Synergy between living bone particles and rhBMP-2 in the healing of large segmental defects in the rat femur

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Significance
Large, segmental, osseous defects often do not heal well. Present methods in clinical use include the application of autograft bone and Infuse™, whose active ingredient is rhBMP-2. While neither of these agents alone is entirely satisfactory, the combination of the two could provide synergies that improve healing and do so more safely and at lower cost.

Introduction
Large, segmental, osseous defects remain a major clinical problem. Common approaches to healing such defects include the use of autograft bone and the application of recombinant, human bone morphogenetic protein-2 (BMP-2) in the form of Infuse™. Neither, however, is ideal. Supplies of autograft are limited and its harvest can be associated with considerable morbidity. BMP-2 is extremely expensive and its clinical performance in long bone healing is modest. Moreover, new analyses of data from the use of BMP-2 in spinal fusion suggest the potential for considerable, adverse side effects. The present study examined the potential for synergy between living bone particles and BMP-2 that, if present, could reduce the need for both autograft and BMP-2, thereby reducing costs and increasing safety. Bone particles were recovered with a device known as the “Reamer-Irrigator-Aspirator” (RIA) that recovers small osseous particles as it reams the intramedullary canal, and is increasingly used as a source of autograft.

Methods
The animal model used a 5mm, critical size, femoral defect, as described previously. Test materials were implanted into the defects and healing monitored by weekly X-ray. After 8 weeks, animals were euthanized and defects examined by micro-computed tomography (µCT), dual energy X-ray absorptiometry (DXA), histology and mechanical testing. Small particles of human bone were obtained from “reamings” recovered by the RIA. Recombinant, human BMP-2 was provided by Medtronic Inc. Initially, athymic rats were used to accept the xenografted human bone, but these animals were found to mount an immune response to human antigens. Because of this, Fischer rats were used and immunosuppressed with a combination of FK506 and SEW2871, which was found to permit xenografting without affecting bone healing under these conditions.

Results
A dose-response experiment for BMP-2 was first performed. This revealed complete healing at 8 weeks when using 11µg BMP-2, and no healing with 1µg BMP-2. A dose of 5.5 µg BMP-2 produced healing in most, but not all, animals at 8 weeks, and the weekly X-ray suggested that healing was slower than when the 11µg dose was used. Surprisingly, bone particles alone provoked little healing. However, they potentiated the actions of BMP-2. A combination of bone particles and 1µg or 5.5µg BMP-2 produced more rapid healing and greater osteogenesis as shown by µCT (figure 1). With 11µg BMP-2, the new bone was more uniform and had thicker cortices.

Discussion
Although preliminary, these data suggest that BMP-2 and living bone particles act synergistically to promote bone healing in large segmental defects in long bones. Given the wide, successful use of autograft by orthopaedic surgeons, the modest effects of bone alone are surprising. The reason for this is unknown, but our data are consistent with the hypothesis that cells within the bone respond to BMP-2 in an osteogenic fashion. The basis for the synergy would thus be the provision of osteogenic cells by the autograft and the provision of an osteogenic signal by the BMP-2. Clinically, this could translate to improved healing with reduced requirement for autografted bone and BMP-2. The reamings recovered by the RIA also contain multipotent mesenchymal cells, which provides the potential for additional osteogenic synergies of clinical relevance.

References