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Editor's Spotlight/Take 5

Editor's Spotlight/Take 5: Adipose-derived Mesenchymal Stem Cells Are Phenotypically Superior for Regeneration in the Setting of Osteonecrosis of the Femoral Head

Seth S. Leopold MD

Some treatments carry so much intuitive appeal that we cannot help but feel cheated when they do not work. No doubt every reader of this has, at one time or another, been drawn to an intervention that seems like it should have been a bigger hit than it was. Perhaps—even worse—the intervention should have been a winner but instead harmed patients. Using critical reading skills and adopting new treatments only when high-quality research supports the concepts behind them can keep us from betting on too many of these wrong horses.

Then there are those treatments that seem to evolve before our eyes. Mesenchymal stem cells (MSCs) come to mind here. Certainly we crave a biological approach driven by a plentiful source of cells that possess a near-limitless potential to regenerate and differentiate into kinds of tissue that don't heal well, such as cartilage and tendon. Yet as intuitively sensible as this approach seems, a two-decade-plus history of inquiry into the topic [6] has delivered little, if any, clinical impact.

But the search continues, and in new ways. Since 2014, *Clinical Orthopaedics and Related Research®* has published two promising papers in human subjects from one group; one of these pointed towards potential future avenues involving amplifying the native MSC response to meniscal injury [3], and the other used synovially derived MSCs to repair articular-cartilage defects in the knee [4]. The latter study, an uncommonly well-designed (if small) clinical series, showed exciting results in terms of histology, MRI appearance, knee scores, and even second-look arthroscopy in a few patients. One of the most interesting elements of that group's work was the source of stem cells they used: They chose synovial MSCs [4], rather than the more commonly used bone-marrow-derived MSCs [5].

Researchers harvest MSCs from a variety of places—from bone marrow and synovium, as noted already, but also from muscle, umbilical blood vessels, dental pulp, and fat, among other inauspicious-sounding sites [7]—with each source of cells having its advantages and

Note from the Editor-In-Chief: In "Editor's Spotlight," *one of our editors provides brief commentary on a paper we believe is especially important and worthy of general interest. Following the explanation of our choice, we present* "Take Five," *in which the editor goes behind the discovery with a one-on-one interview with an author of the article featured in* "Editor's Spotlight."

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drawbacks. Although less is known about adipose-derived MSCs than about bone-marrow-derived MSCs, the former seem especially promising for certain applications. Though adipose-derived cells appear to be less chondrogenic than bone-marrow-derived MSCs, adipose-derived MSCs possess an exciting ability to regenerate bone [2], and, as we see in this issue of *CORR*®, perhaps to begin to move us towards new therapies for one of the most treatment-resistant conditions in all of orthopaedics: Osteonecrosis.

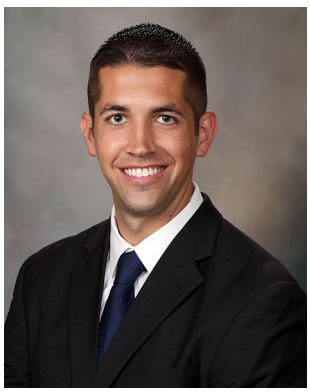
For these reasons, we are delighted to share this paper by Rafael J. Sierra's group at the Mayo Clinic. In a preclinical study, they found that adipose-derived MSCs outperformed bone-marrow-derived MSCs in terms of cell proliferation and osteogenesis when both kinds of cells were harvested from the same patients whose osteonecrotic hips were being replaced. The effect sizes were large. For example, at 20 days, the adipose-derived MSCs were four times as plentiful as the marrow-derived cells. One imagines that this can yield a larger and more-productive source of cells for conditions, like osteonecrosis, which call for bone regeneration and healing. But Dr. Sierra's work has implications far beyond osteonecrosis, and should be of interest to any surgeons who treat patients whose bones, tendons, or joint surfaces need to heal.

As noted earlier, intuitive approaches—such as this one—do not always result in beneficial clinical applications. And preclinical work is just that: Not ready for use in patients. Even so, it is impossible to read this NIH-funded project from the Mayo Clinic and not be excited by the places it might lead; the potential implications of this work are as broad as can be. Join me as I go behind the discovery with the lead author of this project, Cody C. Wyles BS, in the Take-5 interview that follows.

Take Five Interview with Cody C. Wyles BS, lead author of Adipose-derived Mesenchymal Stem Cells Are Phenotypically Superior for Regeneration in the Setting of Osteonecrosis of the Femoral Head

Seth S. Leopold MD: *Congratulations on this exciting paper. For readers who are unfamiliar with the topic, what do you see as the major advantages and disadvantages of the different sources of mesenchymal stem cells (MSCs) for musculoskeletal applications, and why did you choose adipose-derived cells for this project? I will confess that I am surprised that adipose-derived MSCs are so effective at generating bone, and I wonder why this might be so.*

Cody C. Wyles BS: For several years, Dr. Sierra has been using bone-marrow-derived MSCs as a cellular therapeutic for early-stage osteonecrosis. This has resulted in an improvement over core decompression alone, yet 20% of his patients still come to total hip replacement, and this has caused us to search for more-robust treatment modalities. The bone marrow MSC population is the most comprehensively studied for musculoskeletal applications; however, adipose-derived MSCs are quickly gaining prominence. These cells are easily accessible in multiple locations in the body and are more abundant than MSCs in bone marrow. We, too, were surprised by the degree to which the adipose-derived MSCs demonstrated superiority in proliferation rate and bone differentiation. Perhaps this is related to the quiescent environment of adipose tissue compared to the intense physiologic stress that is characteristic of bone marrow. Thus, the



Cody C. Wyles BS

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adipose-derived MSCs may simply have greater reserve capacity when called into action.

Dr. Leopold: *Although you got the cells from patients with osteonecrosis, no doubt you can imagine other orthopaedic applications for cells with the traits you observed. What do you think the most promising uses for these cells may be?*

Mr. Wyles: At this juncture, successful regeneration of bone is closer to widespread clinical application than more complex musculoskeletal tissues such as cartilage, ligament, and tendon. Given the results of our study and other work in the field, one can imagine applications for adipose-derived MSCs to augment bone regeneration in traumatic nonunions, high-risk osteoporotic sites such as the femoral neck, and even in promotion of osseointegration into orthopaedic implants.

Dr. Leopold: *Where do you plan to go next with this research? Animal models? Small clinical series?*

Mr. Wyles: Our laboratory is well-suited for continued translational research through a unique collaboration between Dr. Sierra in the Department of Orthopedic Surgery and the Mayo Clinic Center for Regenerative Medicine led by Dr. Atta Behfar MD, PhD and Dr. Andre Terzic MD, PhD. We are working to establish a rabbit model of osteonecrosis whereby this new stem-cell technology can be tested. We also are developing several different approaches to expedite the recruitment of the stromal vascular fraction (the MSC-rich population) out of adipose tissue and scale it up for clinical applications. These approaches would build on the cell-therapy approaches for osteonecrosis that are currently utilized in our practice at Mayo Clinic. Once optimized, we will soon begin a randomized clinical trial comparing our current standard of bone-marrow-derived MSCs versus adipose-derived MSCs for the treatment of early-stage osteonecrosis in patients with bilateral disease.

Dr. Leopold: *What do you perceive the potential risks might be of stem-cell treatments, and how might you evaluate these in future studies?*

Mr. Wyles: Adult derived stem cells are multipotent and demonstrate resistance to uncontrolled growth, which makes them unique. Thus, in contrast to more plastic pluripotent stem cells (such as embryonic stem cells), we believe the mesenchymal stem cell population serves as an ideal cell resource for therapeutic application with minimal risk for uncontrolled growth. Also, many MSC-based therapies use allogenic MSCs and/or cells that are expanded *ex vivo* in a laboratory before being transplanted back into a patient. These approaches potentially introduce additional risk; therefore, we are working toward strategies that use autologous MSCs that are derived and transplanted in a single procedure. This should increase safety, and decrease regulatory burden and cost.

Dr. Leopold: *What sources can you recommend to the curious clinician about the potential orthopaedic uses of MSCs and also the actual state of the science? Do any of those sources—or can you—help the clinician understand some of the challenges of MSC-driven therapies, and why they seem not yet to have lived up to the "hype"?*

Mr. Wyles: MSCs remain a new technology and many details have to be worked out to ensure that patients receive a high-quality, evidence-based treatment, with minimal risk, at a feasible cost. A crucial ongoing debate revolves around the mechanism of MSC benefit—some believe that MSCs serve as the direct "building blocks" of tissue regeneration, whereas other evidence suggests MSCs are the "orchestrators" of the tissue repair process, exercising their power through paracrine signaling and recruitment of native cells. Issues such as these in addition to determining the best tissue source for harvesting, streamlining cell processing, and improving the mode of delivery will all be critical in further developing the clinical science. There are many excellent reviews on these topics in the

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literature, but I particularly enjoyed a 2013 review by Frank Barry and Mary Murphy [1].

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