

# Therapeutic Angiogenesis Using Autologous Bone Marrow Stromal Cells: Improved Blood Flow in a Chronic Limb Ischemia Model

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*Background.* We evaluated the effect of autologous marrow stromal cells (MSCs) on neovascularization and blood flow in an animal model of chronic limb ischemia.

*Methods.* Chronic hind limb ischemia was created by ligating the left common iliac artery of male Lewis rats. Three weeks after ligation, 5.0 million LacZ<sup>+</sup>MSCs (n = 10) or culture medium (n = 10) were injected into the anteromedial muscle compartment of the left thigh. At 4 and 6 weeks after injection, half the animals (n = 5) from each group underwent femoral artery ultrasonic blood flow measurements of the ischemic and nonischemic limbs to obtain a flow ratio. The animals also underwent angiography and measurements of blood vessel density and arteriolar density. Qualitative histologic assessment of the limb muscles was performed.

*Results.* LacZ<sup>+</sup>MSCs were found to differentiate into endothelium (F VIII<sup>+</sup>), vascular smooth muscle (positive  $\alpha$ -smooth muscle actin), skeletal muscle (positive

desmin), and adipocytes. Ischemic hind limbs where MSCs were implanted had greater vascular density and arteriolar density than control limbs ( $p < 0.001$ ). Femoral artery flow index (left femoral artery flow/right femoral artery flow) was  $0.89 \pm 0.12$  and  $0.90 \pm 0.06$  for rats injected with MSCs measured at 4- and 6-weeks, respectively, compared with  $0.50 \pm 0.15$  and  $0.50 \pm 0.10$  for the control rats ( $p < 0.001$ ). Angiography demonstrated reconstitution of the left femoral artery in rats that received MSC implantation through pelvic and abdominal wall collateral formation.

*Conclusions.* Local MSC implantation induces a neovascular response resulting in a significant increase in blood flow to the ischemic limb. Marrow stromal cells are also capable of spontaneously regenerating the various components of muscular tissues.

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