Stop osteoarthritis by blocking both arms of the inflammatory cycle with a novel inhibitor

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We propose a novel inhibitor molecule for posttraumatic osteoarthritis (PTOA) that follows a traumatic event to the joint. Despite current treatments, individuals who suffer a significant joint injury have a 20 to 50% risk of PTOA, causing lifelong suffering and disability, accounting for 3 billion dollars in societal expenditures. Conventional anti-TNF therapy used to treat autoimmune arthritis is NOT effective for the treatment of PTOA. Thus there is an urgent need to develop novel treatments for PTOA that can be administered by intra-articular injection. PTOA can begin with a single injury that causes an inflammatory storm involving IL-1 and IL-33 via their respective cell receptors. We propose a novel molecular therapy that simultaneously targets both arms of this vicious feedback cycle using a novel single molecule that blocks both IL-1 and IL-33 receptor signaling (both require the common IL-1RAcP accessory protein for inflammatory signaling to occur). We invented a novel technology, protein painting, and used it to create a new type of potent peptide inhibitor called Arg286p, and a monoclonal antibody, that abolish IL-1 and IL-33 interleukin signaling by blocking a specific interaction point between the accessory protein IL1RAcP and the receptor/ligand complex for both ligand/receptor complexes. We will optimize the affinity for ST2/IL33 by a) inserting a hydrophobic moiety on the tail of the inhibitor peptide to anchor it into the cell membrane and b) increasing the rigidity of the IL-1RAcP inhibitor by introducing cyclized and peptidomimetic motifs. This will create a drug-like modified peptide inhibitor based on our existing potent lead compound. The goal will be to use preclinical culture models of IL-33 signaling to test the efficacy of the optimized Arg286p, and the monoclonal antibody to shut down the inflammatory cascade. A novel cell cycle assay based on micropatterning of single cells will be developed to test the efficacy of the optimized inhibitors and antibody. If this preliminary phase is successful, the optimized inhibitors will be tested in preclinical animal models and ex-vivo human tissues. The results of this proposal will be subjects of scientific publications and communications to scientific meetings.