Macrophage-Targeted Alginate Nanoparticles for Anti-inflammatory Gene Therapy in the Treatment of Rheumatoid Arthritis
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Purpose
To develop a safe and effective macrophage-targeted non-condensing alginate based nanoparticle system with encapsulated murine interleukin-10 (IL-10) expressing plasmid DNA for treatment of rheumatoid arthritis.

Methods
External gelation method was used to form calcium alginate nanoparticles encapsulating IL-10 plasmid DNA. Surface of the particles was decorated with tuftsin peptide (TKPR) to target receptors on macrophages. Male Lewis rats (150-170g) were inoculated intra-dermally with 0.05ml of 10mg/ml of heat-killed mycobacterium butyricum suspended in incomplete Freund’s adjuvant to induce arthritis. First signs of inflammation were observed at day 10, post-adjuvant administration. Control groups included naive rats, Arthritic rats (No treatment), Blank-tuftsin modified nanoparticles and naked plasmid DNA. Particles containing plasmid DNA (100μg dose) were administered intra-peritoneally at day 12. Rats were subjected to beam walking test to analyze animal mobility, post-treatment. All animals were euthanized at day 28 and paw tissues were excised for analysis. Histology, Serum cytokine ELISA, and qPCR were performed to evaluate features of arthritis and panel of pro- and anti-inflammatory cytokines.

Results
Optimized peptide-modified nanoparticles formed were spherical in shape with an average size of 286.6+/−1.36 nm and zeta-potential of 19+/−0.4 mV. Average percent increase in terms of paw width was reported to be between 160-180% for arthritis-induced and control treatment groups. Animals treated with unmodified nanoparticles (117.89+/−2.95%) and tuftsin-modified nanoparticles (105.26+/−1.45%) showed a significant decrease in the level of paw swelling till day 18, post-adjuvant administration (p<0.0001). However, at extended time point of day 28, a significant increase in paw width was observed in the case of unmodified nanoparticles as effect of IL-10 plasmid DNA got exhausted faster in this group as compared to tuftsin-modified nanoparticles.

Conclusion
Tuftsin-modified alginate nanoparticles containing IL-10 plasmid DNA were found to be superior in their ability to alleviate inflammation. Currently, we are pursuing studies to highlight the switch in macrophage-phenotype from classical activated M1 state to alternate-activated M2 state upon treatment.