.

Conclusions: In this study, using SPECT/CT we show our prodrug approach delivers higher concentrations of anti-arthritic drugs to inflamed joints than has previously been possible, despite lower and less frequent drug doses.