The Science and Ethics of Stem Cells: A Bright Future

American College of Pediatricians – October 2013

ABSTRACT: The field of stem cell biology has been transformed and gained extraordinary attention in light of its future in regenerative medicine. Human embryonic stem cells have fueled considerable debate across all social and ethnic backgrounds around the world. This paper reviews the various stem cell platforms with emphasis on the emerging science of bioengineered cells that offer embryonic-like properties and the unique promise of regenerative medicine applications for pediatric medicine. Bioengineered stem cells, through induced pluripotent stem cell technology, offer a viable and possibly superior alternative to the use of human embryonic stem cells. Furthermore, this advancing technology demands attention to responsible and ethical research and implementation in the field of regenerative medicine.

The field of stem cell biology has been transformed and gained extraordinary attention in light of yearly discoveries that continue to change the scope and future of regenerative medicine. Of note, human embryonic stem (hES) cells have fueled continued debate across all social and ethnic backgrounds around the world. This paper reviews current stem cell platforms to emphasize the emerging science of bioengineered cells that offer embryonic-like properties and the unique promise of regenerative medicine applications for pediatric medicine. Bioengineered stem cells or induced pluripotent stem cell (iPS) technology offers a novel, yet viable and possibly superior alternative for medical endeavors as it essentially eliminates ethical and resource-related concerns posed by hES cells. Furthermore, the technology offers exciting new potential scientific applications that were never possible with hES cell technology. While the hope and the hype have generated grand visions, the current limitations of this technology must be recognized and medical and scientific goals should be the foundation to fuel ongoing medical advances in regenerative medicine.

Similar to most emerging tools in modern medicine, stem cell technology should be valued only within established ethical, financial, political, and scientific perspectives.[1] The controversy surrounding human embryo destruction to generate stem cells has roots in the standard ethical concepts of nonmaleficence, beneficence, justice, and human dignity.[2, 3] Years of spirited debate have failed to build consensus surrounding deeply held differences of belief regarding the nature of embryonic stem (ES) cells. However, emerging scientific breakthroughs have fundamentally changed these unresolved debates with the ability to bioengineer equivalent stem cells from patient-specific cells such as ordinary skin cells.

Stem Cell Platforms

There are five primary platforms from which stem cell can be obtained: adult, perinatal, embryonic, and two types of bioengineered stem cells (embryonic and induced pluripotent). *Adult stem (AS) cells* are collected from mature sources such as bone marrow, adipose tissue, and adult organ-specific tissues. These cells contain multipotent stem cells, or cells that are capable of giving rise to many types of tissues within different organ systems.[4] Focal (local to specific tissues) and systemic (disseminated into the general circulation as most drugs are given) delivery of adult stem cells have been used for a wide spectrum of diseases.[5-7] The wide range of differentiation capacity and multi-lineage potential of adult stem cells (to give rise to many different types of tissues) provides a common tool for regenerative medicine.[8] This platform is commonplace for hematopoietic (red and white blood cells) clinical applications in most academic medical centers today and is also being investigated with increased frequency in alternative regenerative medicine applications in early phase clinical trials. Furthermore,

various types of tissue-specific stem cells (cardiac, liver, lung, cartilage, etc) are being discovered and isolated from adult tissues for the purposes of regenerative medicine beyond the hematopoietic field.

Perinatal stem cells are collected from umbilical cord blood (UCB). By comparison to adult stem cells, cells isolated from UCB have demonstrated a wider spectrum of developmental capacity due to their greater flexibility and efficiency at differentiating into distinctive tissues beyond the blood system.[9] The diverse pool of progenitor cells (primitive cells with the ability to grow, divide, and differentiate into a specific tissue) contained within UCB offers treatment potentials similar to embryonic stem cells.[10] These multipotent stem cells are also increasingly being collected and frozen for long-term biobanking as speculative "bioinsurance" against unexpected medical conditions that may arise later in the donor's life.[11] Furthermore, the prevalence of this stem cell source makes them an attractive cell type for autologous (self-) applications for children who are diagnosed *in utero* with a congenital disorder.

Embryonic stem cells are collected from early stage embryos in the blastocyst stage after 1-2 weeks of development. Cells within the early stage embryos are pluripotent (uniquely capable of giving rise to all mature tissues of the developing body). Remarkably, despite the current funding stream for research on hES cells, no therapeutic use for these cells has been realized to date; but animal studies in Parkinson's disease and spinal injury,[12] type 1 diabetes,[13] and cardiovascular disease[14] have demonstrated improved function. Clinical trials utilizing hES cells or derivatives are limited to a single Food and Drug Administration (FDA)-approved clinical trial today. The limitations of this technology are due in part to the ethical, legal, and societal concerns of harvesting human embryos, but more importantly to the scientific challenges of safely using this source of cells due to issues in safe collection, manufacture, delivery, and monitoring of cell products for unintended side effects such as tumor growth.

Bioengineered stem cells are generated in the laboratory. *Bioengineered embryonic stem cells* , originated with the concept of cloning (somatic cell nuclear transfer), first demonstrated in mammals in 1997 with the creation of "Dolly" the sheep.[15] The technology involves the transfer of a somatic or ordinary cell nucleus into an enucleated oocyte (egg cell without a nucleus). The artificial embryo created by this process produce a cloned zygote (two cell embryo) from which cloned ES cells can be collected within a few weeks of development in the laboratory.[16] Once enucleated, the tissue cell DNA is reset to its original embryonic state, thus creating an artificial stem cell with true pluripotent capabilities.[17, 18] This first generation technology to re-establish a pluripotent stem cell from a mature adult tissue cell (in combination with a donor oocyte) fully creates a natural embryo which can give rise within the natural environment to a live-birth offspring, as was the case with "Dolly" the sheep. This still raises many of the ethical questions involved in the collection and use of human embryonic tissues.

Induced pluripotent stem cells (iPS) An alternative, completely embryo-independent, strategy to bioengineer stem cells has recently been discovered known as "nuclear reprogramming" that converts ordinary fibroblast cells into embryonic-like stem cells by introducing only a few pieces of DNA manufactured in the laboratory. The DNA is specific for transgenes of stemness factors (Oct4, Sox2, c-Myc, and Klf4) that are naturally expressed as proteins in ES cells. This biomedical breakthrough, which forces ordinary cells to naturally express proteins, is sufficient to transform the cells into what looks and functions as do ES cells. This approach is an innovative technology to achieve fundamental pluripotency (stem cells with unlimited differentiation capacity) using just ordinary cells from an individual to create autologous (self)-cell types that function equivalently to hES cells. These cells are called induced pluripotent stem cells (iPS).[19] The regenerative diagnostic and therapeutic applications of iPS cells for specific patient populations have been demonstrated in various laboratory-based model systems that include sickle cell anemia,[20] Parkinson's disease,[21] hemophilia A,[22] and ischemic heart disease.[23, 24]

It is important to realize that iPS cell technology is not yet ready for clinical applications. Protocols for nuclear reprogramming may result in partially reprogrammed cells with dysfunctional immature cells that contaminate the ideal therapeutic potential of these stem cells.[25, 26] Selected iPS cells have indeed mimicked the fundamental features of hES cells in many aspects as they are capable of giving rise to or differentiating into all cell types of the adult body, such as brain tissue, cardiac tissue, liver cells, etc.

However, restricting subpopulations to specific applications for specific diseases and specific patient populations remains a major challenge for the field to address prior to further clinical translation of this emerging science.

In principle, induced pluripotent stem cells offer unique biological advantages. A major advantage of using reprogrammed somatic cells is that they can possibly avoid the need for allogenic (non-self) transplantation, eliminating the need for immunosuppressive therapy. Then too, iPS cells contain an unlimited capacity to be generated from individual patients whereas hES cells have restrictions as they must be derived from embryos discarded after *in vitro* fertilization (IVF).[27, 28] The skin donation process for iPS cell production is a safer and less invasive alternative for patients than egg donation during IVF.[29] Perhaps most significant, iPS cells avoid the complications of embryo utilization which require the acquisition and consumption of human embryos to produce hES cells. Therefore, the practical and ethical limitations inherent to hES cells are completely eliminated with the emergence of bioengineered iPS cells. However, the challenges of safety, and appropriate clinical applications, still remain to be addressed.

Future of Stem Cell Clinical Applications

With the emergence of the technology to bioengineer pluripotent stem cells from an individual's ordinary somatic cells comes the revolutionary ability to provide genetically identical cells that match to donor cells. There are a growing number of potential uses for this biotechnology in patient-specific therapies, diagnostic tools, and research models for human disease.[27, 30-37] Remarkably, clinical applications showing success today and promising the greatest potential for tomorrow are predominately utilizing adult bone marrow derived stem cells or UCB derived stem cells, not embryonic stem cells. These applications have been pioneered especially by hematology for autologous (self) or allogeneic (non-self) hematopoietic stem cell transplantations. Oncologists have transformed our ability to treat cancer with chemotherapeutics, but the unfortunate and often most limiting side effect has been bone marrow failure among other serious side effects. This dilemma can be efficiently remedied with routine hematopoietic stem cells re-infused following successful chemotherapeutics.

Therefore, the successful bioengineered stem cell technology of today is primed to advance regenerative medicine beyond hematology to stem cell-based therapies for many organ systems such as the heart, lungs, liver, and joints. Today, adult blood and UCB provides the source of stem cells used in hundreds of clinical trials in the USA under the guidance of the FDA. These studies range from degenerative adult disease (such as heart disease, neurodegenerative diseases, autoimmune diseases, and lung diseases) to the standard of practice for blood diseases such as lymphoma and leukemia (cancer of the blood). Tomorrow, we are likely to see a growing list of applications that could also utilize next generation technology such as tissue-directed adult stem cells, and even personalized stem cells, as a product of bioengineering. These successes will come without the use human embryonic stem cells and therefore will not require the harvesting of embryos to achieve regenerative outcomes. Therefore, the ethical, legal, and societal concerns surrounding embryonic stem cells can be scientifically addressed and fully avoided with emerging technologies thus offering distinctive and more certain movement forward for regenerative medicine.

Primary (guest) author: Timothy J. Nelson, M.D., Ph.D.[1,2,3,4]
[1]Division of General Internal Medicine, [2]Department of Molecular Pharmacology and Experimental Therapeutics, [3]Transplant Center, [4]Center for Regenerative Medicine; Mayo Clinic College of Medicine, Rochester, MN
October 2013

The American College of Pediatricians is a national medical association of licensed physicians and healthcare professionals who specialize in the care of infants, children, and adolescents. The mission of the College is to enable all children to reach their optimal, physical and emotional health and well-being.

References

1. Zacharias DG, Nelson TJ, Mueller PS, Hook CC. Impedance of novel therapeutic technologies: The case of stem cells. Clinical and Translational Science. 2012; 5:422-427.
2. Beauchamp TL, Childress JF. *Principles of biomedical ethics*. New York, NY: Oxford University Press, Inc.; 2008.
3. President's council on bioethics. *Human dignity and bioethics: Essays commissioned by the president's council on bioethics*. Washington, D.C. : US Independent Agencies and Commissions; 2008.
4. Wagers AJ, Weissman IL. Plasticity of adult stem cells. Cell. 2004; 116:639-648.
5. Hofstetter CP, Schwarz EJ, Hess D, Widenfalk J, El Manira A, Prockop DJ, et al. Marrow stromal cells form guiding strands in the injured spinal cord and promote recovery. Proceedings of the National Academy of Sciences. 2002; 99:2199-2204.
6. Horwitz EM, Prockop DJ, Fitzpatrick LA, Koo WWK, Gordon PL, Neel M, et al. Transplantability and therapeutic effects of bone marrow-derived mesenchymal cells in children with osteogenesis imperfecta. Nature Medicine. 1999; 5:309-313.
7. Orlic D, Kajstura J, Chimenti S, Jakoniuk I, Anderson SM, Li B, et al. Bone marrow cells regenerate infarcted myocardium. Nature. 2001; 410:701-705.
8. Chamberlain G, Fox J, Ashton B, Middleton J. Concise review: Mesenchymal stem cells: Their phenotype, differentiation capacity, immunological features, and potential for homing. Stem Cells. 2007; 25:2739-2749.
9. van de Ven C, Collins D, Bradley MB, Morris E, Cairo MS. The potential of umbilical cord blood multipotent stem cells for nonhematopoietic tissue and cell regeneration. Experimental Hematology. 2007; 35:1753-1765.
10. McGuckin CP, Forraz N. Potential for access to embryonic-like cells from human umbilical cord blood. Cell Proliferation. 2008; 41:31-40.
11. Hollands P, McCauley C. Private cord blood banking: Current use and clinical future. Stem Cell Reviews and Reports. 2009; 5:195-203.
12. Goldman S. Stem and progenitor cell-based therapy of the human central nervous system. Nature Biotechnology. 2005; 23:862-871.
13. Kroon E, Martinson LA, Kadoya K, Bang AG, Kelly OG, Eliazer S, et al. Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells in vivo. Nature Biotechnology. 2008; 26:443-452.
14. Passier R, van Laake LW, Mummery CL. Stem-cell-based therapy and lessons from the heart. Nature. 2008; 453:322-329.
15. Wilmut I, Schnieke AE, McWhir J, Kind AJ, Campbell KHS. Viable offspring derived from fetal and adult mammalian cells. Nature. 1997; 385:810-813.
16. Yamanaka S, Blau HM. Nuclear reprogramming to a pluripotent state by three approaches. Nature. 2010; 465:704-712.
17. Beyhan Z, Iager AE, Cibelli JB. Interspecies nuclear transfer: Implications for embryonic stem cell biology. Cell Stem Cell. 2007; 1:502-512.
18. Jaenisch R, Young R. Stem cells, the molecular circuitry of pluripotency and nuclear reprogramming. Cell. 2008; 132:567-582.
19. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 2006; 126:663-676.
20. Hanna J, Wernig M, Markoulaki S, Sun CW, Meissner A, Cassady JP, et al. Treatment of sickle cell anemia mouse model with ips cells generated from autologous skin. Science. 2007; 318:1920-1923.
21. Wernig M, Zhao JP, Pruszak J, Hedlund E, Fu D, Soldner F, et al. Neurons derived from reprogrammed fibroblasts functionally integrate into the fetal brain and improve symptoms of rats with parkinson's disease. Proceedings of the National Academy of Sciences. 2008; 105:5856-5861.

22. Xu D, Alipio Z, Fink LM, Adcock DM, Yang J, Ward DC, et al. Phenotypic correction of murine hemophilia a using an ips cell-based therapy. Proceedings of the National Academy of Sciences. 2009; 106:808-813.
23. Martinez-Fernandez A, Nelson TJ, Yamada S, Reyes S, Alekseev AE, Perez-Terzic C, et al. Ips programmed without c-myc yield proficient cardiogenesis for functional heart chimerism. Circulation Research. 2009; 105:648-656.
24. Nelson TJ, Martinez-Fernandez A, Yamada S, Perez-Terzic C, Ikeda Y, Terzic A. Repair of acute myocardial infarction by human stemness factors induced pluripotent stem cells. Circulation. 2009; 120:408-416.
25. Kim K, Doi A, Wen B, Ng K, Zhao R, Cahan P, et al. Epigenetic memory in induced pluripotent stem cells. Nature. 2010; 467:285-290.
26. Yamanaka S. Elite and stochastic models for induced pluripotent stem cell generation. Nature. 2009; 460:49-52.
27. Nelson TJ, Martinez-Fernandez A, Yamada S, Ikeda Y, Perez-Terzic C, Terzic A. Induced pluripotent stem cells: Advances to applications. Stem Cells and Cloning: Advances and Applications. 2010:29-37.
28. National institutes of health guidelines on human stem cell research. Http://stemcells.Nih.Gov/policy/pages/2009guidelines.Aspx. Accessed November 7, 2010;
29. Källén B. Maternal morbidity and mortality in in-vitro fertilization. Best Practice & Research. Clinical Obstetrics and Gynaecology. 2008; 22:549-558.
30. Amabile G, Meissner A. Induced pluripotent stem cells: Current progress and potential for regenerative medicine. Trends in Molecular Medicine. 2009; 15:59-68.
31. Cyranoski D. 5 things to know before jumping on the ips bandwagon. Nature. 2008; 452:406-408.
32. Maherali N, Sridharan R, Xie W, Utikal J, Eminli S, Arnold K, et al. Directly reprogrammed fibroblasts show global epigenetic remodeling and widespread tissue contribution. Cell Stem Cell. 2007; 1:55-70.
33. Nelson TJ, Martinez-Fernandez A, Terzic A. Induced pluripotent stem cells: Developmental biology to regenerative medicine. Nature Reviews. Cardiology. 2010; 7:700-710.
34. Nishikawa S-i, Goldstein RA, Nierras CR. The promise of human induced pluripotent stem cells for research and therapy. Nature Reviews Molecular Cell Biology. 2008; 9:725-729.
35. Park IH, Arora N, Huo H, Maherali N, Ahfeldt T, Shimamura A, et al. Disease-specific induced pluripotent stem cells. Cell. 2008; 134:877-886.
36. Wichterle H, Przedborski S. What can pluripotent stem cells teach us about neurodegenerative diseases[quest]. Nature Neuroscience. 2010; 13:800-804.
37. Belmonte JCI, Ellis J, Hochedlinger K, Yamanaka S. Induced pluripotent stem cells and reprogramming: Seeing the science through the hype. Nature Reviews Genetics. 2009; 10:878-883.