doi:10.1038/mt.2009.215

Molecular Therapy

Translating Stem Cell Therapy to the Clinic: *Déjà Vu* All Over Again

We have been there. It was gene therapy as the cure-all; now it is stem cells as the cure-all. As the baseball icon Yogi Berra famously stated, "It's like *déjà vu* all over again." A caution to our stem cell colleagues: the science is great, the potential is tremendous—but it is a lot harder than it looks to translate genetic medicines from the laboratory to the bedside, and, importantly, there are serious safety issues inherent in stem cell therapy. But there is a bright side. We (the gene therapy community) can help you, and it involves marrying our technology with yours.

What is the issue? Why can't stem cells just follow the exciting promise of "regenerating new organs"? After all, embryonic stem cells (ESCs) can be induced to differentiate into any cell type, mice transplanted with stem cell–derived progenitors can be cured of all kinds of ailments, induced pluripotent stem cells (iPSCs) can be generated from fibroblasts, and, most recently, viable mice can be generated from iPSCs.[1]

As exciting as all this may be, the reality is that—beyond the sociopolitical issues surrounding the generation and use of human ESCs—there are multiple obstacles to translating stem cells to the clinic. Among the many challenges are quality control, efficacy, and safety. All are daunting hurdles. Quality control is an issue because stem cells are complex, and their biology is only partly understood. Beyond the issue of purity, there are myriad possible ways ESCs and iPSCs—and preparations of progenitor cells derived from either—can vary, including genetic and epigenetic variations and reproducibility of responses to differentiation signals.[2] Efficacy is equally challenging. As the gene therapy community found, and the stem cell community will learn from the clinic, humans are not just big mice. Finally, safety concerns for stem cell therapy are not the same as for other new types of therapy like small molecules, recombinant proteins, or monoclonal antibodies. For all these strategies the therapy is dose dependent, and if there is a safety issue, the therapy has a finite, defined, half-life. In contrast, whereas all these pharmaceuticals will be dissipated if the therapy is stopped, stem cell therapy (like some gene therapy vectors) may last forever. Even more challenging from a safety viewpoint, an inherent property of stem cells and their progeny is that the cells can expand in number; i.e., once the therapy has been administered, the stem cell therapist has lost control.

Why is there concern?

Stem cell therapy is riding high: great biology published in good journals, glowing op-ed pieces on the promise of the therapy, weekly international media coverage, and recent approval by the US Food and Drug Administration of the first use of human ESCs to treat a human disorder (spinal cord injury). The concern is not that stem cell therapy will not meet the high expectations of the scientific and lay public but the time it will take to meet those standards and the significant bumps along the road that will slow down (or halt) progress. Remember the history of gene therapy—look back at the scientific literature from the early 1990s, when anything regarding gene therapy was published in a high-impact journal and the international media touted the promise of gene therapy. Just as there are now excellent examples of clinical success with gene therapy, there will be success with stem cell therapy. But it will not come quickly, and there will be many disappointments before success is realized.[3]

The inevitable slow pace to success is not the only concern. Safety of stem cell therapy is a major issue. Although it did not receive media attention, there has already been a significant example of a stem cell therapy gone awry: glioneuronal tumors derived from fetal neural stem cells administered to the central nervous system of a patient with ataxia telangiectasia developed 4 years after the initial therapy.[4] One could argue that this took place in the context of a lax regulatory environment, but, just as has been the case with clinical gene therapy, it will not be the only major adverse event associated with clinical stem cell therapy. The safety concerns regarding translating stem cell therapy to humans include control over stem cell–derived transplants that incorrectly differentiate (e.g., hair growing in the liver), inappropriate localization (beating cardiomyocytes in the retina), generation of more cellular progeny than are needed or are safe (too many pancreatic β-cells), and, as in the case of the patient with ataxia telangiectasia, induction of tumors.

Gene therapy to the rescue

How can the gene therapy community help? By developing strategies to genetically modify stem cells and their progeny *ex vivo* before transplantation, using genes that provide fail-safe mechanisms that will allow the stem cell therapist to control the therapy should safety issues arise. The use of gene therapy to control wayward stem cell progeny is conceptually similar to what the gene therapy field has been working on for decades: strategies to use genetic modification to treat cancer. However, the application of this strategy to stem cell therapy is far easier. Whereas the cancer gene therapist has the challenge of delivering the genetic therapy to preexisting tumors *in vivo*, the stem cell gene therapist has only to genetically modify the stem/progenitor cells *ex vivo* before transplantation. Thus, although there are challenges (e.g., 100% of the stem/progenitor cells must be modified; the genetic modification would need to be integrated into the genome of the target cells with the attendant risks of insertional mutagenesis), *ex vivo* gene transfer is far easier than using *in vivo* gene therapy to control stem cell–derived progeny that could be anywhere in the recipient.

As detailed in a recent Perspective article in *Cell Stem Cell*,[5] the requirement for integration would make retrovirus, lentivirus, and plasmid vectors useful for this purpose. A likely expression cassette would include two elements. The first would include a promoter (constitutive, pluripotent, or regulated, depending on the application) regulating a gene to provide control of wayward stem cell progeny should the need arise (e.g., pluripotent antisense, enzyme prodrug, toxin, apoptotic, or plasma membrane tag to which elimination therapeutics could be directed). The second would include a promoter that regulates a gene used for selection before transplantation (antibiotic-based or a plasma membrane tag). The selection cassette of this dual strategy would allow the stem cell/progenitor cell population to be selected *ex vivo*, ensuring that 100% of the genetically modified cells were used for transplantation. The "control" cassette would provide the therapist with the *in vivo* control to eliminate wayward cells if necessary, using the promoter and specific transgenes to provide the control. These are just a few of the strategies that could be used. As has been published in *Molecular Therapy* and several other journals over several years, the community of gene therapists has numerous creative solutions for eliminating unwanted cells.

When the concept of "genetic modification for control of wayward stem cells" is discussed in stem cell community forums, two points are often made: highly selective purification processes remove the risk of inadvertently transplanting unwanted cells, and there are enough regulatory issues without the addition of gene therapy to the stem cells. In regard to the former, purification may solve the *in vitro* selection of the cells to be transplanted, but it does not solve the problem of what to do if adverse events occur after transplantation. In regard to the regulatory issue, gene therapy does not make approval more difficult in that regulatory groups view the final "package" as the drug; i.e., it would be the genetically modified stem-derived cells, not the individual components, that would be tested for efficacy and toxicity.

The inherent properties of stem/progenitor cells bring unique risks to the translation of this exciting biology to the bedside. Gene transfer can provide a vital fail-safe mechanism to give the stem cell therapist control over stem cell therapy. From the gene therapy community to the stem cell community: we have been there, we share your excitement, we want you to succeed, and we want to help. As we have learned, one major adverse event, with its associated negative international publicity, can set back the field for years. Do not let it be *déjà vu* all over again.

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Correction and Apology

doi:10.1038/mt.2009.212

In the Editorial in the August 2009 issue of *Molecular Therapy*, I mistakenly quoted from a draft memorandum sent to me for review and comment in my capacity as a member of the National Institutes of Health (NIH) Recombinant DNA Advisory Committee by Jacqueline Corrigan-Curay, Acting Director of the Office of Biotechnology Activities (OBA) at the NIH. This occurred because, unfortunately, before submitting my editorial, I did not verify that the language on which I was commenting was retained in the final version that was subsequently widely distributed. For example, the final memo did not in fact reference a "Serious Adverse Event," as I stated in the Editorial, but rather "an event that occurred in a gene transfer study of β-thalassemia Major and Sickle Cell anemia being conducted in France." A quotation referencing "risk calculus" and discussions with subjects was also not in the final version of the memorandum. The final memorandum actually states: "This event raises important questions about whether the use of lentiviral and modified SIN retroviral vectors containing insulators can, as has been the hope among investigators, decrease the risk of insertional mutagenesis in hematopoietic stem cells. In the coming months, OBA will be gathering additional information about the event, including specifics on the vector used, the dose of cells, transduction conditions, and the clinical course of both subjects, and we will organize a discussion at a meeting of the NIH Recombinant DNA Advisory Committee as soon as further data are available."

I apologize to Dr. Corrigan-Curay and to the NIH Office of Biotechnology Activities for inadvertently framing my editorial around a draft document that I received in an advisory committee capacity and that had not yet benefited from full review or input. I have known and worked with Jacqueline for a number of years and did not intend for my comments to reflect negatively on her. As readers of these monthly editorials for the past 5 years will likely recognize, I do have a strong feeling that the regulatory and funding complexity imposed on the field, particularly in the United States, is problematic, and the editorial in question reflects this opinion. That said, Jacqueline is a person of the highest integrity and works very hard to maintain a balanced and fair approach to the issues that the field faces, and misquoting her in this instance does not accurately reflect her input or the OBA staff's handling of this situation.

I also apologize to the readers of *Molecular Therapy* for this mistake.

David A Williams
Editor-in-Chief