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NEWS

Moving stem cell therapies into the orthopedic clinic: what will it take?

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Recent *IBMS BoneKEy* webinar focused on funding, regulatory and scientific hurdles

Stem cells are prized throughout biology and medicine for their capacity of self-renewal and their ability to differentiate into many different cell types. Those unique properties make stem cells particularly appealing for efforts to treat disease and heal injury. In the bone and orthopedics fields, stem cells could have therapeutic utility in a number of settings, including knee, hip and spine surgeries, complex fracture repair, simple fractures, oral and plastic surgeries, genetic bone diseases like osteogenesis imperfecta, osteoporosis and rheumatoid arthritis.

Despite this promise, three main types of challenges—research infrastructure-wise, regulatory and scientific—confront the successful development of stem cell therapies for bone repair and regeneration. Such was the message delivered by William Hill (Georgia Health Sciences University and Charlie Norwood VA Medical Center, Augusta, GA, USA) during 'The Use of Stem Cells for Bone Repair and Regeneration: Dream or Reality', a recent *IBMS BoneKEy* webinar (http://www.nature.com/bonekey/webinars/index.html?key=webinar14). The nature of those challenges, and how they might be overcome, were the focus of Dr Hill's presentation, as well of an interdisciplinary expert panel discussion moderated by Serge Ferrari (Geneva University Hospital, Switzerland), *BoneKEy* editor in chief. The webinar offered no easy or quick solutions to move stem cell treatments for bone repair/regeneration into the clinic; progress is needed on all three fronts. In the meantime, experts are worried that a number of unproven stem cell therapies, promulgated by unregulated private clinics, threatens the perceived credibility of current stem cell approaches those experts aim to build on sound science and convincing evidence, rather than on false hope for desperate patients. That prospect gives added urgency to surmounting the hurdles in front of investigators working to usher in new bone-targeted stem cell treatments.

A Difficult Funding and Regulatory Environment

At this time, the only stem cell therapy with US Food and Drug Administration (FDA) approval is Hemacord, which contains umbilical cord blood-derived hematopoietic progenitor cells that are used in transplantation procedures for certain blood cancers and some inherited metabolic and immune system disorders. There are, however, about 300 clinical trials across the world investigating stem cell therapies using cells derived from bone marrow or adipose tissue, and 51 of those trials—7 of which are in the United States—are testing stem cells (primarily mesenchymal stem cells (MSCs)) for bone repair or diseases, including bone fractures, bone fusion, bone cysts or voids, osteogenesis imperfecta, osteonecrosis, osteoarthritis and cartilage repair.

To move more stem cell therapies for bone repair/regeneration into additional clinical trials, and then into the clinic, researchers have to grapple with the first challenge to which Dr Hill turned: the infrastructure that funds research in the United States is not geared towards developing stem cell therapies. Indeed, the National Institutes of Health (NIH), the major public funder of biomedical research in the United States, is most interested in supporting basic research focused on understanding biological mechanisms and pathways, rather than the translational studies of which the stem cell field is most in need. 'Investigators are concerned that the NIH study sections that review research applications really lack support for translational research,' Dr Hill said. In addition, translating stem cells into the clinic for bone repair/regeneration will require moving from rodent models to larger animal models, in order to better understand both biomechanical and immunological issues that could arise when using stem cells for bone-related purposes. Yet the NIH, Dr Hill said, does not view research that requires larger animal models as innovative. Ethical objections to the use of embryonic stem cells, particularly in the United States, have also hindered federal funding for studies using that particular type of stem cell. At the same time, private sources of funding, including the venture capital and pharmaceutical industries, as well as private philanthropy, are limited.

The stem cell field also faces regulatory obstacles in its path to bring therapies for bone repair/regeneration into the clinic, Dr Hill said. In the United States, researchers must grapple with regulations set by the FDA, the key federal regulatory authority that approves new medications and medical devices; the path to regulatory approval of stem cell therapies can be long and complex at an agency accustomed to evaluating pharmaceutical agents and biological drugs. 'I think the FDA needs to have increased flexibility, speed, and open intra-agency

and inter-agency communication, in terms of developing rules and policies, and in processing [funding] applications,' Dr Hill said. He stressed that one particularly thorny problem the current regulatory setup creates is that it discourages risk-taking: investigators focus on developing therapies for which it will be easiest to gain approval, rather than newer ones that may take longer to pass regulatory muster, but could lead to real scientific breakthroughs, rather than just incremental improvements upon current approaches. The FDA itself is concerned by the lack of innovation in submitted applications, even while it recognizes that its policies and consequential costs discourage that very innovation. This all carries the further risk that the public, regulators and potential investors will all become disenchanted with stem cell therapies—experts are worried that the hype currently generated by unregulated private clinics for their unproven stem cell therapies is already threatening to do just that.

Important Scientific Choices

Which cells?

It is against this daunting regulatory and research infrastructure landscape that stem cell researchers must make some very important decisions, from a scientific perspective; it was to those decisions that Dr Hill then turned. One key choice to make is whether stem cells for bone repair/regeneration should come from autologous (self) or allogenic (donor) sources. 'This is an area that has seen major debate among investigators, clinicians and companies,' Dr Hill said. Although autologous and allogenic sources each have their advantages and disadvantages, Dr Hill believes that autologous sources may be preferable, as they do not pose the immunological issues such as rejection or graft versus host disease that allogenic sources do. As a result, autologous cells may face an easier regulatory path to approval, particularly if the cells do not require *ex vivo* expansion or modification. Still, technological improvements are needed before widespread use of autologous stem cells becomes feasible. At the same time, despite the immunological issues they pose, allogenic sources still have many desirable features, such as 'off-the-shelf,' immediate availability, and may be easier to develop over the short term.

In addition to determining the most desirable stem cell source, investigators must also settle upon the most attractive stem cell type for use in future therapies. Embryonic stem cells are valued because of their pluripotency—their ability to become any adult cell type in the body—and their unlimited expansion ability, but ethical objections, particularly in the United States, to their derivation from human embryos limit their use. Fetal stem cells, such as umbilical cord stem cells, avoid that objection, and though they have a more limited differentiation potential, can still give rise to multiple cell types. However, umbilical cord stem cells are rare cells that will therefore require expansion to increase their numbers, and if those stem cells come from allogenic sources, graft versus host problems could arise.

Adult stem cells from somatic tissues, however, are the largest source of stem cells now being tested for bone repair/regeneration, and look to remain so in the future. Such cells, including bone marrow-derived MSCs, or stem cells derived from adipose tissue, do not carry any of the ethical objections to embryonic stem cell use, and it may be possible to use adult stem cells from autologous sources, or from matched or unmatched allogenic sources. On the downside, adult stem cells can differentiate only to a more limited number of cell types, and it is difficult to define bone marrow-derived MSCs and adipose tissue-derived stem cells, as they exist among a very heterogeneous population of cells in those tissues. Furthermore, specific adult stem cell types, such as bone marrow-derived MSCs, exist only in limited numbers. In this regard, Dr Hill pointed to pericytes, which exist within vascular walls, as a possible adult stem cell type that can be derived from adipose tissue in much greater numbers; pericytes also have other appealing characteristics. 'Often they engraft in the bone marrow better than MSCs do, and potentially they can be more precisely characterized because of their cell markers,' he said. Finally, induced pluripotent stem cells—adult somatic cells that have been reprogrammed to have the characteristics of embryonic stem cells—are another option. Such cells could be used autologously, which would help avoid immunological issues and ethical objections, and could even be used in combination with gene therapy, Dr Hill said.

Interestingly, rather than take stem cells out of the body, expand them *ex vivo* and then inject them back into patients, there is increasing interest among stem cell investigators, Dr Hill said, in another approach: mobilizing endogenous stem cells and targeting them to sites of injury/disease. Indicating the promise of that approach in the bone repair/regeneration arena, a recent study found that insulin-like growth factor 1, in combination with an antagonist of a receptor involved in mobilization of MSCs, mobilized bone marrow MSCs *in vivo*, which aided bone healing in a mouse tibial fracture model.[1] Meanwhile, another recent investigation[2] used a bifunctional molecule that binds to both MSCs and to bone, in order to direct MSCs to osteogenic surfaces, which resulted in increased bone formation and bone mass in xenotransplantation studies and in immunocompetent mice (see Herberg and Hill[3] for recent commentary on *BoneKEy*). Dr Hill said that endogenous cells could also potentially be targeted to scaffolds that provide physical and other support to stem cells. Regarding scaffolds, panelist Todd McDevitt (Georgia Institute of Technology and Emory University, Atlanta, GA, USA) noted that scaffolds can help not only with concentrating stem cells and keeping them in a particular location upon injection, but can also serve other purposes. 'Now that more is known about stem cell biology, there is an effort to introduce adhesive ligands [to scaffolds] that can promote specific survival and instructive signals to the cells,' he said.

Which diseases?

While debate continues about which particular stem cells will be most useful, researchers are also left to grapple with another question: for which diseases should they put the cells to use? One possibility is to concentrate on what is easiest to do from a regulatory perspective. For instance, Dr Hill noted that currently in the United States, most clinical trials of stem cells for bone repair/regeneration focus on bone fusion, particularly spinal fusion. Bone fusion is a procedure for which use of autologous whole bone marrow already meets FDA requirements as a 'minimally manipulated cell product' that just requires registration, not approval, and therefore using isolated, unmanipulated autologous MSCs instead should also not require FDA approval. Further, use of expanded autologous MSCs might mean an easier time with regulatory authorities as those cells are close to what is already allowed, though

such cells will still need investigational and premarketing approvals. However, the risk with these approaches is that they may only provide a marginal improvement, rather than a true breakthrough. Another possibility is to simply focus on where the dollars are. The US Department of Defense, for instance, has been interested in funding stem cell work on trauma injury repair.

Yet another tactic would be to focus on where the number of potential procedures that could use stem cells is highest—that approach could have the greatest clinical impact and also please investors. In the orthopedics arena, millions of bone fractures, hundreds of thousands of hip replacements, knee replacements and spinal fusions, as well more than 1.5 million allograft transplantations, occur each year in the United States. In addition, ~700,000 vertebral compression fractures resulting from osteoporosis also take place in the 44 million individuals who suffer from that disease.

The webinar's panel discussion focused primarily on the potential use of stem cells in the osteoporosis setting. Interestingly, in that environment, injecting stem cells themselves into patients—cell-based therapy—may not be the best strategy. 'For osteoporosis in particular, I have some skepticism that [cell-based therapy] is going to be a competitive approach, as opposed to small molecule or other peptide therapies,' said panelist Sundeep Khosla (Mayo Clinic, Rochester, MN, USA). Instead, Dr Khosla said that it might be more advantageous to study stem cells *in vitro* for high-throughput drug screening purposes, to discover new compounds that could then be put to work on endogenous stem cells. Along similar lines, panelist Moustapha Kassem (University of Southern Denmark, Odense, Denmark) said that for systemic therapies like osteoporosis, stem cells in and of themselves might be less valuable than the humoral factors they secrete. 'There are many studies, in the non-bone field in particular, where there are therapeutic effects resulting not from stem cells differentiating to a particular cell type, but rather from the cells' ability to produce a number of molecules that are important for tissue regeneration,' Dr Kassem said.

In fact, osteoporosis is a particularly challenging disease for cell-based approaches, Dr Hill cautioned, because it is difficult not only to target MSCs to the bone marrow microenvironment but also to prod them to engraft there. Furthermore, even if the cells do engraft successfully, they will exist in a diseased environment in which it may be difficult for them to repair disease on their own. 'In the short term, this [cell-based therapy] is not something that's going to work out' for osteoporosis, he said. 'We need much more work on the development of approaches to get the cells to target the bone marrow and to change the bone marrow microenvironment for the cells to act appropriately,' Dr Hill said.

The panel agreed that cell-based approaches will be much more suitable at the local level—for spinal fusions or to repair fracture non-unions, for instance. Interestingly, though, if the focus is at the local level, those cells need not be stem cells, according to panelist Dominique Pioletti (École Polytechnique Fédérale de Lausanne, Switzerland). Indeed, he suggested that a differentiated cell, like an osteoblast, might have great utility, just as chondrocytes have been shown to have great utility for cartilage repair.

Still, panelist Céline Colnot (INSERM U781, Paris, France) reminded the webinar audience to remember the unique ability of stem cells to self-renew, which may help to drive long-lasting, rather than transient, bone repair/regeneration. 'It is a real challenge to be able not only to drive cells to form bone, but to form bone that will be sustained and not resorbed,' Dr Colnot said. 'An approach using stem cells might be more appropriate in order for transplanted cells not only to differentiate into osteoblasts or chondrocytes, but also to go to the stem cell niche, self-renew and allow long-term bone formation,' she said.

The Future

Researchers with an interest in bone hope that many new clinical trials of stem cells for bone repair or disease will be added to the current count of 51. For those trials to succeed, investigators will have to grapple with the ongoing infrastructure, regulatory and scientific challenges to which Dr Hill spoke during the webinar. What is the best way to navigate a difficult funding and regulatory environment? Should investigators focus on stem cell therapies that will provide incremental improvements, or rather on those that could offer revolutionary advances? Should they choose allogenic or autologous cell sources? Which diseases should they focus on and why? Only when such questions are answered will the dream of using stem cells in the orthopedic setting turn into reality.

Conflict of Interest

The author declares no conflict of interest.

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