

P006 Identifying the molecular basis of arthritis
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Cleavage of cartilage aggrecan, by the aggrecanase family of proteases is a critical initiating event in arthritic disease.

Aggrecanases belong to the ADAMTS (a-disintegrin and metalloproteinase with thrombospondin motifs) family, a large and functionally diverse group of proteases. Precisely which are responsible for aggrecan breakdown in human arthritic disease is uncertain. Evidence from knockout mice suggests ADAMTS-5 as a prime candidate, with ADAMTS-4 and -9 also possibilities. We aim to engineer human cartilage lacking each of these candidate enzymes in turn, in order to ascertain which are crucial to the degradation of tissue in response to inflammatory stimuli.

We have shown that ADAMTS-4, -5 and -9 are the major ADAMTS transcripts induced by pro-inflammatory cytokines in primary human articular chondrocytes, and have designed and generated retroviral RNA interference (RNAi) constructs to suppress expression of all 3.

By transfection into chondrocyte cell-lines, we have demonstrated reproducible but limited reduction of expression of ADAMTS-5 and -9 mRNAs with some of our constructs. Our immediate aim is to use these constructs to produce recombinant retrovirus that can be transduced and will hopefully function more efficiently to reduce expression of these genes. Once effective knockdown has been achieved, we will transduce primary chondrocytes in order to engineer knockout human tissue.