

**Title:** Primitive adult hematopoietic stem cells can function as osteoblast precursors

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## Abstract

Osteoblasts are continually recruited from stem cell pools to maintain bone. Although their immediate precursor is a plastic-adherent mesenchymal stem cell able to generate tissues other than bone, increasing evidence suggests the existence of a more primitive cell that can differentiate to both hematopoietic and mesenchymal cells. We show here that the "side population" (SP) of marrow stem cells, defined by their ability to rapidly expel a DNA-binding dye and to regenerate the hematopoietic compartment, can differentiate to osteoblasts through a mesenchymal intermediate. When transplanted into lethally irradiated mice, single gene-marked murine SP cells reconstituted depleted osteoprogenitor pools, such that a large proportion of the osteogenic cells in the epiphysis of long bone carried the donor SP cell marker. These findings suggest that the developmental capacity of SP cells is not restricted to the hematopoietic lineages but extends to osteogenic differentiation. This property not only elucidates a previously unrecognized step in osteoblast development, but also has intriguing implications for the use of SP cells in clinical orthopedics and stem cell-based disorders of bone.