Calosyn Pharma Inc.

Novel Therapies for Osteoarthritis

The pathophysiology of osteoarthritis

Osteoarthritis is characterized by the progressive loss of articulating cartilage in a synovial joint, and temporal escalation of pain and disfunction of the affected joint. Current treatments include analgesics at the earliest stages, oral NSAIDS and narcotics in the middle to late stages, viscosupplementation at all but the latest stages, and eventual surgical intervention via total joint arthroplasty. However, current pharmacologic therapies, whether intra-articularly administered, or not, do not meet the needs of many patients and providers in terms of the benefit to risk ratio.

Over the past several years, much has been learned about the pathophysiology of osteoarthritis, and through such learning, new targets for pharmacotherapy have been identified. In general terms, OA begins with mechanical trauma that is a result of sports overuse, obesity, or other traumatic mechanical insult. Macrophages and synovial cells in the synovium are activated by the insult, and release IL1-beta, TNF-alpha, COX2, IL6, and other inflammatory mediators, resulting in nociceptive pain. An inflammatory cascade follows, with the release of matrix metalloproteinases (MMPs) being the hallmark of OA pathophysiology. The MMPs degrade the cartilage in the joint and may also have degradative activity on nerve endings in the synovium, resulting neuropathic pain, while the collagen fragments released by MMPs feed forward to cause additional inflammation.

The ideal OA treatment would stop the inflammatory feedforward loops as high as possible in the cascade

Dr. Waddell and his colleagues discovered that synovial cells harvested from osteoarthritic patients expressed 4 times as many calcium gap junctions than expressed by non-osteoarthritic synovial cells (Marino, Waddell, Kolomytkin, Albright, et al, Clinical Orthopedics and Related Research, May 2004, 422:224-232). They also showed in cultured HIG82 rabbit synovial fibroblasts that the release of MMPs from IL1-beta stimulated synovial cells is a calcium-dependent event, and that calcium channel blockers prevent the release of MMPs (Kolomytkin, Marino, Waddell, Albright, et al, American Journal of Physiology and Cell Physiology, January 30, 2002, 282:C1254-60). Others have shown in whole blood assays that calcium channel blockers block the release of TNF-alpha and IL1-beta from macrophages. Additionally, we have shown in

vivo in the rat meniscal tear model that calcium channel blockers inhibit the release of MMPs, and blunt the progression of tissue degradation following injury.

Taken together, these data suggest that calcium channel blockers would likely act at the highest point in the osteoarthritic pathway, inhibiting nociceptive pain, MMP release, and neuropathic pain. It is for this reason that we are investigating the use of calcium channel blockers as an intra-articular therapy for osteoarthritic pain.