16 TARGETING THERAPEUTICS TO ARTHRITIC JOINTS BY ANTIBODY SPECIFIC TO POST-TRANSLATIONALLY MODIFIED COLLAGEN TYPE II

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Background The aim of our study is to target anti-inflammatory proteins to arthritic joints, in order to improve efficacy and reduce side-effects of current therapies.

Methods The authors chose type II collagen (CII) as a target as it is uniquely present in cartilage. In the arthritic joint, CII is damaged by reactive oxidant species (ROS) generated in the inflammation process. The authors used ROS-modified CII to select a human single chain fragment variable (scFv) specific to ROS-CII.

In order to target therapeutic proteins to the inflamed joints, the authors have fused anti-ROS-CII scFv to anti-inflammatory proteins via an MMP cleavage site linker. MMPs are up-regulated in arthritis, and therefore when the fusion protein is localised to inflamed areas by the scFv, the therapeutic is liberated, and is free to engage its target.

Results The authors were able to demonstrate binding of anti-ROS modified CII scFv,1-11E to damaged cartilage from rheumatoid arthritis (RA) and osteoarthritis (OA) patients but not to intact cartilage.

Accordingly, imaging studies have shown that fluorescently labelled 1-11E scFv localises specifically to inflamed joints in arthritic mice.

1-11E fused to mTNFR2-Fc is able to bind modified CII in ELISA, and is cleaved at the linker site by incubation with MMP-1. Biological activity of mTNFR2 was also demonstrated in vitro. Moreover, the authors show that by fusing mTNFR2-Fc to 1-11E, the therapeutic efficacy in arthritic mice is enhanced.

Conclusion The authors have a proof of principle that therapeutics targeted by anti-ROS-CII to the joints have augmented anti-inflammatory properties. Future work will involve optimising the fusion proteins with a view to development towards the clinic, including targeting alternative therapeutic molecules.