

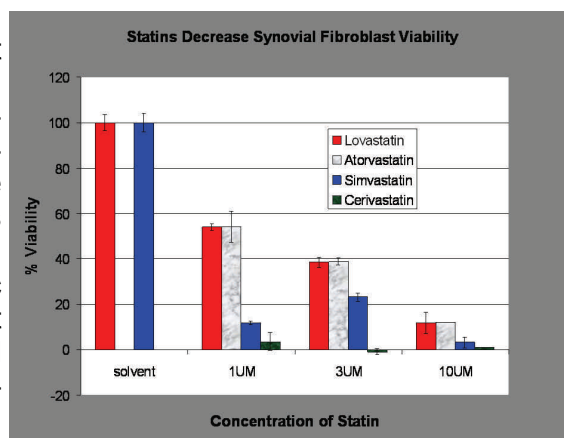


A Parenteral Formulation of Statins for Rheumatoid Arthritis And Other Inflammatory Conditions

Overview of Technology:

Rheumatoid Arthritis (RA) is a chronic inflammatory disease that causes progressive joint destruction, deformity and disability. In RA, the joint space fills up with cells of the immune system that stimulate increases fibroblast-like synoviocytes (FLS). FLS are found in normal joints however they are dramatically increased in number and activated in RA. FLS contribute to joint damage by further stimulating immune cells and releasing cartilage-damaging enzymes. In RA, FLS expand in number in part due to resistance to a normal process of cell death.

Research at UHN has demonstrated that statins, drugs that are commonly used to treat hyperlipidemia, can reverse the resistance of the FLS to cell death and 'normalize' the response of these cells. These studies indicate that statins target intracellular signaling pathways that are stimulated by the cytokine Tumor Necrosis- α (TNF- α). This property adds to previously identified anti-inflammatory effects of statins and suggests that if statins are delivered appropriately in arthritic joints, they will not only exert anti-inflammatory actions but may also act as disease modifying agents with the potential for preventing joint damage caused by activated synovial fibroblasts.



Simvastatin is an off-patent, poorly water soluble statin widely used in the treatment of hyperlipidemia. Simvastatin is particularly effective in reversing RA FLS resistance to TNF- α . The bioavailability of simvastatin in arthritic joints is limited however when taken orally due to the difficulty of achieving sufficient local doses for the time required for its effects. To address this limitation, the inventors have developed a novel liposomal formulation of simvastatin suitable for direct injection. This formulation uses a new highly efficient liposomal encapsulation technique termed Micelle-liposome exchange that was also developed by the inventors. Liposomal encapsulation increases the solubility of simvastatin more than 1,000 fold. Preliminary studies in human plasma and synovial fluid indicate excellent stability.

Related Publication:

Connor A.M., Berger S., Narendran A.,Keystone E.C.: *Inhibition of protein geranylgeranylation induces apoptosis in synovial fibroblasts. Arthritis Res Ther.* 2006;14:R94.

Patents:

PCT/CA2006/000114 - Filed Jan. 30, 2006 and US11/832,214 filed Aug. 1, 2007 (US Continuation In Part Application on statin formulations utilizing new liposomal encapsulation method).

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UHN Reference # - 6032