Background: Spinal arthrodesis is commonly performed for the treatment of degenerative spinal pathologies. Clinical outcomes may be compromised by failure of spinal fusion with non-union rates for postero-lateral arthrodesis approaching 40% in some series. In an attempt to improve fusion rates and at the same time eliminate autograft harvest problems, the use of exogenously administered recombinant growth factors to promote spinal fusion has been recommended.

Bone morphogenic proteins (BMPs) are growth factors possessing osteoinductive properties and have been reported to promote lumbar fusion in animal studies as well as in human clinical trials. Successful fusion with the use of rhBMP 2 placed inside a metal cage inserted anteriorly into the human lumbar disc space has been reported. Postero-lateral arthrodesis represents a more challenging environment for achieving fusion and direct application of rhBMPs 2 and 7 in this location have met with inconsistent success rates. Further limitations of the use of rhBMPs include the supra-physiologic doses of recombinant protein required to achieve fusion and the high cost associated with the use of this technology.

Targeted gene therapy approaches to spinal fusion may circumvent some of the difficulties and limitations associated with use of recombinant proteins. Successful spinal fusion using adenoviral delivery of osteoinductive genes has typically required expansion of delivery cells for several weeks prior to implantation, long viral transduction times, or the use of supplementary osteoinductive agents. These factors may compromise the ability to easily apply these techniques in the clinical setting.

Purpose of the study: This study was designed to determine whether postero-lateral spinal fusion can be reproducibly achieved using autogenous fresh bone marrow aspirate transduced with adenoviral vectors expressing BMP-2, BMP-6, or BMP-9 for 20 minutes.

Methods: Recombinant adenoviruses expressing human BMP-2, BMP-6, BMP-9, and green fluorescent protein (GFP) (as a control) were constructed using the AdEasy system. Skeletally mature New Zealand White Rabbits underwent postero-lateral spinal arthrodesis. The bone marrow was first aspirated from the tibia under general anaesthesia. 5cc of bone marrow aspirate (BMA) was then infected with AdBMP-2, AdBMP-6, AdBMP-9, or AdGFP (as control) (~10⁷ pfu per infection) for 20 minutes. Postero-lateral arthrodesis at two levels (i.e., L2-3; L5-6) was performed bilaterally using adenovirus-transduced autogenous BMA soaked collagen sponges (randomized for implantation levels, and 2 rabbits per treatment). Exogenous BMP production by marrow cells was confirmed by RT-PCR. Rabbits were sacrificed at 4 weeks and 8 weeks post-arthrodesis and the lumbar spines were evaluated with gross, radiographic, CT and histological examinations.

Results: In AdGFP-transduced BMA implant sites, no evidence of spinal fusion was seen at either time point. At both 4 and 8 weeks, no motion was detected with manual palpation across the levels treated with BMA-transduced with all three BMPs. X-Ray analysis revealed solid fusion across all AdBMP-treated levels at 8 weeks. Quantitative CT scans at 4 weeks confirmed robust bridging bone across the treated level with all three AdBMP constructs. Histologic analyses suggest mature "fusion masses" achieved with BMA-AdBMPs.

Discussion: In the present study, bone marrow aspirate transduced with genes expressing BMP-2, BMP-6 or BMP-9 was able to promote spinal fusion in a rabbit model. Successful fusion was achieved with ex vivo transduction of untreated bone marrow aspirate for 20 minutes without requiring prior cell expansion.

Clinical Relevance: In this study, we demonstrate the ability of bone marrow aspirates infected for clinically-relevant times with adenoviruses expressing BMP-2, BMP-6 and BMP-9 to induce spinal fusion in one month after treatment. Bone marrow aspirate has been clinically used to promote osteogenesis and contains stem cells that have the ability to differentiate along an osteoblastic cell lineage. Autogenous bone marrow aspirate is easily obtained and appears to be a promising carrier for adenoviral vectors expressing osteogenic genes to promote spinal fusion.