Non-viral gene therapy approaches for osteoarthritis

Jason G. Fewell¹, Majed M. Matar², Jennifer S. Rice¹, Renwen Zhang², Khursheed Anwer¹

¹Biology and Pharmacology, Expression Genetics, Huntsville, AL; ²Orthobiologics Group, Stryker Orthopaedics, Mahwah, NJ

jfewell@egencorp.com

Introduction: Disability associated with osteoarthritis (OA) is a significant medical complication that is compounded by poor treatment options. Gene therapy may have applications for treating osteoarthritis by offering the ability to produce the local and sustainable levels of therapeutic proteins required to achieve a positive clinical outcome or to provide a mechanism whereby deleterious gene products can be inhibited (RNAi). Use of non-viral delivery vectors for gene based therapeutics may have benefits over viral based vectors by potentially allowing for multiple administrations and offering reduced safety concerns¹. Additionally, polymeric non-viral delivery systems are amenable to chemical modifications that allow for functionalized delivery systems to promote DNA protection, cellular uptake and cell targeting. Here we present work evaluating use of non-viral polymeric delivery systems for intra-articular (IA) plasmid delivery.

Materials and Methods: An initial study was performed to evaluate the ability of various polymeric-based delivery systems to promote plasmid uptake following IA administration into the rat knee. For this study female Sprague-Dawley Rats were injected (under anesthesia) IA into the right and left knees with 100 μg formulated plasmid in a total volume of 100 μl. The plasmid (pLuc) encoded for the luciferase reporter gene driven by a CMV promoter. One day following injection animals were sacrificed and tissues of the joint were harvested and analyzed for luciferase activity using a commercially available assay. Evaluation of an optimized polymer delivery system (NCPB-1) was performed in a rat model of OA². In this model OA was surgically induced by performing a medial meniscectomy along with transection of the ligaments. Following a 4 week recovery period 250 μg reporter gene plasmid (pSeAP or pGFP) formulated with NCPB-1 was injected IA two times (once/week). At the termination of the study (one day after second injection) the animals were euthanized, treated knees were harvested and prepared for immunohistological analysis using standard procedures in order to evaluate transgene expression distribution. Serum was collected for determinations of systemic SeAP expression levels.

Results: Initial studies were performed to evaluate transfection efficiencies of various polymeric-based delivery systems following IA delivery into the rat knee (Figure 1). From these studies polymer 4 and excipient 2 were selected for further evaluation and optimization studies where it was determined that a combination of these (named NCPB-1) led to the highest transfection efficiencies.

Discussion: In summary the data indicate that polymeric delivery systems may be useful for gene therapy applications in the treatment of diseases of the joint. The data suggest that long-term local and systemic transgene expression can be achieved with the ability for repeated injections which will likely be a requirement for treatment of chronic degeneration associated with OA. Future work will focus on proof-of-concept studies utilizing therapeutic genes and the further functionalization of polymeric delivery systems in order enhance uptake and to also provide additional therapeutic benefit independent of the delivered gene.


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