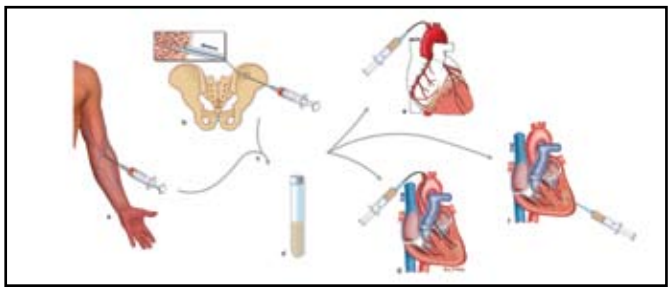
Cell Therapy: Current State and Future Directions

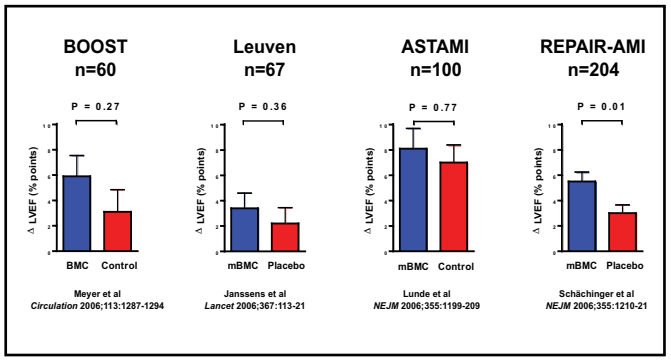
Bone marrow cells (BMCs) have the potential to differentiate into heart cells through a process called transdifferentiation. BMCs can be harvested either indirectly from the peripheral blood or directly through bone marrow aspiration and then administered in the heart via catheter-based intracoronary or intramyocardial injection during open heart surgery, or through retrograde coronary venous delivery (Figure 1).

Figure 1. Cell Harvest and Administration.



Ketil Lunde, MD, Rikshospitalet University Hospital, Norway, shared his thoughts on BMC studies conducted to date in acute myocardial infarction (AMI). Four recent trials investigating the effect of BMC administration on left ventricular ejection fraction and cardiovascular events in patients with AMI were reviewed (Figure 2). In all four trials, the efficacy of BMCs in improving ventricular function and preventing reinfarction or revascularization was modest. Dr. Lunde offered several explanations for the unsuccessful results observed with this therapy so far.

Figure 2. Results on LVEF in Clinical Trials with Bone Marrow Cells in AMI.



First, only a relatively small number of BMCs were transplanted to the heart using this technique, compared with the extent of cell damage in an AMI. The left ventricle of the heart contains roughly 5 billion cardiomyocytes, whereas only approximately 200 million BMCs were infused with progenitor cell treatment (Assmua. *NEJM* 2005). It is therefore possible that there may not be enough cells infused to repair the cellular damage. Second, research suggests that many of the transplanted BMCs are trapped in the lungs, while few remain in the heart (Hou et al. *Circulation* 2005); thus, transplanted BMCs might not be migrating to the location of injury. In Dr. Lunde's opinion, the technology is still in its infancy, and many methodological questions remain unanswered, such as the best cell types for transplantation, how to improve homing and engraftment of these cells, the best route of administration, and the ideal timing of administration.

Scott Solomon, MD, Harvard Medical School, Boston, MA, elaborated on the future of cell therapy research. "The solutions that we engineer will have to overcome enormous hurdles, namely, that up to a billion myocytes are lost in a typical myocardial infarction within hours. No matter how promising the therapy we consider, this is an overwhelming burden to overcome," cautioned Dr. Solomon. Echoing Dr. Lunde's comments, Dr. Solomon agreed that the optimal cell type, dose, and timing are yet to be determined. Skeletal myoblasts harvested from gluteal muscle, mesenchymal stem cells, resident cardiac stem cells obtained from biopsies, as well as embryonic stem cells, are possible candidates for cell therapy investigation. The choice of endpoints to be used in the studies will also be critical. "We tend to pick surrogate endpoints that we are most comfortable with, rather than the ones that make the most sense for the therapy. For example, a therapy that improves regional function substantially may only improve ejection fraction minimally," said Dr. Solomon. It is possible that the small number of subjects, inherent biological variability, and imprecision in measurements have led to somewhat random results in the trials conducted thus far. The traditional partnership between industry and academia that has brought cardiovascular therapies forward in the past may not be viable in the cell therapy arena due to uncertain intellectual property issues. In his closing remarks, Dr. Solomon called for creative funding mechanisms in order to continue this important research. "Far more public support will be needed for this field to mature," concluded Dr. Solomon.