The Ochsner Journal 13:8–10, 2013

Bioethics in Practice

A Quarterly Column About Medical Ethics

Stem Cell Ethics

Deryk Jones, MD

Sports Medicine Institute, Ochsner Clinic Foundation, and The University of Queensland School of Medicine, Ochsner Clinical School, New Orleans, LA

The term stem cell refers to the pluripotential nature of the cell. These amazing cells have the ability to transform into one of the 220 different phenotypic cell types found in humans. They also possess great regenerative power and can multiply infinitely in addition to their phenotypic capabilities. Three stem cell types exist: embryonic, adult, and induced pluripotent stem (iPS) cells.

Embryonic stem cells are pluripotent—having the ability to become any phenotypic cell type in the body. Once cells begin to divide, they differentiate several times into one particular phenotype by expressing genes specific to this cell type. Most cells in our body can be described as adult cells and have a specific phenotype. However, some cells maintain their ability to multiply and change phenotypes. Termed adult stem cells, these special cells exist within small regions of certain tissues that require regenerative capabilities to respond to damage or excessive use. Adult stem cells have been isolated from skin, bone, fat, muscle, intestine, vascular, and brain tissues.[1-3] Unlike the pluripotential abilities of embryonic stem cells, adult stem cells are multipotential and can be changed into several different phenotypes but cannot differentiate into all 220 phenotypes that exist in nature. Initially, researchers believed that bone marrow aspirates were a good source of mesenchymal stem cells, but their harvest required the use of a trocar to obtain a bone specimen and further steps to isolate the small number of stem cells present.[4-6]

Using an in vitro model, I was able to demonstrate the presence of multipotential stem cells in the periosteum, the tissue that covers the surface of the bone.[7] The cambium, or inner layer of the periosteum, contains mesenchymal stem cells. Clinically, we use this periosteum to cover articular cartilage defects during the CARTICEL autologous chondrocyte implantation procedure (Genzyme, Cambridge, MA).[8] The inner layer of the periosteum is placed toward the articular cartilage defect on the surface of the knee joint. However, our in vitro study revealed a gradual senescence of the stem cells with periosteal age.[7] As a result, we currently use a young patient's own perisoteum because the multipotential stem cells present within the periosteum may contribute to successful outcomes. In middle-aged and older individuals, senescence leads to a more limited contribution by the individual's periosteum in healing the defect. As a result, a replacement graft (cadaveric or xenographic) is recommended for these individuals to avoid excessive surgical time and increased incision size.

Recently, through genetic induction, cells have been pushed backward through their development, creating a pluripotential state.[3,9-11] These induced cells from numerous sources are in a pliable condition and can be used to regenerate tissues and potentially treat clinical disease processes. In 1962, Dr Gurdon at the University of Cambridge produced living tadpoles by transferring the adult nucleus from an intestinal cell into a frog egg from which the nucleus had been removed.[12-15] In 1997, his technique was repeated in a sheep model, producing the cloned sheep named Dolly and broadening public awareness surrounding genetic modification and its future applications.[16-19] In 2007, Dr Yamanaka demonstrated the ability to add 4 key transcription factors to adult cells through viral transmission, creating the iPS cells.[20,21] Drs Gurdon and Yamanaka won the 2012 Nobel Prize in Physiology or Medicine for their contributions to stem cell research.[22]

Dr Huard and his associates at the University of Pittsburgh Stem Cell Research Center have used muscle-derived cells to change the phenotypic character of these cells.[3] Numerous basic science

studies have demonstrated the potential clinical use of these cells to treat a variety of conditions, including ligament injuries, acute and chronic articular cartilage injuries, bone defects, meniscus tears, macular degeneration, spinal cord injuries, and chronic neural conditions such as Duchenne muscular dystrophy, Alzheimer disease, and Parkinson syndrome.[5,11,23-27]

The public debate surrounding stem cells heightened during the George W. Bush administration.[28] When public access to this technology was limited in the United States during the second Bush presidency, other countries seized the opportunity and began developing their own research techniques and clinical treatments, opening the door for stem cell tourism.[28] With increasing public awareness regarding stem cells and increased use in the clinical setting, the opportunity for misuse increased.

The typical patient inquiring about stem cell therapy has a chronic, debilitating, and incurable condition. These vulnerable individuals will pay large sums for unproven treatments. Einsiedel and Adamson examined 23 stem cell tourism websites; among them, only one website contained a brief mention of one clinical study.[28] Despite the unproven nature of these therapies, clinicians providing them charge prices as high as $39,500. Several investigative articles surrounding the use of adult stem cells recently appeared in *Nature*[29-31] and other journals.[32,33] A Houston, Texas, company named Celltex Therapeutics Corp. currently pays physicians a fee for administering stem cells to patients and charges patients for the treatment of numerous conditions through intravenous infusion techniques. At the same time, Celltex conducts research on these treatments. The *Nature* articles raised the question of whether the research should be performed to determine efficacy prior to implementation of standard use of these treatments. Apparently, Celltex executives are aware of the ethical issues raised by these activities. The company recently hired the current editor-in-chief of the *American Journal of Bioethics*, Glenn McGee, as president for ethics and strategic initiatives.[31] This move raised further questions about conflict of interest, and some in academics have asked McGee to step down from his editorial position.

Certainly, some individuals with chronic degenerative conditions such as multiple sclerosis will desire and have begun to use stem cells to treat their conditions prior to proven efficacy. Placebo-controlled, blinded clinical trials may be able to answer the question of clinical efficacy, but some patients will not wait because their conditions are progressive. Once again, technology has advanced more rapidly than our ethical considerations, and some patients may suffer harm as a result.

Case reports of complications in patients treated with stem cells are beginning to trickle in to the literature.[34,35] Israeli doctors recently reported the development of a brain tumor in a young boy who had received fetal neural stem cells in Russia. This individual had a rare degenerative neural condition, and the Israeli doctors linked the tumor to cells introduced during stem cell therapy.[34] A medical report from China implicated stem cell therapy in several cases of meningitis following treatment for spinal cord injuries.[35]

As is the case in all fields of medicine, physicians serve as a safety net for desperate individuals seeking stem cell treatment, weighing the risks of treatment with stem cells against the expected outcomes. Similarly, clinicians must understand and communicate the benefits of stem cell therapy to patients while remaining honest about the potential complications. In the end, the physician must follow the Hippocratic Oath: "Do no harm."

REFERENCES

1. Chen CW, Corselli M, Péault B, Huard J. Human blood-vessel-derived stem cells for tissue repair and regeneration. *J Biomed Biotechnol*. 2012;2012:597439. Epub 2012 Feb 2.
2. Matsumoto T, Ingham SM, Mifune Y, et al. Isolation and characterization of human anterior cruciate ligament-derived vascular stem cells. *Stem Cells Dev*. 2012 Apr 10;21(6):859-72. Epub 2011 Aug 17.
3. Usas A, Mačiulaitis J, Mačiulaitis R, Jakubonienė N, Milašius A, Huard J. Skeletal muscle-derived stem cells: implications for cell-mediated therapies. *Medicina (Kaunas)*. 2011;47(9):469-479. Epub 2011 Dec 2.
4. Dozza B, Gobbi G, Lucarelli E, et al. A rapid method for obtaining mesenchymal stem cells and platelets from bone marrow aspirate. *J Tissue Eng Regen Med*. 2012 Jun 19. Epub ahead of print.
5. Duygulu F, Demirel M, Atalan G, et al. Effects of intra-articular administration of autologous bone marrow aspirate on healing of full-thickness meniscal tear: an experimental study on sheep. *Acta Orthop Traumatol Turc*. 2012;46(1):61-67.
6. Masquelet AC, Benko PE, Mathevon H, Hannouche D, Obert L; French Society of Orthopaedics and Traumatic Surgery (SoFCOT). Harvest of cortico-cancellous intramedullary femoral bone graft using the Reamer-Irrigator-Aspirator (RIA). *Orthop Traumatol Surg Res*. 2012 Apr;98(2):227-232. Epub 2012 Mar 7.
7. Youn I, Suh JK, Nauman EA, Jones DG. Differential phenotypic characteristics of heterogeneous cell population in the rabbit periosteum. *Acta Orthop*. 2005 Jun;76(3):442-450.
8. Jones DG, Peterson L. Autologous chondrocyte implantation. *J Bone Joint Surg Am*. 2006 Nov;88(11):2502-2520.
9. Chen BY, Wang X, Chen LW, Luo ZJ. Molecular targeting regulation of proliferation and differentiation of the bone marrow-derived mesenchymal stem cells or mesenchymal stromal cells. *Curr Drug Targets*. 2012 Apr;13(4):561-571.
10. Pei M, Shoukry M, Li J, Daffner SD, France JC, Emery SE. Modulation of in vitro microenvironment facilitates synovium-derived stem cell-based nucleus pulposus tissue regeneration. *Spine (Phila Pa 1976)*. 2012 Aug 15;37(18):1538-1547.

11. Wang Y, Zhao Z, Ren Z, et al. Recellularized nerve allografts with differentiated mesenchymal stem cells promote peripheral nerve regeneration. *Neurosci Lett*. 2012 Apr 11;514(1):96-101. Epub 2012 Mar 3.
12. Gurdon JB. The developmental capacity of nuclei taken from intestinal epithelium cells of feeding tadpoles. *J Embryol Exp Morphol*. 1962 Dec;10:622-640.
13. Gurdon JB. The transplantation of nuclei between two species of Xenopus. *Dev Biol*. 1962 Aug;5:68-83.
14. Gurdon JB. Adult frogs derived from the nuclei of single somatic cells. *Dev Biol*. 1962 Apr;4:256-273.
15. Gurdon JB. Multiple genetically identical frogs. *J Hered*. 1962 Jan-Feb;53:5-9.
16. Turner L. A sheep named Dolly. *CMAJ*. 1997 Apr 15;156(8): 1149-1150.
17. Beardsley T. The start of something big? Dolly has become a new icon for science. *Sci Am*. 1997 May;276(5):15-16.
18. Pennisi E, Williams N. Will Dolly send in the clones? *Science*. 1997 Mar 7;275(5305):1415-1416.
19. Blacksher E. Cloning human beings. Responding to the National Bioethics Advisory Commission's Report. *Hastings Cent Rep*. 1997 Sep-Oct;27(5):6-9.
20. Takahashi K, Okita K, Nakagawa M, Yamanaka S. Induction of pluripotent stem cells from fibroblast cultures. *Nat Protoc*. 2007; 2(12):3081-3089.
21. Nakagawa M, Koyanagi M, Tanabe K, et al. Generation of induced pluripotent stem cells without Myc from mouse and human fibroblasts. *Nat Biotechnol*. 2008 Jan;26(1):101-106. Epub 2007 Nov 30.
22. Wade N. Cloning and stem cell work earns Nobel. *N Y Times (print)*. 9 Oct 2012:A9.
23. Jackson WM, Alexander PG, Bulken-Hoover JD, et al. Mesenchymal progenitor cells derived from traumatized muscle enhance neurite growth. *J Tissue Eng Regen Med*. 2012 May 3. Epub ahead of print.
24. Mifune Y, Matsumoto T, Ota S, et al. Therapeutic potential of anterior cruciate ligament-derived stem cells for anterior cruciate ligament reconstruction. *Cell Transplant*. 2012;21(8):1651-1665. Epub 2012 Jun 20.
25. Moroz A, Bittencourt RA, Almeida RP, Felisbino SL, Deffune E. Platelet lysate 3D scaffold supports mesenchymal stem cell chondrogenesis: An improved approach in cartilage tissue engineering. *Platelets*. 2012 May 30. Epub ahead of print.
26. Nakamura M, Tsuji O, Nori S, Toyama Y, Okano H. Cell transplantation for spinal cord injury focusing on iPSCs. *Expert Opin Biol Ther*. 2012 Jul;12(7):811-821. Epub 2012 Apr 20.
27. Ota S, Uehara K, Nozaki M, et al. Intramuscular transplantation of muscle-derived stem cells accelerates skeletal muscle healing after contusion injury via enhancement of angiogenesis. *Am J Sports Med*. 2011 Sep;39(9):1912-1922. Epub 2011 Aug 9.
28. Einsiedel EF, Adamson H. Stem cell tourism and future stem cell tourists: policy and ethical implications. *Dev World Bioeth*. 2012 Apr;12(1):35-44.
29. The darker side of stem cells. *Nature*. 2012 Feb 29;483(7387):5.
30. Cyranoski D. China's stem-cell rules go unheeded. *Nature*. 2012 Apr 11;484(7393):149-150.
31. Cyranoski D. Stem-cell therapy takes off in Texas. *Nature*. 2012 Feb 29;483(7387):13-14.
32. Arnold C. Texas stem cell rules may impede clinical research. *Lancet*. 2012 May 12;379(9828):1776.
33. Di Bernardo G, Piva R, Giordano A, Galderisi U. Exploiting stem cell therapy: The 3rd meeting of Stem Cell Research Italy. *J Cell Physiol*. 2012 Aug 27. Epub ahead of print.
34. Amariglio N, Hirshberg A, Scheithauer BW, et al. Donor-derived brain tumor following neural stem cell transplantation in an ataxia telangiectasia patient. *PLoS Med*. 2009 Feb 17;6(2):e1000029.
35. Barclay E. Stem-cell experts raise concerns about medical tourism. *Lancet*. 2009 Mar 14;373(9667):883-884.