

CELL THERAPY FOR BONE REPAIR: NARROWING THE GAP BETWEEN VISION AND PRACTICE

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Abstract

This position paper summarises a vision of how cell-based therapies can be applied clinically to regenerate bone, as well as the steps needed to narrow the gap between that vision and clinical reality. It is a result of the presentations and discussion of the “Cell Therapy for Bone Repair” breakout session at the AO Foundation Symposium “Where Science Meets Clinics” in Davos, Switzerland from September 5-7, 2013. Participants included leaders from science, medicine, and industry from around the world. The session included clinical and scientific presentations, as well as an extended discussion among participants. Bone tissue has an innate regenerative capacity that in most cases allows functional healing at damage sites. However, there are a number of serious conditions in which bone does not fully heal and the result is significant morbidity. The clinical need for new therapies is clear, and the breakout session participants were enthusiastic about the potential impact on cell-based therapies for bone repair in the clinic. However, they also recognised the significant challenges that face the development of commercially viable cell therapy products. This paper outlines a vision in which patient selection is based on expected therapeutic outcome to create a consistently successful, cost-effective, cell-based therapy for bone repair. The need for a more complete understanding of bone repair, a better infrastructure for preclinical studies, and the need for collaboration among stakeholders is discussed.

Keywords: Bone grafting; bone tissue engineering; cell transplantation; progenitor cells; non-unions; osteonecrosis; spinal fusion.

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Introduction

Bone has a remarkable regenerative capacity following injury, characterised by a tightly orchestrated sequence of events involving a number of cell types. In most cases, bone fractures do heal and the resulting repair tissue has structural and functional properties similar to the original tissue. However, there are conditions in which bone healing is impaired or incomplete. Reconstruction of large bone defects created by trauma, infection, or tumour resection is challenging because of the large volume of tissue required for complete healing. These cases are relatively small in number, but are associated with significant morbidity and clinical impact. In addition, conditions such as atrophic non-unions, avascular necrosis, and recalcitrant spinal fusions are characterised by an impaired bone healing environment. Such complex and challenging clinical scenarios often require interventions to promote complete healing and prevent complications.

Only cells can make bone, and therefore there has been an increasing interest in augmenting the healing process through the recruitment or addition of bone-forming cells to the wound site. Enhanced mobilisation and homing of endogenous cells is one approach to increasing wound site cellularity, but has not been explored extensively in the clinic. A potentially more direct approach is the transplantation of cells or tissue to fill the defect with a bone-forming material. While distraction osteogenesis is the treatment of choice for very large defects and septic non-unions, the “gold standard” for many small and medium defects and for aseptic non-unions remains autologous bone grafting. Living bone grafts have a mixture of cellular components involved in bone formation, including differentiated osteoblasts, as well as an appropriate matrix of cancellous bone. However, the limited availability of grafting material and morbidity at the donor site has spurred the development of tissue engineering approaches to bone regeneration. In most cases these approaches combine progenitor cells and/or growth factors with a scaffold material to mimic the function of a bone graft.

Cell-based therapies for bone repair have now reached the stage of human trials for a number of indications. Transplantation of marrow suspensions as well as purified progenitor cell populations has been explored. In a study on percutaneous delivery of concentrated marrow for the treatment of atrophic diaphyseal non-unions, it

was found that union was achieved in 53 of 60 patients and that the efficacy was positively correlated with the number of progenitor cells in the graft (Hernigou *et al.*, 2005). A review of tissue engineering approaches in seven human trials focused on bone defect healing found that transplantation of purified mesenchymal stem cells in combination with scaffolds was generally associated with bone formation at the implant site, but was usually not sufficient to bridge large defects (Chatterjea *et al.*, 2010). A trial using *ex vivo* expanded bone marrow mesenchymal stem cells for the treatment of early stage osteonecrosis in the femoral head showed that cellular treatment improved outcomes at five years, compared to core decompression (Zhao *et al.*, 2012). A more recent study using skeletal stem cells in combination with decellularised allograft for the treatment of avascular necrosis in the femoral head resulted in three patients remaining asymptomatic at 22- to 44-month follow up, and retrieval of tissue from a fourth implant showed regeneration of mature bone (Aarvold *et al.*, 2013). Spinal fusion in humans has also been performed using cellularised transplants. A study of posterior spinal fusion in 41 patients using peri-operatively enriched autologous mesenchymal stem cells and a tricalcium phosphate matrix produced a 95 % fusion rate (Gan *et al.*, 2008). Cellular allograft bone matrix has also been used in a trial of 40 patients undergoing extreme lateral interbody fusion, and showed complete fusion in 90 % of cases (Tohmeh *et al.*, 2012).

While initial clinical trials of cell-based therapies for bone repair have shown promise in key indications, there is a great need for further development of improved therapies. There is a wide range of possible progenitor cell sources that have been shown to be able to produce osteoblasts, including embryonic stem cells, induced pluripotent stem cells, and adult stem cells derived from marrow, muscle, fat, periosteum, perivascular tissue, and blood. In addition, a large number of matrix and scaffold materials have been developed for delivery of cells to bone defects. These materials can have various influences on bone regeneration, including being osteoconductive, osteopromotive or osteoinductive. Combinations of cells and materials have been tested in a variety of small animal models in both orthotopic and ectopic sites. Comprehensive studies in large animal models are less common, and it has proven a challenge to translate experimental results from small to large animal studies. In particular, there are key differences in mechanics and vascularity between small and large animals. Further complicating the conception of new therapeutic approaches is the fact that animal models do not fully or accurately reflect the clinical scenario, since they are different both in terms of anatomy and aetiology of the defects (Mills and Simpson, 2012).

The development of commercial products based on cellular therapies has progressed. However there are significant barriers to overcome in order for these products to reach the market. Scale-up and GMP manufacturing of human cell-based therapies remain challenging, though the field has renewed its efforts to improve bio-manufacturing. Safety concerns, including tumour risk, are also not fully resolved and are particularly relevant to approaches involving totipotent progenitor cells. The heterogeneity

observed in response to some treatments has made it difficult to definitively prove efficacy of a therapy and has made patient selection and treatment-matching key issues. These challenges contribute to the regulatory burden that must be overcome in order to bring a product to market. In addition, new therapies must not only be effective, but must show a favourable cost-benefit profile in order to gain reimbursement and market acceptance.

In spite of the challenges that face cellular approaches to bone repair, the field has tremendous potential and it is likely that there are some conditions that will only be fully addressable using a cell-based therapy. In an effort to better define the challenges in the field and the path to making such therapies a broad clinical reality, the AO Foundation sponsored a symposium entitled “Where Science Meets Clinics” in Davos, Switzerland from Sept 5-7, 2013. The sections below summarise the discussion between participants in the “Cell Therapy for Bone Repair” breakout session at that meeting. The group was tasked with describing a vision for the field of cell-based bone repair, as well as with outlining the measures that need to be taken to narrow the gap between vision and practice. Approximately 40 scientists, clinicians, and industrial representatives attended the breakout discussion, and their input has been condensed below.

Summary of Breakout Session

Vision for the field

A main component of the breakout panel’s vision for cell-based therapies for bone repair was a clearer and more specific definition of the scope of the clinical problems that can be addressed using this approach. In particular, there is a need for criteria that can be used by the clinician to identify cases in which cell-based therapies are warranted. Cell-based therapies that are currently being developed will require solid justification in order to be used in place of conventional treatment options.

In addition, to better define the clinical problems that are amenable to cell-based approaches, the discussants included in their vision an improved ability to predict patient outcomes and to match therapies based on patient backgrounds and histories. This component of the vision was influenced by recent advances in personalised medicine, since some of these concepts may also be applied to cell-based therapies. If patient identification and selection are improved, it was felt that cell-based therapies can have a clinical impact on the treatment of complex pathologies such as large bone defects, recalcitrant non-unions, osteochondral injuries, and bone injuries complicated by age, diabetes and/or smoking.

The overarching vision of the clinicians and researchers in the breakout session was to produce a consistently effective therapy that decreases morbidity, while also being cost effective and marketable in the current regulatory and business environment. It has been suggested that any new therapy will need to be at least as effective, and preferably less costly, than autogenous bone grafting, which is currently widely used to enhance bone repair. While cell therapies have the potential to meet this challenge, there

are significant technical, regulatory, and policy hurdles that will need to be addressed before this vision can be achieved.

There was consensus among the breakout session participants that a key part of the field's future requires the generation of a more complete knowledge of how wounds heal in general, and more specifically how musculoskeletal tissues heal. The key processes of inflammation and immunity must be more rigorously understood in order for cell-based therapies to have consistent beneficial effects. Interactions between host cell types in the wound, as well as their interactions with transplanted cells, must be characterised and controlled. Overall, the group agreed that a deeper mechanistic understanding of bone healing will be needed to bring cell-based therapies more broadly to the clinic.

While acknowledging the challenges that face the creation of new, broadly used cell therapies for bone repair, the breakout session participants also recognised that our field has made important progress over the past decade. There is a need to integrate the latest high quality research with what is being practiced in the clinics, so that these scientific advances can have a therapeutic impact. A greater degree of flexibility on the part of regulatory bodies and clinical practitioners may be needed to ensure that new technology is adopted and reaches the patient.

Narrowing the gap between vision and practice

When discussing the steps needed to narrow the gap between our vision for the field and its translation into clinical practice, the session participants returned again to the need for a more defined scope of the clinical bone repair problems that can be addressed by cell-based therapies. They also reiterated that better ways of identifying and selecting patients must be developed, so that outcomes can be predicted and clinical benefit will be more consistent. The discussion also returned to the need for a better understanding of bone pathophysiology, and the mechanisms by which bones do (or do not) heal. It was noted that it is not necessarily required to mimic nature in a clinical treatment, but understanding the natural process will certainly provide guidance on the development of more effective therapies.

The discussants emphasised the need to adopt the latest advances in science when developing cell-based therapies. Investigators are still unravelling the complex processes involved in wound healing. As scientific advances are made, they need to be applied to improving the effectiveness and consistency of cell-based approaches, which ultimately must be translated to clinical practice. The breakout session participants mentioned the advantages of learning from the pharmaceutical industry on how to screen and develop therapeutic approaches.

There is a need for improved infrastructure to advance the development of cell-based therapies for bone repair. Better and more standardised animal models are needed to aid in comparison of results across studies. Stronger clinical research networks would also enable better data sharing and more informed clinical trial design. The discussants also mentioned the need for better access to cell production facilities that meet the current Good Manufacturing

Practices (cGMP) guidelines, which represents a current bottleneck in larger scale cell cultivation.

Overall there was consensus across disciplines that the complexity of bringing cell-based therapies to the clinic will require close collaboration between clinicians, scientists, funding agencies, and the biomedical industry. Each of these stakeholders possesses a different perspective on development of a new therapy, and each must be considered in order to successfully create a new clinical therapy. In addition, policy makers and consumers must be properly educated on the risks and benefits of new cell-based approaches, so that they have an appreciation of what the field is trying to accomplish.

Conclusions and Perspectives

The discussions at the 2013 AO Symposium were forthright and productive. The participants were enthusiastic about the potential impact of cell-based therapies on the clinical treatment of bone defects, but also acknowledged the significant amount of preclinical development and clinical testing that needs to be done to bring such products into broad use. The overarching vision of the field is to create therapies that are consistently more successful than current treatments, while also being cost effective and marketable. A key component of this vision is to better identify which clinical indications are best suited for treatment with cell-based therapies, and the ability to select patients based on expected outcomes. To achieve these goals, scientists and clinicians need a more complete understanding of the biology and physiology of bone healing, in particular the processes of inflammation and immunity. The infrastructure and standardised models needed for performing complex preclinical studies must be improved. In parallel, clinicians and regulatory bodies must be prepared to help move new scientific advances to the clinic, and the biomedical industry must have the information it needs to develop competitive products. Achieving the potential of cell-based approaches will require the active participation of scientists, clinicians, funding agencies, regulatory bodies, policy makers, and the biomedical industry.

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The abstracts from this meeting are available at:
<http://www.ecmjournal.org/journal/supplements/vol026supp08/AO13.htm>

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Editor's Note: All comments/questions by the reviewers were answered by making changes in the text. There is hence no Discussion with Reviewers section.