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CORR Insights

# *CORR* Insights®: Do Mesenchymal Stromal Cells Influence Microscopic Residual or Metastatic Osteosarcoma in a Murine Model?

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## Where Are We Now?

Osteosarcoma is the most common malignant bone tumor, particularly frequent in childhood during skeletal growth. Major incidences of osteosarcoma can be found in the appendicular skeleton [4, 14]. Although a patient's prognosis improves significantly when osteosarcoma is localized, treatment in all cases requires the removal of the primary tumor, resulting in large bone defects, and sometimes, amputation [10]. When limb savage is possible, allografts often are used to help repair large bone defects. However, adjuvant chemotherapy combined with the critical size of the bone defects, frequently result in complications of the regenerative process, including infection, nonunion, and allograft failure [2].

Through their differentiation capacity into chondrocytes and osteoblasts, as well as paracrine properties, mesenchymal progenitor cells (MSCs) offer therapeutic potential for the treatment of complex bone fractures and nonunion, whether used in combination with allografts or biomaterials or through systemic infusions [5, 7]. However, important safety concerns remain. High-grade osteosarcoma can metastasize to the lungs; when this occurs, survival decreases dramatically. Previous studies [3, 9, 11] have shown that when implanted or systemically infused, MSCs could target osteosarcoma and other tumor cells, promoting its growth and metastatic potential. Therefore, before exploring their therapeutic potential, the role of MSCs on pulmonary metastasis progression and local recurrence of osteosarcoma needs to be clarified.

## Where Do We Need To Go?

While several animal models have been developed, there is a lack of standardization and important differences exist regarding the presence of primary tumor, used osteosarcoma cell lines, and spontaneous metastasis versus direct implantation of the

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osteosarcoma cells in the lungs [3, 9, 11]. As a result, comparison of results from different groups has been difficult. Therefore, the question of whether MSCs activate metastasis remains unanswered. Here, Aanstoos and colleagues developed an orthotopic model of residual osteosarcoma and evaluated the role of adipose tissue-derived MSCs (AD-MSCs) in pulmonary metastasis and in recurrent residual osteosarcoma. This model is sound on many levels. First, the orthotopic model more accurately reflects the interactions of MSCs with osteosarcoma cells in the environment where the residual tumor develops. Previous models assessed MSCs-osteosarcoma interactions in the presence of the bulk tumor, hindering clinical extrapolations since MSCs would be infused or implanted after the primary tumor has been resected. Second, the model by Aanstoos and colleagues possesses spontaneous metastasizing capacity. While previous models demonstrated that MSCs enhanced metastasis growth, the approach was based in tail vein infusion of tumor cells together with MSCs, resulting in accumulation of both cell types in the lungs—a condition difficult to find in a clinical setting. The model by Aanstoos and colleagues has the potential to more accurately answer whether MSCs truly trigger metastasis or accelerate the growth of metastases.

## How Do We Get There?

With the model presented here, Aanstoos and colleagues showed that local recurrence was not affected by AD-MSCs, neither when systemically infused nor when implanted in the resection tumor site. Although infused AD-MSCs do not increase the number of metastasic foci in the lungs, it is noteworthy that there was a shortening in lung metastasis detection time. Nevertheless, whether systemic infusion of MSCs will be clinically valuable remains unknown, especially since there is evidence that the regeneration potential of infused MSCs is only modest, and engraftment limited even in rodent models [6]. On the other hand, direct implantation of MSCs is a much more promising alternative, and Aanstoos' results in this regard are truly encouraging. Still, further confirmation will be needed, which should take the form of increasing animal numbers using both routes of administration, as well as through replication by other research groups. Other questions remain including whether the origin of the MSCs may modify the osteosarcoma cells behavior and change outcome. Bone-marrow-derived MSCs are widely used in bone regeneration approaches, and several authors postulate that periosteum may contain MSC populations more suitable for bone tissue engineering purposes [1, 8, 12, 13]. The model and results in the current study may trigger interesting studies that examine the further use of MSC-based therapies such as critical size defects models of nonunion.

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