

The Promise of Cell Therapy: Is History Repeating Itself

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The iPS “revolution” has dominated most aspects of stem cell biology over the past five years culminating in the award of the Nobel Prize in Physiology or Medicine to Dr. John B. Gurdon of the University of Cambridge and Dr. Shinya Yamanaka of Kyoto University for their seminal contributions to this field. Dr. Gurdon was the first to successfully generate living tadpoles via somatic cell nuclear transfer [1,2] and Dr. Yamanaka demonstrated that somatic cell reprogramming to an embryonic state could be achieved by ectopic expression of four genes [3]. Indeed, Yamanaka’s achievement validated the work of many scientists who painstakingly delineated the roadmap of gene regulatory networks activated during embryogenesis and responsible for establishing a pluripotent state [4-8].

Although a number of controversies still exist concerning the fitness of iPS cells [9], the field has rapidly advanced toward exploiting these cells in clinical medicine. For example, numerous labs are using patient-derived iPS cells to recapitulate stages of neuro-degeneration in a variety of neurologic disorders. These “disease in a dish” models represent powerful tools for understanding disease pathogenesis at the molecular level and also for pharmacologic testing of chemical compounds to identify new treatment modalities for these diseases [10,11]. Reprogramming technology also provides a means to generate stem cells from tissues and organs that lack a well-defined endogenous stem/progenitor pool *in vivo* or where access to the pool is limited. Based on these advances, the use of iPS-derived stem/progenitor cells as therapeutic agents to treat human disease is greatly anticipated. However, the question remains as to whether iPS-based therapies will provide a durable therapeutic benefit to a broad patient base.

Advances in cell-based therapy made over the past decade may provide an answer to this question. Currently there are over 1800 open clinical trials exploring the safety and/or therapeutic efficacy of adult stem/progenitor cells in human patients (www.clinicaltrials.gov). The growing number of clinical trials reflects the expectation that stem cell therapy offers novel and effective treatments for a large array of ailments. These expectations closely mirror those for the field of gene therapy several decades earlier, which were largely unmet [12]. Indeed, expectations surrounding stem cell therapy exceed that of gene therapy and may be even more damaging to the field. For example, the regulated use of viral-based vector technology insulated to a large extent the gene therapy field from the general public. In contrast, the wholesale marketing of unproven cell-based therapies poses a major threat to patient safety and jeopardizes the integrity of the entire cell therapy field. Remarkably, the reported deaths of several patients linked to rogue cell therapies [13-15] has not curtailed demand for such treatments, which is largely fueled by unrealistic hopes of the desperately ill and disabled [16,17]. The problem is pervasive as the number of clinics offering cell therapies continues to increase. Moreover, while the FDA has been working toward strengthening the guidelines for non-homologous use of cell therapy products, this has not been without controversy [18].

Other federal agencies are also finding themselves at the forefront of the cell therapy debate, whether by circumstance or design. For example, the Italian government has been embroiled in a controversy regarding cell-based therapies offered by the Stamina Foundation for the treatment of terminally ill patients suffering from various neurologic disorders [19]. A large number of scientists have opposed these treatments based on lack of efficacy data and concerns surrounding

methods used to manufacture cells [20]. Although strong public support has allowed these therapies to continue, albeit under strict regulatory guidelines, new evidence indicating that the company’s patent application contained duplicated data from unrelated publications [21] will certainly result in further governmental and scientific scrutiny. Ironically, the therapy in question employs Mesenchymal Stem Cells (MSCs), which have rapidly moved to the forefront of cell-based therapy due to their ready availability, amenability to large-scale culture expansion, and lack of infusion related toxicity in human patients. Completed phase I and II clinical trials employing MSC-based therapies have reported statistically significant benefits in patients with steroid resistant graft-versus-host disease [22], severe systemic lupus erythematosus [23] and complex peri-anal fistulas [24]. However, the proposed use of MSCs for treating neurologic disorders in Italian patients has spurred a heated debate among leaders in the field as to the practical limits of MSC-based therapies [25-29]. Since MSCs are well entrenched in the cell therapy arena, the outcome of this debate likely will serve as a litmus test for the industry as a whole.

In the United States, the National Institutes of Health has engaged the field by steadily increasing funding for stem cell research, offering more small business grants for phase I and II clinical trials, and providing financial support for biotech companies engaged in cell therapy [30]. However, these efforts are diluted due to the growing number of stem and progenitor cell types being evaluated in clinical trials, some of which are incompletely characterized. For example, Very Small Embryonic Like Cells (VSELS), which are described as pluripotent, are moving into Phase 2 studies even though the cells have not been shown to generate chimeric mice via tetraploid complementation, the gold standard assay of pluri-potency. Hence, the translation of basic science to clinical therapy is rapidly accelerating, and is driven in part by the fact that many scientists/physicians developing such therapies are affiliated with companies that are in the business of making profits. While some scientists have been very vocal about their opposition to the commercialization of cell therapy [31], the scientific establishment including peer-reviewed journals, societies, and regulatory bodies must accept responsibility for the current state of the field. Moreover, the viewpoint of a few outspoken scientists is unlikely to significantly change its course. Alternatively, strong consensus building among scientists, physicians and caregivers to develop strong policies that move beyond academic borders and affect local, state, and federal policies is desperately needed.

In closing, it is imperative to point out that careful selection of a stem/progenitor cell for clinical intervention is only the first step in achieving an efficacious therapy. Outcomes are also highly dependent

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on the dose and route of administration of the cells and the processes used for manufacturing, which can also affect composition, genomic stability and biological potency. Proper trial design using readily identifiable and quantitative metrics is also essential. Considering the political, regulatory, economic, and scientific challenges facing the cell therapy field today, it is hard to imagine how current expectations will be met. Therefore, it appears that history is repeating itself.

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