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Commentary

# Tracking Cells Without Leaving a Trace

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Despite the many advantages of cell therapy for regenerative medicine, one limitation of cellular transplantation is the inability to track the cells and determine if the cellular graft is retained and functioning. For metabolic liver diseases, an improvement of the patient's clinical condition is used as surrogate markers of the presence and continued function of donor cells. However, independent verification of the presence of donor cells is needed, especially in cases where rejection is suspected. Because many liver functions are suppressed in the presence of viral or bacterial infection and the associated cytokine release, it may be impossible to distinguish temporary suppression of cell graft function from symptoms of graft loss due to rejection without invasive procedures such as biopsy. In the this issue of *Cell Medicine*, Raschzok et al. (7) have approached the issue of cell tracking in a large-animal (swine) model. They report the successful noninvasive monitoring of cell presence using magnetic resonance imaging. The authors report the labeling of hepatocytes with micron-sized iron oxide particles (MPIO) that could be followed out to 8 weeks posttransplantation. In addition to assessing sensitivity and the longevity of the cell graft, the tracking technology was used to identify the most efficient routes of cell administration. Some wrinkles remain to be ironed out, however, as the agent used for the current studies is not approved for clinical application.

Labeling and tracking their location following transplantation is an active area of research. Choi et al. (3) previously reported the use of bioluminescent imaging techniques to track and locate hepatocytes transplanted into mice. However, the bioluminescent techniques, as currently practiced, may not work on larger animals or human subjects and the procedure requires transfection or infection with viral vectors that may not be compatible with clinical protocols. Recent studies determined that human embryonic stem cells could be labeled with an FDA-compatible reagent, indocyanine green, and later visualized with optical imaging technology (1). Those very preliminary studies only imaged the cells in culture. Additional studies will be needed to determine if this technology can be translated to in vivo conditions. Puppi et al. (6) reported that hepatocytes could be labeled with clinically approved superparamagnetic iron oxide nanoparticles (SPIOs) and tracked to the liver of a mouse following transplantation. It is not known if this technology could be translated to larger animals or humans. There are also concerns for the affect of iron particles on the viability and function of the target cells. Schafer et al. (8) and Nohroudi et al. (5) reported that labeling mesenchymal stromal cells with iron particles adversely affected cell function and migration, which in one case led to an increase in disease severity (8). Later studies by Crabbe et al. (4) showed that safe and effective concentrations of clinically approved SPIO nanoparticles could be identified that allowed MRI-based visualization of transplanted mesenchymal stem cells while not affecting cell viability, migration, or differentiation potential.

Although the studies of Raschzok et al. (7) are only preclinical and have used reagents that are not clinical grade in their present form, the studies have shown proof of concept with large animals. At present, the only application of hepatocyte labeling and tracking of the hepatocytes following transplantation in an actual clinical procedure was that described by Bohnem et al. (2) more than 10 years ago, using indium 111 oxyquinolone solution. Although a protocol providing sufficient sensitivity for clinical procedures has not been achieved in any of these more recent studies with SPIOs, the success at each level suggests that, with modification, this technology might one day be useful to track donor cells in real time following transplantation.

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