EXPERIMENTAL ARTHRITIS

Oral aggrecanase inhibitor may slow postinjury cartilage breakdown

AGG-523, an aggrecanase inhibitor, reduces synovial fluid levels of Ala-Arg-Gly-aggrecan (a major cartilage matrix breakdown product) in a rat model of knee injury, new findings show. “Our study suggests the potential of postinjury aggrecanase inhibition to stop or slow down immediate cartilage degradation as well as development of osteoarthritis years after injury in humans,” explains lead investigator, Priya Chockalingam.

The researchers developed a highly sensitive and specific enzyme-linked immunosorbent assay, using commercially available reagents, which revealed elevated levels of Ala-Arg-Gly-aggrecan in synovial fluid from animals and humans with knee injury. Levels of this fragment in human knee synovial fluid increased by an average of 13.6-fold in the 12 weeks after cruciate ligament rupture and 8.1-fold after meniscal injury. Although Ala-Arg-Gly-aggrecan levels then declined, they were still

elevated 1 year after injury—by an average of 3.3-fold and 1.4-fold, respectively.

This trend was mirrored in a rat model, in which Ala-Arg-Gly-aggrecan levels were fourfold higher than those of controls 4 days after meniscal tear and decreased over 8 weeks. However, three oral doses of 1 g/kg AGG-523 given over 2 days, 1 week after meniscal tear, rapidly reduced synovial fluid levels of Ala-Arg-Gly-aggrecan to levels seen in control animals.

Chockalingam and colleagues suggest that this assay and the rat meniscal tear model could provide a platform for preclinical studies of postinjury aggrecanase inhibition.

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Original article Chockalingam, P. S. *et al.* Elevated aggrecanase activity in a rat model of joint injury is attenuated by an aggrecanase specific inhibitor. *Osteoarthritis Cartil.* doi:10.1016/j.joca.2010.12.004