Cell Stem Cell
Forum

Stem Cell Therapies Could Change Medicine… If They Get the Chance

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Stem cell therapies have the potential to revolutionize the way we practice medicine. However, in the current climate several barriers and false assumptions stand in the way of achieving that goal.

The first two precepts of the modified Hippocratic Oath, which all M.D. graduates pledge are, in paraphrase: first, do no harm; and second, the primary obligation of a physician is to the health of the patient (to which I add "and future patients"), and a physician will not let issues of race, creed, religion, politics, or personal ethics to stand between the patient's health and his/her actions. The stem cell field, probably more than any I know of in medical science, is plagued by failures to act responsibly on both precepts.

While I am usually an optimist, I must admit that there is a possibility that we will continue to be in the Dark Ages of medicine for quite some time. I fear that therapies using purified tissue and organ-specific stem cells—the only self-renewing cells in a tissue or that can regenerate that tissue or organ for life—will remain elusive. Before I go further, just think about that statement: *regenerate that tissue or organ for life*. No pharmaceutical, no biotech-developed protein, and no other transplanted cells can do that. If we can deliver purified stem cells safely and effectively as a one-time therapy, we can change medicine, especially for diseases that drugs and proteins can't touch. Moreover, if we manage the costs and charges carefully, this form of therapy could lower overall health care costs dramatically. This vision is based on solid scientific evidence that stem cells regularly maintain, and, if necessary, regenerate tissues in a homeostatically controlled process. So it's worth the extra effort to find a way to make it happen.

Doing Harm

One of the barriers to practicing stem-cell-based regenerative medicine is the existence of fraudulent clinics and individuals who claim unproven therapies without underlying scientific backing. In many cases, they use cells that have never been tested experimentally for their "stemness," have not been through IRB-approved protocols that demand experimental evidence to justify the human experiment, and lack both independent medical monitoring of patient safety and oversight by a state or country regulatory system such as the FDA. It is critical that, as the community that speaks for stem cell biology and stem cell medicine, we find ways to warn patients and caregivers effectively about these concerns (Taylor et al., 2010).

There is also a fine line between these clearly fraudulent practices and questionable ones that use the stem cell label, but are not in fact stem cell therapies. For example, cultures of adherent cells from bone marrow, cord blood, or adipose tissue are regularly claimed to be mesenchymal stem cells (MSCs), but in such cultures true stem cells that both self-renew and differentiate to mesenchymal fates such as bone, cartilage, fibroblasts, and adipocytes are rare. Mesenchymal stromal cells, as a population, may contain cells that produce immunomodulatory and/or angiogenic factors, but are not sufficiently purified or defined to be a characterized entity for research or clinical transplantation. Finding markers that help define these populations was an important step (Dominici et al., 2006), but until there is a better understanding of how many of these cells can self-renew and give robust regeneration, I do not think they should be called stem cells.

There are also many claims that mesenchymal and/or hematopoietic cells can transdifferentiate without gene modification to make brain, liver, heart, skeletal muscle, or other tissues. However, these claims lack rigorous scientific support (Wagers and Weissman, 2004). Highly visible athletes and politicians are among the many patients who have received such "treatments." Recently, the Texas Medical Board approved a policy that allows licensed physicians to transplant investigational agents, including MSCs, with IRB approval but without a requirement for FDA approval of safety and efficacy. In my view, this lack of a requirement for FDA oversight and approval for both safety and efficacy is a giant step backward.

Another example of questionable stem cell practices comes from some commercial private cord blood banks. Cord blood does contain both HSCs and mesenchymal progenitors. The number of HSCs in each cord is sufficient to give rapid generation of blood only in infants and very small children, and above the age of ~7, several HLA-matched cords are needed. The development of public cord blood banks is an important, life-saving advance for patients needing hematopoietic cell transplants but lacking matched donors. However, this activity is very different from the private cord blood banks that charge significant amounts to initiate freezing of cord blood cells and then maintain them in case the child from whom the cord is obtained needs therapy. These companies often list a broad range of diseases that now or someday will be treated with stem cells without warning the patients or caregivers that the evidence that cord blood cells will be useful for treating such diseases is still very limited, and in any case the stored cord blood has the same genetic background as the child from whom the cord was obtained. The overall cause of legitimate stem cell therapy would be greatly

advanced by greater control and oversight of these and other organizations making unsupported claims about the potential of stem-cell-based treatments.

The Therapeutic Entity Is the Stem Cell Itself

Very few "adult" stem cells have been prospectively isolated, and only prospectively isolated blood-forming stem cells (HSCs) and brain-forming stem cells (NSCs) have been transplanted in clinical trials (Baum et al., 1992; Uchida et al., 2000). Grafts of other tissues, such as skin and bone marrow, depend on the stem cells in that tissue, but prospectively isolated stem cells are usually not used. Instead of using cells as the therapy, as a general rule, large drug companies are approaching the use of disease specific iPSCs or adult stem cells as tools for chemical or protein screens to find compounds that can be taken as conventional drugs to treat diseases. Some of these efforts are focused on differentiated cells derived from stem cells, but others aim to address diseases where altered or insufficient numbers of stem cells are central to the disease. The principal property of stem cells that makes them special is their ability to self-renew and reconstitute cell populations. Inducing self-renewal in vivo could be difficult to achieve because many factors affect stem cell regulation. It seems unlikely that single molecules will be able to activate all of the necessary pathway genes appropriately to expand a stem cell pool and allow robust and physiologically significant regeneration. Thus, I think this approach is likely to fall short as a method to replace tissue stem cells in vivo, and efforts will need to focus more on transplanting the cells themselves. However, stem-cell-regulating agents derived from screening could still be used as adjuvants for transplanted stem cells.

At a broader level, HSCs themselves form a foundation on which the rest of the regenerative medicine field could be built. When engrafted, purified HSCs can replace the hematopoietic system. By doing so, they also render the host permanently tolerant to other organs, tissues, or tissue stem cells from the same donor without further immune suppression (Weissman and Shizuru, 2008). In the future, the isolation of HSCs and other tissue stem cells (e.g., NSCs) from the same donor could come from pluripotent stem cell lines, and not living or recently deceased donors. Pluripotent ESC or iPSC line production of HSCs is still not practical, and working out the pathways to achieve that objective remains a critical roadblock to expanding the field of regenerative medicine.

In Vivo Veritas

The experiments that validated human, purified HSCs for hematopoietic transplants and human brain-stem-cell-derived neurospheres for neural disease transplants used immune-deficient mice that were crucial in testing the potential therapeutic effectiveness of these cells in vivo (Weissman, 2002). Although the derivation of patient- and disease-specific iPSCs can allow experiments in a petri dish, the disease pathogenesis caused by inherited mutations would be more completely understood if the cells could mature in a more physiological setting. One way to study them would be to develop blastocyst chimeras that are implanted and allowed to develop. Mouse ESCs and iPSCs can already be studied using this type of approach. Currently, human ESCs/iPSCs do not form chimeras if placed in mouse blastocysts and implanted. However, human pluripotent stem cell lines are mainly at the epiblast stage, and not the preimplantation blastocyst, and even mouse epiblast cells cannot form long-term blastocyst chimeras. If the substantial practical and ethical issues could be overcome, blastocyst chimeras with human iPSCs might provide insights into the cellular and molecular mechanisms of human disease pathogenesis, and the gene expression programs that allow embryonic tissue stem cells to mature.

An Unexpected but Potent Barrier: Business Development

Growing up in America, it is obvious to all of us that the transition from discovery to therapy almost always involves for-profit entities. Ingenuity and innovation are hallmarks of our society, and so it is natural that the prospective identification and isolation of adult or tissue stem cells leads to business enterprises. I myself have cofounded several companies that have done discovery, preclinical proof of principle, and even phase I/II clinical trials in the stem cell field. Each has succeeded in the discovery and preclinical phases, but found that the results of the clinical trials can take a back seat to business decisions. For example, SyStemix Inc. was a 1988 Palo Alto startup that identified a method to prospectively isolate and transplant clinically relevant numbers of human HSCs. The company entered a relationship with Sandoz, Inc. to explore autologous and allogeneic HSC therapies. Purification of mobilized peripheral blood HSCs resulted in depletion of various metastatic cancer cells by 115,000- to 245,000-fold (Prohaska and Weissman, 2009), and thus could be used to reconstitute the hematopoietic system after therapy with a reduced risk of reintroducing tumor cells. This finding led to clinical trials.

Twenty-two patients with metastatic breast cancer underwent transplantation of previously mobilized HSCs after very-high-dose chemotherapy. Although the trials were small, two hypotheses were tested: (1) can one improve the outcome of patients with chemoresistant metastases? And (2) can one improve the outcomes of relapse patients with both metastases and chemoresponsive cancers? The therapy did not help the patients with chemoresistant breast cancers. However, at 3 years the chemoresponsive cohort who received cancer-depleted HSCs appeared to be doing better than patients with standard mobilized peripheral blood transplants. At that point, Sandoz merged with CIBA to form Novartis, and within a few years the stem cell program was cancelled. Last year Antonia Müller and Judy Shizuru published the follow-up of the patients 13–15 years later (Müller et al., 2012). One-third of the patients who received purified HSCs were still alive, contrasting with the 7% overall survival of 78 contemporaneous Stanford patients with stage IV breast cancer who received standard, unpurified, mobilized peripheral blood transplant therapy. Of the five long-term surviving patients who had received purified HSCs, four had no recurrence of their breast cancers.

Attempts to reinitiate the program in another startup, helped by Novartis management, were halted when consultant oncologists advised investors that stem cell therapies in breast cancer had failed, citing a study indicating that "stem cell" rescue of high-dose chemotherapy patients with metastatic

breast cancer was no better than chemotherapy alone, that is, only ~6% disease-free survival at 2 years (Stadtmauer et al., 2000). However, Stadtmauer et al. transplanted unfractionated mobilized blood, not purified HSCs, and no amount of evidence about the difference could counter the words "stem cell" in the title of the NEJM article. This particular problem could have been avoided by more rigorous editorial standards regarding the use of the term "stem cell," and I would argue that improved accuracy in this respect would benefit many areas of the field.

How can we resolve this conflict of goals, that of a company to make a profit, and that of the biomedical researcher to advance medical science for the benefit of patients? The largest and best funding experiment I have seen so far comes from the California Institute of Regenerative Medicine. CIRM's charter allows it to fund promising stem-cell-based discoveries to and through phase I trials, taking out the risk that leaves our field bereft of suitable funds and in the "valley of death." However, to overcome the types of problems that the SyStemix trial encountered, this funding would need to be taken beyond initial trials to a point at which the evidence for clinical efficacy was irrefutable.

In Closing....

So, whom have I failed to annoy here? In one way or another, I have called out almost all of the different stakeholder groups involved in developing stem cell therapies. I wish I had a better story to tell, but I am convinced that we need to identify and reveal those who directly or indirectly do harm with phony medicines, and those who generate barriers to finding and transplanting adult tissue/organ stem cells for financial, religious, political, or other reasons. Unless we do, it will be difficult to usher in the era of stem cell regenerative medicine. Remember, right now our patients, friends, and families are contracting diseases that have a very short window of opportunity in which regenerative therapies can save them, and each delay removes a cohort of them from possible cures. We should not fail them.

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