

## **Development of a New Family of Small Molecule Therapeutics for the Treatment of Chronic Inflammation and Autoimmune Diseases**

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Periodontitis and rheumatoid arthritis share similarities as both are chronic inflammatory diseases with characteristic destruction of connective tissue and bone. Studies have identified the presence of fibroblasts and the production of cytokines such as IL-1 $\beta$ , IL-6, TNF- $\alpha$ , and MMPs as hallmarks of both diseases. Halofuginone (HF), a halogenated derivative of febrifugine, has been shown to inhibit the activation of genes and cytokines that regulate fibrosis and chronic inflammation. The goals of this study are to elucidate the mechanisms of actions of HF and its effect on various cell lines. Once the mechanisms are revealed, novel derivatives with improved therapeutic properties can be developed for the treatment of autoimmune disease, chronic inflammatory disease, and fibrosis. The effects of halofuginone on TGF $\beta$  treated and untreated groups was evaluated *in vitro* on hPDF cells using biomolecular techniques such as cell culture and treatment, quantification of mRNA by real-time quantitative reverse transcription PCR, and western blot analysis. Treatment with TGF $\beta$  resulted in an induction of profibrotic genes. Furthermore, administration of halofuginone caused a decrease in mRNA expression of the examined profibrotic genes such as COL1A1, COL4A1, p311, and FN1 and cytokines such as IL6 and COX2. This inhibitory effect on pro-inflammatory signature genes and cytokines has promising pharmacologic applicability. Dental implications for these findings include potential therapeutic applications for periodontitis and Sjogren's syndrome. Future experiments will focus studying the effect of halofuginone on additional cell lines and *in vivo* models as well as expanding the scope of the project through microarray and microRNA analysis.