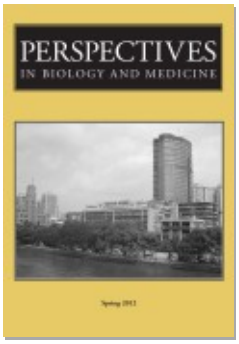
Stem Cell-Based Therapies: Promises, Obstacles, Discordance, and the Agora

Kathleen K. Eggleson



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ABSTRACT Stem cell research has entered the public consciousness through the media. Proponents and opponents of all such research, or of human embryonic stem cell research specifically, engage in heated exchanges in the modern public forum where stakeholders negotiate, the agora. One common claim that emerges from the fray is that a particular type of stem cell research should be pursued as the most promising path toward the reduction of suffering and untimely death for all of humanity. Upon evaluation, experimental data regarding the potential role of stem cells in regenerative therapies for three conditions—spinal cord injury, type 1 diabetes, and cardiovascular disease—tell distinct, complex, and inconclusive stories. Further analyses in this article incorporate realistic considerations of a broad range of relevant factors: limited funding for biomedical research, media motives, the discordance hypothesis of evolutionary medicine, the relationship between religion and science, medical care in developing nations, and culture wars over abortion. Holistic investigation inspired by the current agora conversation supports the need to drastically change interactions regarding stem cell research so that its potential to benefit humanity may be more fully realized.

THE COMMUNICATIVE RELATIONSHIP between science and society has metamorphosed with the dawn of the 21st century, as articulated by Michael Gibbons in 1999. In this new social contract, "socially robust" production is expected—the "reliable" knowledge produced under the previous social contract no longer suffices. Barriers between sectors have become more permeable than

Center for Nano Science and Technology, University of Notre Dame, 275 Fitzpatrick Hall, Notre Dame, IN 46556.
E-mail: keggleso@nd.edu.

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before, and "the sites at which problems are formulated and negotiated have moved from their previous institutional locations in government, industry, and universities into the 'agora'—the public space in which both 'science meets the public' and the public 'speaks back' to science" (pp. C81–C84). With respect to stem cell research, factions of scientists and citizens alike have displayed more passion than rationality in the agora. More inflamed than informed, the public is especially vulnerable to manipulation, and multiple media outlets capitalize on erupting battles in the culture wars. Also, public statements about the imminent arrival of cures derived from stem cells have victimized suffering patients and their loved ones by exaggerating to the point of false—or at least unsubstantiated—hope. This practice diminishes public trust in biomedical science at a time when trust in science and scientists seems to be on the decline, as exemplified by persisting public doubts about the validity of climate change science and vaccine safety (Blakemore 2007; Mooney 2011). Analyses and lamentations of this state of affairs abound, including the thought that what is truly deficient is media literacy more than climate literacy. In Caren B. Cooper's (2011) words: "The data collected and conclusions reached by scientists do not carry their due weight if the public is not knowledgeable, engaged, and empowered (not deceived) through science literacy, public engagement, and media literacy, held together by the common thread of critical thinking" (pp. 231–37). Critical thinking and the expression of reasoned analyses are urgently needed concerning topics that the media has latched onto. Though some scientific research projects have escaped "medialization," mass media coverage of stem cell research has met the analytical criteria for medialization: it is extensive, strongly pluralized, and controversial (Schafer 2009).

Proponents of embryonic, alternative, and adult stem cell research cite potential positive outcomes for humanity and the alleviation of suffering as the primary reasons for their advocacy, though many supporters of adult and alternative stem cell research are highly motivated to oppose the practice of research involving human embryo destruction by any legal and effective means. Messages about imminent potential cures for devastating diseases through the development of stem cell–based regenerative therapies resonate powerfully in compassionate listeners. Since stem cell research has been so highly medialized, however, additional steps are necessary to inform both conscience and reason. In this article, I will provide evidence against an assessment of stem cell–based therapies as standalone "magic bullets" that are nearly ready to fire at the devastation of degenerative disease. Progress reports in the scientific literature clearly demonstrate that a more apt metaphor for the current state of affairs in stem cell–based therapy is slow progress though treacherous uncharted territories. Based on this assessment, I argue against an intensive focus upon stem cell research as the most expedient means for alleviating suffering and generating positive outcomes for humanity, and I question the notion that stem cell research will ultimately benefit those in the developing world.

Instead, in consideration of scientific and financial realities, I advocate greater emphasis on prevention of chronic degenerative diseases attributable in part to lifestyle factors. Evolutionary medicine illustrates the inherent challenges to lifestyle changes that prevent disease, and it also provides a biologically based explanation for why education about healthy choices and harmful effects has not been effective in reversing the obesity epidemic. Every public dollar spent on research involving experimental therapies is one not spent on research that more directly addresses the health needs of the most vulnerable populations, or on treatment alternatives that may be more cost effective and distributed more justly. Through my analysis, I mean to convey that a choice to advocate for a particular scientific pursuit that has entered public consciousness through medialization alone is neither likely to reflect wise and just stewardship of resources, nor to be in the interests of good and dignity for humanity as a whole—even when the potential for some significant benefit to human health seems clear.

Therapeutic Potential of Stem Cells: Issues from the Outset

Adult stem cell research, including work using induced pluripotent stem cells (iPSCs), is an alternative to embryonic stem cell research in the quest to manipulate these cells for potential therapeutic use. For some diseases, stem cells may be used indirectly in the quest for therapies, for understanding disease mechanisms or screening (Thonhoff, Ojeda, and Wu 2009). The boldest statements of therapeutic promise have been based upon the idea that pluripotent stem cells could be propagated and delivered to the desired physiological site, where they could alleviate pathology from damage or disease. Without biomedical analysis, this prospect may seem as plausible and promising as some in the media and in the field have claimed.

However, most biologists and physicians acknowledge some obvious hurdles with this approach. The immune system constitutes one of the major obstacles to the clinical efficacy of stem cell–based therapies. For example, stem cell therapy is mentioned frequently in conjunction with type 1 diabetes, though its therapeutic potential is severely limited by the fact that additional functioning β cells would not solve the underlying autoimmune problem. These β cells too would be subject to attack, rendering the approach a diminishment of effect rather than cure of cause. (Some strategies to circumvent autoimmunity are under experimental investigation and will be described briefly later in this paper.) In the first place, assuming that a human clone is not involved, implantation of human embryonic stem cells or their derivatives into a diseased or damaged body would be allogenic—in other words, non-self into self. Just as in organ transplantation, the foreign biological matter would be prone to immune rejection, and immunosuppressive treatment would be required to protect the transplanted cells, rendering the host vulnerable to infection. Second, when func-

tioning normally, immune surveillance detects the inappropriate proliferation of self-cells and by destroying the offending cells nips most would-be tumors in the bud. Unfortunately, autologous—self into self—stem cells inserted for therapeutic purpose could suffer the same fate (Dressel et al. 2010).

Furthermore, when self-cells do proliferate out of context or immune control, a tumor can result. The transplantation of multipotent adult stem cells thus could give rise to atypical growth in the form of a tumor instead of (or in addition to) the intended therapeutic function, though even tumor-sensitive immunodeficient mice (severe combined immunodeficiency or SCID) have remained teratoma-free in some studies (Dimomeletis et al. 2010). Human embryonic stem cells separated from the controls of native context retain a natural propensity for rapid growth and may also cause teratomas (Tzukerman et al. 2003). Because of this risk, many current visions of therapeutic promise for pluripotent stem cells now incorporate an additional step: partial differentiation in an in vitro context before introduction into a patient or model organism.

Spotlights on Stem Cell–Based Therapy: Who Shines Them, and Why?

Why and how have stem cell–based research and therapies attracted so much attention? For defenders of the sanctity of human life from conception to natural death, the basis for ardent opposition of human embryonic stem cell research is obvious. Likewise, those who defend abortion rights have found support for human embryonic stem cell research naturally consistent with their beliefs. Thus, the subject of stem cell research has become a new battleground in the ongoing culture wars over abortion, or human life before birth more generally. To date, this appears to be the primary reason for the disproportionate attention given to stem cell research and potential medical outcomes relative to other biomedical research with potential clinical implications. Though often crudely portrayed by the media, the debate surrounding abortion connects to the sacred and profound in complex ways that are beyond the scope of this paper.

What might be a less powerful or obvious factor in the intense attention is that stem cell research is flashy, "sexy" science. Flashy science attracts attention that is not based on merit or accomplishment, and pertinent experimental results are often given priority acceptance by high-profile scholarly journals and coverage by the mainstream media. An example of this phenomenon occurred in 2006, when the editors of *Science* retracted two fraudulent stem cell research papers by Hwang et al. (Kennedy 2006). The scientific community collectively knows that flashy science is often not the best science in terms of experimental design, rigor, reproducibility, or implications. A trained bench scientist also knows that forward progress in research does not come easily, even when no impediments to success can be anticipated at the outset. Even if the major blockades can be overcome, more subtle biological circumstances could also render

therapeutic attempts unsuccessful. For some of the specific conditions being mentioned in conjunction with potential stem cell–based therapy, such as type 1 diabetes, Parkinson's disease, and Alzheimer's disease, fundamental etiological mechanisms are not yet adequately understood, and thus the sweeping promises of healing that have excited politicians and the press are at this time both unfounded and inappropriate. From the perspective of a biological scientist, the possibility that interventions derived from pluripotent stem cells may be futile (particularly in the context of autoimmunity, as in type 1 diabetes) or amount to playing with fire (in the form of tumors and other potential adverse effects) means that circumventing obstacles to therapeutic success should be explored thoroughly and concomitantly with potential positive effects—despite the fact that such studies are decidedly less flashy.

Yet the justification for increased hope in the future of regenerative medicine is now in place. Detailed knowledge about natural regenerative processes could be combined with therapeutic interventions to stimulate them and selectively dismantle native blockades to the process. The increasing availability of novel biocompatible materials accelerated by the nanotechnology revolution also supports an optimistic outlook for engineering regeneration, including protection from immune attack, in the human body.

"FOR ALL HUMANITY": REALLY?

Which human bodies will benefit from stem cell–based therapies? As with other major issues where biology and justice intersect—such as climate change, sustainability, invasive species, and infectious diseases—broad and critical evaluation of stem cell–based regenerative therapies appropriately includes the context of globalized society. Statements about outcomes of stem cell research benefitting human welfare in total or each person are common, as in "The scientific objective should be to maximize the potential therapeutic benefits of embryonic stem cell research for all humanity" (BNAC 2004).

Such sweeping and all-inclusive language about the benefits of stem cell research for humanity provokes skepticism about a point of great significance. Stem cells may be employed to counter some injuries and chronic degenerative diseases that cause a high proportion of morbidity and mortality in the developed world. However, if current trends continue, novel regenerative therapies generally do not stand to benefit our billions of global neighbors in middle- and low-income nations. This is not to say that poorer nations do not experience morbidity and mortality from injuries or chronic degenerative diseases. Although proportionally less common as a cause of death, each individual case of chronic disabling disease arguably causes *more* suffering in the developing world, due to the direct effects of the quality and quantity of health care available to the patient, as well as indirect effects upon other family members, including lost income and sacrificed education (Adeyi, Smith, and Robles 2007). In considering

the potential for regenerative medicine to improve the health of people in developing countries, an international panel of experts has recommended that the research and development budgets of industrialized nations fund a grand challenges initiative on non-communicable diseases, and that governments and biotechnology sectors in developing countries collaborate effectively with one another and with industrialized nations (Greenwood et al. 2006). This set of recommendations is a tall order indeed, one that acknowledges that all of humanity will not benefit automatically from the achievement of scientific objectives, as some promoting stem cell research have implied. However, although an abundance of therapies of proven efficacy exist, patients in the developing world do not reap much benefit from them relative to their counterparts in affluent nations now. There is no basis for the confident assertion belief that the development of novel treatments would fundamentally change this state of affairs in the future.

Further, the targets of some research on stem cell–based therapies are so-called "diseases of affluence," those in which lifestyle aspects and choices prevalent in high-income nations are known risk factors. These diseases, such as type 2 diabetes and coronary heart disease, affect enormous numbers of those with lifestyle factors common in affluent nations. Diet and exercise, together with environmental and genetic factors, contribute heavily to the incidence and progression of these diseases. Yet despite the prevalence of exacerbating lifestyle factors, chronic degenerative disease patients in affluent nations fare better than their counterparts in poorer ones—access to health care more than compensates for detriment caused by lifestyle factors (Adeyi, Smith, and Robles 2007). In cases like these, the relative consequences of individual choice and societal context are most clearly revealed when globalized society is examined through the lens of biological science.

Stem Cell–Based Regenerative Therapy for Three Disease States

I will now turn the lens of biological science upon the potential use of stem cell–based therapies for three of the most commonly cited examples, since they fall into broad categories that allow extrapolation to other cases: regeneration to repair injury to the spinal cord, type 1 diabetes, and cardiovascular disease. I mean to convey some broad themes: the biological complexity of each disease state, including the underlying cause(s); what is still unknown or not understood about the disease state; a therapeutic landscape where stem cell–based therapies are but one of many options; the risks inherent to cell-based therapy for each disease state; and critical evaluation of cell-based therapies with multifaceted ethical, medical, and financial criteria. My overarching aim for these sections is to make clear that the prospects of stem cell–based regenerative therapies are so distinct from one another with regard to basic science, medicine, sociology, and ethics that appropriate evaluations must distinguish between specific applications

and acknowledge the holistic complexity involved. Along the way, I strive to provide substrates for reason-based analysis of the therapeutic promise of stem cell-based regenerative therapies.

Spinal Cord Injury

The spinal cord is vulnerable to catastrophic injury that can cause loss of sensory and motor functions, including permanent loss of limb movement, somatosensation, and function of bladder, bowels, and reproductive organs. Each year, more than 130,000 spinal cord injuries are estimated to occur in the global human population, and although some spontaneous recovery of function occurs, it is rarely complete for serious injuries (Fawcett et al. 2007). Although robotic prostheses and altering neuronal connectivity are also therapeutic opportunities that could potentially involve stem cells, the limited scope of this article allows me to touch only briefly upon the goals of axon regeneration, remyelination, and increasing the population of functional cells (which could occur through death minimization, stimulation of neurogenesis, or transplantation; Thomas and Moon 2011).

The central (brain and spinal cord) and peripheral (central nervous system out to various regions of the body) nervous systems have different populations of myelin-forming cells, resulting in neuronal fibers that can propagate action potentials rapidly through saltatory conduction on axons at nodes between areas insulated by myelin. In addition to this myelin-forming function, Schwann cells of the peripheral nervous system can actively facilitate the regeneration of a severed axon, whereas the oligodendrocytes of the central nervous system cannot, although mature oligodendrocytes do re-extend processes that intercalate between axons without ensheathing them (Keirstead and Blakemore 1997). Marked loss of neurons and myelinating cells occurs not just with the injury event and aftermath, but also progressively over time (Crowe et al. 1997). Natural molecular barriers to axonal regeneration in the central nervous system exist in myelin (NOGO, myelin-associated glycoprotein, and oligodendrocyte myelin glycoprotein), and more are added through the scar that results from the cellular response to the injury, such as chondroitin sulfate proteoglycans (Fitch and Silver 2008; Kwon, Sekhon, and Fehlings 2010; Rowland et al. 2008; Silver and Miller 2004). Further, axon demyelination can occur at the periphery of the cystic cavity formed at the site of injury (Guest, Hiester, and Bunge 2005; Hill, Beattie, and Bresnahan 2001; Kakulas 1999). Clearly, obstacles to regeneration at the site of a spinal cord injury on the cellular and molecular levels combine to form a complex and multifaceted scene of devastation, one that will be difficult to overcome by a single intervention, including transplantation of stem cells (Kwon, Sekhon, and Fehlings 2010; Thuret, Moon, and Gage 2006).

Stem cells and spinal cord regeneration. As with other stem cell therapy situations, there are threats to positive outcomes with every approach. Injected cells could migrate to unintended sites or cause pain. Along with motor recovery, hypersen-

sitivity has been documented with adult neural stem cells in a rat model of spinal cord injury (Hofstetter et al. 2005). The inherent risks of immunosuppression and tumor formation accompany transplantation of allogenic cells. Indeed, transplantation of neural stem cells of human embryonic origin directly resulted in brain tumor formation in one diseased patient (Amariglio et al. 2009). With iPSCs of neural origin, increased tumor formation after transplantation into brain or spinal cord has been observed in some cases, and epigenetic memory from the mature parent cell is also a concern (Kim et al. 2010; Miura et al. 2009; Tsuji et al. 2010). Establishing a bank of allogenic stem cell lines has also been proposed, though monitoring of changes in genotype and phenotype over time and many rounds of division is a major concern (Thomas and Moon 2011). To summarize results to date, rodent and primate animal models of spinal cord injury have shown moderate functional recovery when stem cells, both allogenic and autologous, are transplanted one to two weeks after injury, but this effect is greatly diminished or eliminated altogether months later (Thomas and Moon 2011; Thuret, Moon, and Gage 2006).

However, there are major caveats. In general, many animal research studies are not designed and conducted according to the highest scientific standards. A 2009 literature survey of animal research revealed that 86% of papers did not report blinding, and 87% did not report randomization when allocating treatments (Kilkenny et al. 2009). Some of the most promising results involving therapies for spinal cord injury that are not stem cell based could not be replicated upon reassessment (Pinzon et al. 2008; Sharp et al. 2010; Steward et al. 2006, 2008). With spinal cord injury, recovery due to early therapeutic intervention cannot be clearly distinguished from spontaneous recovery. Further, a direct role for transplanted cells has been called into question due to their low survival rate and the facts that some gain of function has been observed with many cell types, and that even killed cells can be reparative (Arboleda et al. 2011; Thomas and Moon 2011). Indeed, in most cases direct causal links between the transplanted cells, changes in morphology, and recovery of function have not been established empirically (Thomas and Moon 2011; Thuret, Moon, and Gage 2006). Also, the roles of endogenous factors, timing, and cellular dynamics of the wound environment are not well understood (Almad, Sahinkaya, and McTigue 2011).

Without more clarity about the biological factors and mechanisms that contribute to recovery, it is difficult to imagine a safe and consistently effective therapy for spinal cord injury within the next decade. Nonetheless, in pursuit of the first-to-market advantage (Thomas and Moon 2011), Geron (2011) began a Phase 1 clinical trial with a human embryonic stem cell-derived treatment in October 2010. Amidst substantial ethical and scientific controversy, treatments have been administered to two subjects with no results reported to date (Regaldo 2011). Even strong proponents of stem cell research warn patients that most stem cell–based therapies, including those for spinal cord injury, are experimen-

tal and are not known to be safe, superior to existing therapies, or effective at all (ISSCR 2008).

Despite this fact, some desperate patients and their caregivers take enormous risks with black-market embryonic stem cell therapies administered in fly-by-night clinics (Regaldo 2011). Faced with the sudden crisis of a spinal cord injury today, the injured person or caretaker may agonize while weighing options: the possibility of regeneration or detriment through experimental stem cell–based therapy; a wait-and-see approach with hope for natural restoration; a previous standard of care now called into question by some medical experts (as in the case of methylprednisolone); and a variety of other new/experimental therapies that act by blocking inhibitors of regeneration, preventing cell death, reducing neuroinflammation, and other mechanisms (Kwon, Sekhon, and Fehlings 2010). Extensive research and results collected over many years stand between the meager and shaky offerings of today and the proven, highly effective therapy options, fervently sought now, that will offer hope for treatment of spinal cord injuries in the future.

Type 1 Diabetes: Genetic Autoimmune Condition

Type 1 diabetes mellitus, also known as juvenile or insulin-dependent diabetes, is an autoimmune disorder that affects >1% of the population worldwide. The cause of the autoimmunity underlying type 1 diabetes is still unclear, though multiple genetic loci and environmental factors have been implicated (Hirschhorn 2003; Krishna, Rao, and Rao 2007). With type 1 diabetes, β cells from the islets of the pancreas that secrete insulin in a glycemic responsive manner are targeted for T cell–mediated immune attack. Since β cells give rise to additional β cells, the primary means for replenishing the insulin-producing β cell population is also destroyed. The consequent insulin depletion results in hyperglycemia and decreased cellular uptake of glucose. Insulin depletion can also perturb fatty acid metabolism, leading to an overproduction of ketones that is fatal if not treated. Several multiorgan morbidities may occur in type 1 diabetes by early adulthood, including blindness, peripheral vascular disease, neuropathy leading to amputations, renal failure requiring dialysis, and cardiovascular events (myocardial infarction, stroke).

The life expectancy of type 1 diabetics is reduced, and current treatment options leave much to be desired. Insulin injections are necessary for the survival of a type 1 diabetic, but monitoring and injections are not equivalent to the exquisite sensitivity of glycemia-stimulated insulin secretion by β cells (Wagner et al. 2010). Although transplantation of pancreatic or purified insulin-producing islets can result in reduced insulin dependence and increased glucose stability, a lack of suitable donor tissues and the potential for adverse long-term effects such as graft rejection or nephrotoxicity (kidney damage) caused by immunosuppressive agents prevent widespread therapeutic use (Bromberg et al. 2007;

Campbell et al. 2007; Shapiro et al. 2006; Vardanyan et al. 2010). Some evidence suggests that continuous subcutaneous insulin infusion via insulin pump offers lifestyle and clinical advantages compared with multiple daily insulin injections, but psychosocial issues such as pump visibility and physical restrictions are significant disadvantages to wearing a device 24 hours per day, particularly for young patients (Alsaleh, Smith, and Taylor 2011). Stem cell–based approaches have entered the scene and offered some hope for providing patients with type 1 diabetes with an endogenous source of insulin.

β cells wanted: Could stem cells meet the need? The promise of stem cells to increase β cell mass in patients with type 1 diabetes has been explored on multiple fronts. In addition to pluripotent embryonic or iPSCs, facultative stem/progenitor cells from the spleen, liver, bone marrow, endometrium, and pancreas (endocrine α and preexisting β cells, as well as exocrine acinar and duct cells) have been investigated as potential wells to be tapped for β cell regeneration (Li et al. 2010; Wen, Chen, and Ildstad 2011). Following proteomic analysis of splenic stem cells for markers of multipotency, Faustman and Davis (2010) explain a key concept in this quest:

> In a series of experiments, we asked which expressed proteins are associated (with) splenic stem cells' multi-lineage capacity. The second order question was "how early" are the proteins expressed along the commitment trail? Cells that are too early along the lineage trail may be too unstable and thus pose a risk of carcinogenesis, whereas cells that are too far along in the commitment process might be safe but do not have enough versatility to be stem cells beyond one or two tissues. (pp. 1578)

Investigations to empirically determine whether transplantation of stem cells from the spleen, liver, or bone marrow have therapeutic potential for type 1 diabetes, and their mechanisms of action, are ongoing. Trans-differentiation of various types of liver cells into pancreatic lineages through viral delivery of pancreatic transcription factors have been demonstrated, including therapeutic proof-of-concept studies by Yechhoor et al. (Aviv et al. 2009; Manohar and Lagasse 2009; Nagaya et al. 2009; Yechoor et al. 2009a, 2009b; Zalzman, Anker-Kitai, and Efrat 2005). Stem cells from the spleen have been shown to reverse diabetes in a mouse model when autoimmunity was kept at bay (Kodama et al. 2003). Whether CD45- splenic stem cells positive for Hox11, an embryonic transcription factor, are capable of generating β cells or not remains controversial (Chong et al. 2006; Dieguez-Acuna et al. 2010; Faustman and Davis 2010; Lonyai et al. 2008; Nishio et al. 2006).

Low oncogenic potential for splenic stem cells, much later on the commitment trail than embryonic stem cells or iPSCs, has been touted as a major potential benefit of their therapeutic use (Dieguez-Acuna et al. 2010; Faustman and Davis 2010). A number of strategies to circumvent the tumor risk associated with embryonic and iPSCs approaches have been proposed. Employment of available cell sorting technologies to ensure that cells differentiated in vitro prior to ther-

apeutic use are not contaminated with still-pluripotent cells that can give rise to teratomas is being widely discussed as one possible solution, though the sorting process may be detrimental to the quantity or quality of cells injected (Maehr 2011; Wagner et al. 2010). Apoptosis-inducing suicide genes can be introduced to pluripotent cells by viral transduction without loss of function. The integrated suicide genes then function as switch, flipped upon drug (nontoxic preform) administration (Kiuru et al. 2009; Zhong et al. 2011). Thus, suicide genes seem to be another promising option for safeguarding patients from tumors derived from pluripotent cells, though there is risk inherent to the genomic integration the technique requires (Schuldiner, Itskovitz-Eldor, and Benvenisty 2003). Finally, shrinking established teratomas is possible through the inhibition of a specific transcription factor, Nanog, by disruption of its regulatory pathway (Moretto-Zita et al. 2010).

The autoimmune problem and unanswered questions. Increasing the number of glycemia responsive β cells, like the addition of exogenous insulin, is a treatment for type 1 diabetes, but it is highly unlikely to be a cure because the transplanted β cells would also be targeted by the immune system (Azzi et al. 2010). Metaphorically, pouring more functional β cells into the system does help alleviate the drought, but the system cannot be adequately saturated because the drain caused by the autoimmunity underlying type 1 diabetes is so large and remains open constitutively. The most effective intervention strategy for type 1 diabetes will be a combination approach that addresses both reestablishing a self-replenishing supply of cells capable of glycemia-stimulated insulin secretion and protecting these cells from attack by the immune system, ideally without need for risk-inherent immunosuppression (Krishna, Rao, and Rao 2007; Wainwright et al. 2006).

One approach proposed to address the autoimmune component of type 1 diabetes involves modeling and understanding the initiation and progression of the disease by using patient-specific iPSCs cells in vitro or in humanized rodent systems (King et al. 2008; Maehr 2011). While this approach could identify novel targets for treatment or system components for modulation, cloaking strategies have also been pursued. Encapsulation of stem cells, shielding them from immune attack while allowing for insulin efflux, has yielded promising results: they have been shown to be clinically effective (glucose levels, body weight), not tumorigenic, and isolated from the immune system in a mouse model (Dean et al. 2006; Ngoc et al. 2011; Shao et al. 2011). Another means for addressing the β cell autoimmune attack is inherent in specific stem cell types: hematopoietic stem cells and mutipotent mesenchymal stromal/stem cells. Transplantation of hematopoietic stem cells, native to the bone marrow, has been used for the treatment of autoimmune disease (Couzin-Frankel 2010). Clinical studies involving transient immunoablation to "reset" the immune system, followed by reconstitution with autologous hematopoietic stem cells, have demonstrated some positive results, even after multiyear follow-up, for patients with type 1 diabetes (Burt et al. 2002; Couri et al. 2009; Diabetes Research Group 1998; Milanetti et al. 2010 Snarski

et al. 2011; Voltarelli et al. 2007). However, there are lingering nontrivial concerns, such as the common occurrence of adverse effects, efficacy that is restricted to the new-onset period, and concerns about study design (Couri et al. 2009; Rosengren et al. 2009; Ross and Philipson 2007; Voltarelli et al. 2007).

Mechanisms of action behind the observed positive results of autologous hematopoietic stem cell transplantation have yet to be clearly elucidated, but results suggest the immune tolerance may be achieved through reduced autoantibody titers, cytokine effects, and cellular alterations (Voltarelli et al. 2008). Though not thought to become β cells themselves, hematopoietic stem cells may promote increased β cell mass through enhanced neovascularization, decreased apoptosis, or stimulation of proliferation (Hess et al. 2003; Lechner et al. 2004; Rosengren et al. 2009; Taneera et al. 2006). Multipotent mesenchymal stromal/stem cells also originate from bone marrow. Their immunomodulatory properties have been demonstrated, including increased Treg cells (Berman et al. 2010). Animal models for type 1 diabetes have demonstrated the therapeutic efficacy of mesenchymal stromal/stem cells (Jurewicz et al. 2010; Madec et al. 2009; Neshati et al. 2010), although whether or not these cells give rise to β cells or serve to enhance or support β cell function in addition to their immunomodulatory effects remains controversial (Chandra et al. 2009; Fiorina et al. 2009; Kang et al. 2009; Lee et al. 2006; Sordi et al. 2010). Interestingly, it seems that β cells do not fully mature in vitro, and that in vivo niche factors are essential for the final steps of the process (Kroon et al. 2008; Naujok et al. 2009; Wagner et al. 2010). In order for the promise of stem cells in type 1 diabetes treatment to be realized with maximum benefit and minimization of adverse effects, more detailed and comprehensive answers to the relevant fundamental questions are needed. What causes the autoimmune targeting of β cells? What factors are necessary for glycemia-stimulated insulin secretion? Which stem cells can give rise to β cells?

Cardiovascular Disease

In 2007 (the most recent year for released mortality data), cardiovascular disease accounted for 1 in 2.9 deaths in the United States. The likelihood of death from heart disease increases dramatically with each passing decade of life. In the United States, the death rate (per population) increases 2.3 fold between 55- to 64- and 65- to 74-year-olds, another 2.84 fold between 64- to 74- and 75- to 84-year-olds, and an additional 3.25 fold between 75- to 84-year-olds and all of those 85 and older (NCHS 2011). Over two-thirds of deaths attributed to cardiovascular disease occurred at 75 years of age or older (Roger et al. 2011). In considering intervention, it is useful to distinguish whether the goal is to reduce the instances where cardiovascular disease is the cause of death, as is appropriate for suicide, accidents, or drowning, or whether the goal is compression of morbidity, or reducing the span of disability preceding a death that is not premature—a goal of healthy aging (Adeyi, Smith, and Robles 2007). In monetary

terms, cardiovascular disease costs Americans more than any other diagnostic category, including all cancers and benign neoplasms combined.

Risk factors for cardiovascular disease have been well established, are prevalent in the U.S. population, and are not well controlled, despite broad dissemination of information, clinical advising, and social supports for responsible self-care. One in five Americans is a cigarette smoker, a proportion that holds even among students in grades 9 through 12 (Roger et al. 2011). Despite numerous forms of promotion that encourage a healthy lifestyle by exercising more and eating less, actual behavior is trending in the opposite direction. Between 1971 and 2004, average total energy consumption by adult American men has increased by 9% in men and by 17% in women (NCHS 2011). Thirty-six percent of adults admit to engaging in no vigorous activity whatsoever. Children 6 to 11 years of age have exhibited a dramatic change in the prevalence of obesity over three decades, from approximately 4% to over 20%. In 2008, the proportion of American adults meeting criteria for overweight and obese is approximately two-thirds, with half meeting body mass index criteria for obesity. Incidence of diagnosed diabetes mellitus (with the vast majority of patients type 2, adult onset) has risen dramatically along with the proportion of overweight and obese to 8% in 2008, with 37% exhibiting abnormal fasting glucose levels or prediabetes (Roger et al. 2011). Data from a three-year nationwide survey reveal that over a third of adults in the United States have hypertension, that one-fifth of these are not aware of their condition, and that less than half of those aware of their condition have it under control (CDC 2010).

This bleak picture provides the backdrop for rampant cardiovascular disease, and although the scene could be radically changed by modification of human behavior on a population level, many patients experience damage, such as left ventricular remodeling and dysfunction, that cannot be reversed without direct medical intervention. Existing treatment options include medications, bypass surgery, or angioplasty. However, one-year mortality rates for acute myocardial infarction (heart attack) remain as high as 13%, and approximately 20% for heart failure (Mathiasen, Haack-Sorensen, and Kastrup 2009; Mozid et al. 2011). For this reason, the quest to improve outcomes with new intervention strategies is the subject of active research. Regenerative stem cell therapy is one of the treatment options currently under investigation for myocardial infarction and heart disease.

Cardiac regeneration via stem cell therapy. Although the human heart contains progenitor cells capable of self-renewal, the intrinsic repair mechanism is insufficient to restore myocardial contractile function to compensate for the extensive tissue damage associated with a myocardial infarction (Bergmann et al. 2009; Marban 2007; Nadal-Ginard et al. 2003). In order to contribute to cardiac function, therapy-derived cardiomyocytes must integrate with native cardiomyocytes electrically and mechanically (Segers and Lee 2008). A number of allogenic and

autologous stem cell types have been investigated in animal models of cardiovascular disease, as well as in human patients in some cases.

Although other cell types have shown promising results, heart failure and left ventricular damage due to myocardial infarction have been investigated in two main cell types: skeletal myoblasts and bone marrow–derived stem cells (Christoforou et al. 2010; Mozid et al. 2011). Engraftment of skeletal myoblasts improved cardiac function in animal models of myocardial infarction, but early clinical trials revealed elevated levels of ventricular tachyarrythmia, and the study was halted prematurely. This disappointing result has been attributed to the lack of connexin-43 expression in skeletal myoblasts post-transplantation, causing a failure of electrical integration with host myocardium. Transplantation of bone marrow–derived stem and progenitor cells has also resulted in improved cardiac function. Although administered cells integrate into myocardium, genetic data suggest that the mechanism of therapeutic action is derived from their paracrine effects, rather than proliferation and function of the cells themselves (Balsam et al. 2004; Murry et al. 2004; Nygren et al. 2004). These paracrine effects include neovascularization, restoration of extracellular matrix, recruitment of endogenous stem cells, and anti-apoptotic effects. Low retention of stem cells in the infarcted area, failure of transplanted cells to survive long-term, and functional substitution of cell-free bone marrow extracts for intact cells support the finding that cardiac regeneration via stem cell therapy is accomplished indirectly through paracrine effects rather than the transplanted cells (Lee et al. 2011; Muller-Ehmsen et al. 2006; van der Bogt et al. 2008; Yeghiazarians et al. 2009). A subpopulation of stem cells derived from bone marrow, mesenchymal stem cells, are notable in that they appear to possess immunoprivilege, which could allow for allogenic transplantation (Pittenger and Martin 2004). Bone marrow–derived stem cells are also pragmatically favorable for autologous use, since procedures for harvest and ex vivo expansion are well established. Investigations of the potential therapeutic use of bone marrow–derived stem or progenitor cells have advanced to clinical trials.

Other heart health strategies. Cutting-edge treatment options extend beyond exogenous stem cells alone. Resident cardiac stem cells combined with growth factors improve cardiac function (Urbanek et al. 2005). The ultimate approach to cardiac tissue regeneration may be a carefully orchestrated combination of cardiac stem cells, transplanted stem cells, growth factors, and biomaterials (Madonna and De Caterina 2011). Although many years stand between the present and a future time when such a complex approach has been refined and tested for general medical use, experts in the field are intent on developing an effective strategy: "Given our increasing ability to control the fates of cells and tissues, the debate over whether the heart is intrinsically terminally differentiated seems anachronistic, for the heart does not exist apart from the person who knows how to manipulate it. It is more useful to ask what we can do to promote cardiac regeneration best, and then do it" (Laflamme and Murry 2011, p. 334).

Fortunately, the means for controlling many cases of myocardial infarction and heart disease are already in our hands. Established and readily available strategies, such as beta blockers and aspirin, should be used more consistently and effectively (Braunwald 1997). For example, aspirin was administered in less than half of myocardial infarction cases in multiple studies (Mathews et al. 2010; Saketkhou et al. 1997). We also know of another safe, inexpensive, and extremely effective approach: prevention through healthy eating and regular exercise. In the Surgeon General's National Prevention Strategy, released June 16, 2011, healthy eating and active living are two of the seven priorities articulated (National Prevention Council 2011). The document highlights food insecurity and the fact that 23 million Americans live in "food deserts" peppered with fast food restaurants and convenience stores but without access to the healthy offerings of a supermarket. The first goal articulated in the healthy eating section of the strategy document is to "increase access to healthy and affordable foods in communities" (p. 34). The active living section points out factors of the modern lifestyle such as "screen time," as well as the obstacles faced by ethnic minorities who disproportionately inhabit communities perceived as too unsafe for outdoor exercise. Yet these sociological realities are not the only factors that explain our difficulty in disease prevention through diet and exercise. To identify and make sense of some of the biological factors, it is helpful to consider them in the light of evolution. As Theodosius Dobzhansky (1964) succinctly put it: "nothing makes sense in biology except in the light of evolution, *sub specie evolutionis*" (pp. 449).

The discordance hypothesis and cardiac tissue damage. Human history has outpaced human evolution. Although we possess many evolution-refined biological traits that contribute to human flourishing in a modern cosmopolitan lifestyle, some long-standing and once-beneficial traits are destructive out of context. In the field of evolutionary medicine, this phenomenon of mismatch between genome and lifestyle is called the "discordance hypothesis" (Eaton, Cordain, and Lindeberg 2002; Eaton et al. 2002). When food was scarce, energy was expended in obtaining it. This inherent exercise and lack of opportunity for overeating means that self-control was not needed to prevent obesity. In fact, craving and tendency to consume abundant quantities of sweet or fatty foods would confer a survival, and thus selective, advantage (Nesse and Williams 1998). Additionally, the propensity to become sedentary upon opportunity would shield an individual from predation and conserve energy for food acquisition and reproduction, which would also confer a selective advantage.

These inborn tendencies to avoid unnecessary exercise and eat fatty and sweet foods in combination with the attributes of a cosmopolitan lifestyle—sedentary-but-stressful work, plentiful food that maximizes shelf life and consumer appeal over nutritional value, little time allotted for food preparation, and reliance upon transportation—add up to explain today's rampant obesity and related disease states in the United States and other developed nations. Interestingly, chronic degenerative diseases, including heart disease and type 2 diabetes related to obe-

sity, are only rarely observed in modern foragers, even at advanced ages (Eaton et al. 2002). Prevention of obesity-related chronic degenerative diseases in a modern environment requires deliberate effort against nature's current, as it has been established by biological evolution. Specific genes, interpersonal interactions, life events, and microenvironments can render this effort even more challenging for some individuals, and obesity frequently becomes a lifelong problem (Knowles 2009).

Biomedical Research and Stewardship of Limited Resources

Though covering the demographic data is beyond the scope of this article, it is important to acknowledge that some racial and ethnic minorities suffer from obesity-related diseases at rates much higher than the general population. Effective prevention programs must acknowledge the importance of long-standing cultural traditions and reluctance to change them, out of respect for the traditions themselves and for social justice reasons. Individuals and societies can be responsible for understanding the human body, including areas of antagonism between the products of historical and evolutionary trends, and learn to better care for it. Supporting a potential "magic bullet" of stem cell–mediated tissue regeneration at the expense of attention and commitment to maintaining health and avoiding obesity-related tissue damage in the first place is an error in judgment and strategy.

Are we making that error today? In a recent article in the *New England Journal of Medicine*, Yanovski and Yonovski (2011) state that: "As increasing recognition of the public health impact of obesity leads to implementation of programs and policies, it is also essential that outcomes be evaluated so that we know what works and what doesn't and can direct our energies and resources toward strategies that are most likely to be successful" (p. 989). Yes, but what if we cannot collectively afford the strategies (such as surgeries or other intensive treatments) that are most likely to be successful? Although it is a nation of great wealth, resources for biomedical research in the United States are quite limited, access to them is extremely competitive, and many qualified researchers are denied the means necessary to do promising work. In FY2010, only 22.6% of reviewed National Institutes of Health (NIH) grant proposals were funded (NIH 2011a, Table 205-A). There are nearly 7,000 rare diseases, yet we have therapies for fewer than 200 of them (Collins 2011). Thus, every decision about resource allocation for research, even when not directly involving the unborn or epidemic lethality, is life or death for someone, now and in the future. Evaluating allocation of funds for basic and biomedical research toward responsible stewardship of limited collective resources is hardly a simple task, as publicly available estimates of funding through the Research, Condition, and Disease Categorization (RCDC) system

of the NIH presents figures for categories that are not mutually exclusive and determined by data mining. Since "the NIH does not expressly budget by category" (NIH 2011b), critical evaluation and open debate regarding the relative distribution of resources based upon data analysis are in effect discouraged.

Whose voices are audible in the conversations that determine resource allocation? Chronic degenerative diseases related to obesity affect many adults, and therefore many people who vote in a democracy. Elected officials demonstrate commitment and prioritization primarily by allocation of financial resources, and this is an effective means of advancing research and social programs that support the common good. However, at times dollars are shuttled toward a problem even when resource-intensive methods are not the best means of solving it at that moment, because this action is the most straightforward and because it appeases and pleases the greatest number of people. Burkitt's axiom—that reduction of disease incidence is not accomplished by improving diagnosis and therapy alone—applies to obesity-related disease. The recent release of the Surgeon General's National Prevention Strategy is an encouraging move in the direction of a collective and state-supported emphasis on prevention (National Prevention Council 2011).

Manifold Discord: A Hazard to Individual and Public Health

Prevention strategies for reducing disease-related suffering seek to engage and aid both mind and body. Both the Cartesian dichotomy of mind and body and the inextricable link between body and soul described by Aristotle may be useful for analyzing human health through the lens of evolutionary medicine. With regard to the Cartesian dichotomy, the difficulty is the increasing discordance between a physiological form shaped by biological human evolution and a mind encountering an environment shaped by sociocultural evolution. The gap continues to widen because biological evolution generally advances at a very slow pace, especially compared to the radical changes in the human habitat instigated primarily by human behavior. The most recent two or three centuries and the small number of generations therein are minute compared to the time over which biological human evolution has occurred (Eaton et al. 2002). With regard to Aristotle, the notion that the body and soul are inextricably linked, though distinct, leads to the conclusion that the proper care and keeping of a human being encompasses both (Stauffer 2010). Ideally, this care would occur in harmonious balance, as simultaneously as possible, throughout the lifespan of each person, rather than expressing behaviors selected for during biological evolution, accruing physiological damage as a result, and then turning to the products of sociocultural evolution—such as modern medicine, including stem cell–based regenerative therapies—to repair or replace damaged components of the physical form.

If self-understanding through an evolutionary lens is one key to the stewardship of our bodies and collective public health resources, why isn't this powerful argument put forward more broadly? Konner (2001) laments that: "One can only wonder how many lives might have been saved if Darwin's *Origin of Species* had been incorporated into medical school curricula when it was published in 1859. Or even, alas, a century later" (p. 361). However, the practice of medicine is most often focused on the individual patient at one moment in time. Health interventions imposed at the population level, such as water fluoridation, may be met with suspicion and intense scrutiny (Bryson 2004; Doull 2006). Also, science illiteracy and media illiteracy among the American public, including some religious believers who reject evolution on religious grounds, means that attempts to introduce evolution-based medicine would likely provoke widespread hostility, and therefore prove self-defeating. These same traits have led to ignorant condemnation of all stem cell research. This is an extremely worrisome state of affairs, because irrational and vitriolic conflict between the scientific and religious communities in the agora will surely continue to damage both, and future generations will pay the greatest price.

Against Oversimplification and Dichotomy in the Agora

At present, the agora is dominated by impassioned, irrational, and combative conversation about stem cell research toward regenerative therapies. As this article has illustrated, the realities surrounding stem cell research and its aims are multidimensional and fraught with complexity. Black-and-white rhetoric sells: it puts dollars behind research projects and lucrative advertising into media products. Responsible evaluation of options related to stem cell–based regenerative therapies will entail eschewing black-and-white thinking and confronting complexity, as well as uncertainty, ethical issues, and prioritization.

The three disease states explored in this paper suffice to illustrate profound biological and sociological differences between potential uses of stem cells for therapeutic purposes. Clearly, "stem cell research" and "regenerative medicine" do not describe well-defined endeavors, but represent broad categories encompassing significant heterogeneity. By considering biological areas individually, we can begin to formulate penetrating, real-life questions that extend beyond the realm of science. Which disease states should be targeted for treatment by regenerative medicine? Which patients? At what cost? How are cell-based therapies evaluated against other alternatives? Is the goal of regenerative medicine best illustrated by beneficially altering an inherent disease state in young children (as in type 1 diabetes), by restoring lost physiological function to young adults healthy enough for high-risk physical activity (as in spinal cord injury), or by repairing or replacing damaged or worn out parts in older adults (as in cardiovascular disease)? All of these? Why?

Apart from the common stem cell means, the aims in these cases are quite distinct, and they merit rational evaluation that acknowledges differences as well as commonalities and respects different human stakeholders more than the broad aims of cause advancement and political positioning. If the primary aim of those engaged in the stem cell debate is to prevail in a new battleground in the ongoing right-to-life versus abortion-rights war, then one side or another may have something to celebrate. However, if there is truth to the claim that the primary aim of stem cell research advocacy is positive outcomes for humanity and the alleviation of suffering, then the current conversation in the agora is itself an impediment to the pursuit of this noble goal and a collective failure to apply the best of our capabilities when human lives are at stake.

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