Deconstructing the promise of embryonic stem-cell research

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On Tuesday November 2, 2010, a brief article appeared, well within the depths of the *London Times*, noting that “Stem cell restores woman’s sight.” Apparently, an elderly woman who travelled to China, in September, for treatment of giant-cell arteritis, has regained eyesight after receiving an undefined form of stem-cell therapy. The trip and treatment were paid for by a local fundraising effort at a cost of nearly \$30,000 USD.

Given nearly a decade of research since the original descriptions of human embryonic stem cells, and the parade of reports identifying the healing potential of endless varieties of stem cells to suit patient- or disease-specific needs, how is it that a therapeutic advancement of this magnitude becomes relegated to the darkest corner of a major newspaper? In part, the publisher’s discretion may have been wisely exercised, due to the preliminary and/or experimental nature of treatments like this, while awaiting firmer evidence from the clinical team(s) undertaking such bold approaches to what must be accepted, at least on face value, as a feather in the cap of regenerative medicine—so one would like to think!

On the other hand, the true promise of stem-cell research, including that of the embryonic variety, has been difficult to deconstruct, for professional and prospective

consumer alike. Matters arising through political, scientific, ethical and legal viewpoints continue to brew as an admixture of debate for which there is little consensus. For our part, the community of scientists and clinicians that will bring clarity to this field will continue to rely upon the publication of peer-reviewed original research, upon which the foundations and infrastructure for regenerative medicine will be realized. In taking this task to hand, JARG, with this issue, is initiating a series of papers that highlight advances in the field of stem-cell research likely to sustain the kind of research effort required on a global level. That a global imperative be acknowledged is both within the purview of our readership, spanning the basic-science to clinical-application domains, and accepting the role of ART practitioners in educating our patients and policy makers so as not to delay the conduct of much-needed research.

A case in point, with respect to the role of science education in deconstructing the public mystique, occurred on August 23, 2010, when a US District Court judge issued an injunction that blocked NIH funding for all forms of research that would draw upon the use of embryonic stem cells. The injunction was stayed in September, and the ASRM has been actively involved in seeing that such a debilitating action not further retard progress on currently funded NIH grants, as well as evaluation of future applications. That efforts continue in the US and abroad to avail much-needed support for this science is buttressed further by the fact that broad-based research initiatives into the very origins of the embryonic stem cell have been lacking in an unrealistic atmosphere that demands results consonant with the hyperbole adorning the early phases of research. One example of how primordial the stem-cell field is can be found in our lead article this month.

Gonzalez et al. have returned to the scene of the original “crime,” the mouse embryo, to re-examine two fundamental

Capsule Realizing the therapeutic potential of stem cells will require more research into their origins in the early embryo.

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parameters of embryonic stem-cell derivation: blastomere developmental stage and culture conditions. As they note in their paper, nearly all efforts to derive human embryonic stem cells take advantage of the use of blastocysts and media formulations as varied as the number of stem-cell types you can count on one hand. This study very elegantly demonstrates that the blastocyst is a relatively inefficient source when compared to earlier stages of development and that readopting the inclusion of ACTH in the culture media further enhances the yield of cells expressing a standard array of biomarkers for totipotentiality. While there remains much to do in validating the differentiation potential, genetic stability, and sustainability of these new lines—as the authors duly recognize—these studies highlight several fundamental issues that have yet to be explored in either the venerable mouse model or the human.

First, recent advances in understanding the process of ICM and trophectoderm allocation in the mouse continue to emphasize the importance of cell-cell interactions in sorting the relevant molecules that will condone one or the other lineages. It is safe to say that, at this level, we have no information for the human embryo and will once again be left to the whims of empiricism before any further progress would be made.

Second, while many differences have been uncovered in the transcriptome of mouse-versus-human embryonic stem

cells, and distinct culture formulations are recognized to be of necessity (e.g. whether or not to use LIF), only an occasional attempt can be found in the literature where cells were derived from earlier cleavage-stage embryos. It is possible, then, that what have been as attributed to species differences are, in fact, sentinels of the stem-cell phenotype solely attributable to the selection efficiency of “older” cells from the ICM, the humanesque paradigm.

Finally, the delicate balance between genetic contributions and those more characteristic of epigenetic phenomena should heighten our awareness of the relative contributions of *de novo* zygotic genes, compared to the maternally invested epigenes that drive the emergence of the pristine embryonic stem-cell phenotype. Again, we have meager knowledge of this problem in the human due—not surprisingly—to the lack of materials that would represent the earliest stages of development in zygotes which would not have been subjected to the rigors of cryopreservation.

Clearly, efforts such as these, in appropriate animal models will set the stage for the next decade of embryonic stem-cell research. To move forward, supporting basic research into the true origins of this remarkable cell is an imperative that, if met, will do much to represent accurately the therapeutic potential of this and other lines of stem-cell research. JARG is proud to bring our readership the opportunity to participate in this venture, at whatever level you might choose.