STEM CELLS TRANSLATIONAL MEDICINE®

PREVIEWS

Previews highlight research articles published in the current issue of STEM CELLS TRANSLATIONAL MEDICINE, putting the results in context for readers.

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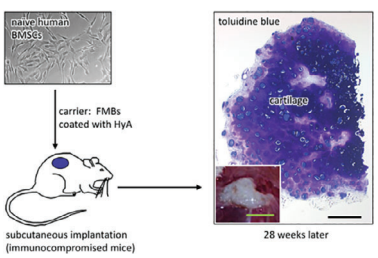
Cartilage covers and protects the ends of the long bones and plays a major structural role in multiple body components. Loss of or damage to cartilage can lead to the onset of conditions such as osteoarthritis, where the continual thinning of articular (a subset of hyaline) cartilage produces unwanted bone-on-bone contact within the joint, leading to pain and reduced motion. While we lack the endogenous healing capacity to fully recover from cartilage damage, the efficacy of current medicinal and surgical approaches also remains low [1]. Furthermore, we also lack a relevant supply of donor cartilage-producing chondrocytes for advanced tissue engineering approaches. However, studies have demonstrated that human bone marrow-derived mesenchymal stem cells (BM-MSCs) can differentiate into a spectrum of skeletal tissues, including cartilage [2], suggesting that transplantation of BM-MSCs into affected areas may promote cartilage defect repair given appropriate support. However, no protocols currently exist for the efficient in vivo generation of functional hyaline cartilage by BM-MSCs [3]. As an alternative approach, the secretion of protective, immunomodulatory, and regenerative factors by MSCs following transplantation has the potential to enhance previously unviable surgical approaches, such as the transplantation of allogeneic chondrocytes for cartilage defect repair. In our first Featured Article from *Stem Cells Translational Medicine* this month, Kuznetsov et al. provide the first in vivo demonstration of stable cartilage formation by human BM-MSCs, thanks to the support of fibrin microbeads coated with hyaluronic acid acting as a scaffold [4]. In a Related Article from *Stem Cells*, de Windt et al. report on a successful phase I trial that tested the one-stage application of allogeneic MSCs mixed with recycled defect-derived autologous chondrons for the treatment of cartilage defects [5].

Neutrophils are a type of phagocyte typically found in the bloodstream and are a vital component of the defense system against infection in humans. In patients undergoing stem cell transplantation or intensive chemotherapy, low levels of neutrophils (neutropenia) represent a significant risk for life-threatening bacterial and fungal infections. As treatment with broad-spectrum antibiotics and colony-stimulating factors still suffer from a 20% mortality rate in neutropenic patients, animal trials have begun to test neutrophil transfusions as a means to resolve infections, with some very encouraging results already reported [6, 7]. However, neutrophil transfusions used to treat infection in human neutropenic patients will require massive numbers of cells per kilogram body weight according to studies in infants [8] and another prospective randomized study [9]. Can the differentiation of neutrophils from induced pluripotent stem cells (iPSCs) provide the substantial number of neutrophils required for transfusions? In our second Featured Article from *Stem Cells Translational Medicine* this month, Trump et al. provide proof-of-concept for the efficient differentiation of human iPSCs into neutrophils that phagocytose bacteria in vitro and in vivo [10]. In a Related Article from *Stem Cells*, de Witte et al. tracked MSCs following intravenous infusion, discovering that monocytes, another phagocytic cell type with crucial roles in the immune system, engulf MSCs in the lungs and then migrate to other body sites to mediate, distribute, and transfer the immunomodulatory effect of MSCs [11].

## FEATURED ARTICLES

### First In Vivo Demonstration of the Formation of Stable Human Mesenchymal Stem Cell-Derived Cartilage




Current strategies employing human BM-MSCs as a means to regenerate cartilage and treat conditions such as osteoarthritis normally induce cells into a chondrogenic phenotype before transplantation in the hope of the formation of endogenous-like cartilage in vivo; however, these studies have failed to provide encouraging results [12]. Now, researchers from the laboratories of Pamela G. Robey (National Institute of Dental and Craniofacial Research, Bethesda, Maryland, USA) and Raphael Gorodetsky (Sharett Institute of Oncology, Jerusalem, Israel) have devised a novel strategy to generate high-quality cartilage from BM-MSCs. In their new *Stem Cells Translational Medicine* article, Kuznetsov et al. report the first demonstration of abundant,

hypertrophy-resistant, ectopic hyaline-like cartilage formation following subcutaneous implantation of undifferentiated (naïve) human BM-MSCs into immunocompromised mice [4]. For this feat, the authors attached BM-MSCs to a specialized scaffolding material—dehydrothermally crosslinked stable fibrin microbeads covalently coated with hyaluronic acid (HyA). Previous reports demonstrated that anchorage-dependent cells such as BM-MSCs bind tightly to a fibrin matrix, inspiring the development of dense fibrin microbeads as a scaffolding material [13]. Encouragingly, analysis of BM-MSC-derived cartilage tissue proved its human origin, and for the first time, the study reported long-term cartilage stability in vivo. Overall, the authors believe that this new strategy holds great promise for the restoration of damaged cartilage in human patients.

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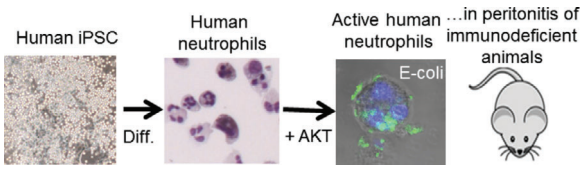
## Engineered iPSC-Derived Neutrophils: A New Treatment Option for Neutropenic Patients?




The differentiation of patient-specific iPSCs into neutrophils [14] may provide the vast number of cells required for this potentially exciting approach to neutropenia treatment. To this end, researchers led by Jose A. Cancelas and Carolyn Lutzko (Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA) recently reported on the comparative activity of engineered iPSC-derived neutrophils in the hope that they will represent an important future resource for transfusion purposes. In their recent *Stem Cells Translational Medicine* article, Trump et al. first reprogrammed peripheral blood mononuclear cells into iPSCs and then generated neutrophils from iPSC-derived hematopoietic cells. Interestingly, the authors discovered that while their iPSC-derived neutrophils produced reactive oxygen species at a similar level to normal peripheral blood neutrophils, they displayed a significant reduction in the phagocytosis of *Escherichia coli* (*E. coli*) bacteria and the induced formation of neutrophil extracellular traps [10]. Subsequent analysis suggested that impaired AKT (protein kinase B) activity in iPSC-derived neutrophils prompted these functional discrepancies, although the expression of a constitutively activated AKT restored most phagocytic activity and neutrophil extracellular trap formation. Furthermore, AKT-corrected iPSC-neutrophils migrated to the peritoneal fluid in an analogous manner to peripheral blood neutrophils in a model of bacterial-induced peritonitis in immunodeficient mice and displayed robust phagocytic activity. Overall, the authors anticipate that their new engineered iPSC system will supply the large number of functional neutrophils required for future applications as a treatment strategy in neutropenic patients.

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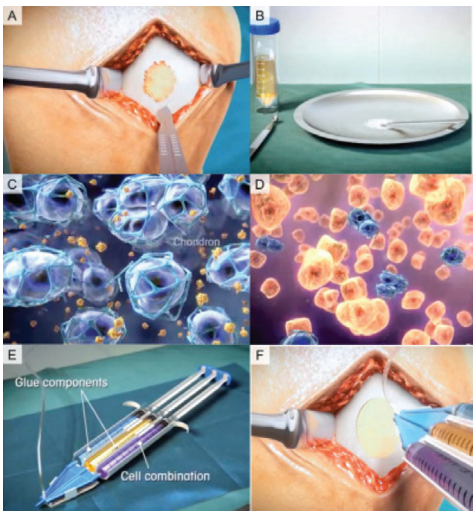
### Related Articles

## First-in-Man Trial Suggests Safety and Efficacy of Allogeneic MSCs for One-Stage Cartilage Regeneration




Previous research from the laboratory of Daniel B. F. Saris (University Medical Center Utrecht, The Netherlands) demonstrated safety and efficacy in preclinical [15] and early clinical [16] studies using the investigator-driven Instant MSC Product accompanying Autologous Chondron Transplantation (IMPACT). Their subsequent research, published in *Stem Cells*, provides a comprehensive description of a completed first-in-man trial with 18 months follow-up [5]. The trial assessed the one-stage application of allogeneic MSCs mixed with 10%/20% recycled defect-derived autologous chondrons (the chondrocyte and its pericellular microenvironment) for the treatment of cartilage defects in 35 patients. The trial failed to report any treatment-related serious adverse events, but the authors did observe significant improvements in clinical outcomes. Furthermore, magnetic resonance imaging and second-look arthroscopies revealed consistent newly-formed cartilage tissue, while biopsies from the center of the repaired tissue displayed hyaline-like features with a high concentration of proteoglycans and type II collagen. Interestingly, DNA short tandem repeat analysis revealed that the regenerated tissue held patient DNA only, suggesting that MSCs stimulated a regenerative host response via the release of paracrine acting factors and cellular communication instead of differentiating toward a chondroprogenitor-like fate. Overall, the results of this trial demonstrate the safety and efficacy of allogeneic MSCs for human use and one-stage cartilage regeneration without the need for cell grafting, which could lead to a cost-effective approach when compared with the other cellular cartilage repair therapies.

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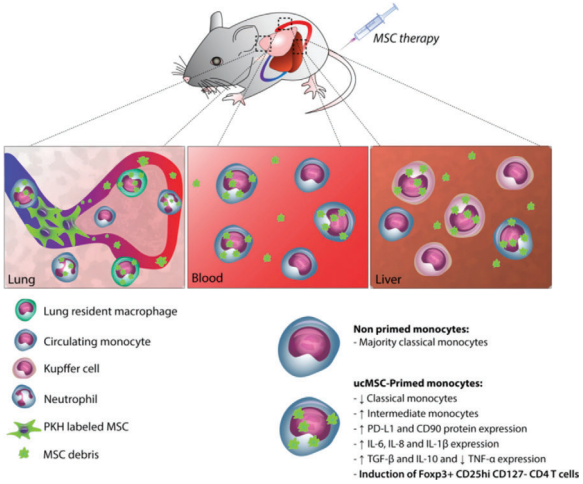
## Phagocytosis by Monocytes Promotes Immunomodulation Following Mesenchymal Stem Cell Infusion




While the ability of MSCs to modulate the immune system is readily apparent, their mechanism of action following administration has generally remained something of a mystery [17]. Systemically infused MSCs generally become trapped in the microvasculature of the lungs and are generally lost within 24 hours [18]; however, this does not interfere with their long-lasting effectiveness. To examine the mechanisms determining the fate of infused MSCs and the associated immunomodulatory response, researchers led by Martin J. Hoogduijn (Erasmus MC, Rotterdam, The Netherlands) tracked viable and dead umbilical cord blood-derived MSCs post intravenous infusion in a mouse model [11]. Writing in *Stem Cells*, de Witte et al. discovered that viable MSCs appeared in the lungs soon after infusion; however, within the next 24 hours, all cells had died and were discovered contained inside monocytes displaying an anti-inflammatory phenotype. While these monocytes were generally spread throughout the body, they exhibited a significant enrichment in the lungs and liver. To confirm these finding, the authors moved to in vitro analysis, establishing that monocytes became polarized to an anti-inflammatory phenotype following phagocytosis of MSCs and displayed the ability to induce Foxp3+ regulatory T cell formation in mixed lymphocyte reactions. Therefore, the authors suggest that the phagocytosis of MSCs by monocytes and their subsequent migration and induced phenotypic alteration can modulate the activity of cells of the adaptive immune system, thereby mediating, distributing, and transferring the immunomodulatory effect of MSCs.

DOI: 10.1002/stem.2779

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