Engineered Atsttrin Protein Stabilizes Dysregulated Macrophage Polarization, Subsequent Osseous and Cartilaginous Tissue Remodeling in Ankylosing Spondylitis

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Therapeutic targets for Ankylosing Spondylitis (AS) pathology are non-specific, and the cellular mechanisms that drive tissue proliferation in AS are poorly understood. This study investigated the efficacy of the novel biologic Atsttrin—which specifically targets to Tumor Necrosis Factor Receptors—in an in vitro and in vivo model of AS, and determined the extent at which the efficacy of Atsttrin can be attributed to an inhibitory effect on complement system activation. Murine macrophages were cultured under varying conditions of inflammation and complement system activation, and treated with Atsttrin. A murine tissue model of AS was also established, with Atsttrin-treated (n=6), vehicle-treated (n=6), and wild type (n=2) groups. A downregulation of iNOS, a marker for M1 macrophage polarization, was found in Atsttrin-treated cartilage ($p<0.0001$), intervertebral discs ($p<0.0001$), and vertebral marrow ($p<0.01$). Treatment with Atsttrin also resulted in significantly less osteoproliferation ($p<0.01$), intervertebral disc degeneration ($p<0.05$), and cartilage damage ($p<0.01$) than with vehicle, indicating that Atsttrin may have induced limited skewing to the anabolic M2 macrophage subtype, spurring healthy tissue growth but not to an extent that AS pathology worsened. Micro computed tomography revealed administration of Atsttrin inhibited destructive changes at the vertebral endplate, and indicated that Atsttrin may help stabilize bone turnover in AS through interactions between macrophages, TGF-ß1, and BMP-2. Atsttrin emerges as a promising biologic, and the greater insight into the role of macrophages in AS pathology offered by this study may inform the design of even more targeted treatments for AS in future.

Awards Won:
Fourth Award of $500