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Ethical Considerations in Stem Cell Research on Neurologic and Orthopedic Conditions

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Abstract

The range and gravity of ethical considerations in stem cell research are remarkable and, quite possibly, unprecedented. From the point of securing stem cells for implantation, through the translational and first-in-humans process, and then proceeding through clinical trials culminating in product or service line launch, the entire research trajectory is replete with risk, uncertainty, and problems overweighing foreseeable harms against hoped-for benefits. This article offers an overview of some of the most salient ethical challenges of stem cell research, including ones involving moral status, the intersection of research risks and informed consent processes, methodologic considerations in early phase 1 trials, the temptation to exaggerate the benefits of research discoveries, managing conflicts of interest, and the ethical obligation to conduct various monitoring practices throughout a trial, which could last years. The article will conclude with a glimpse into the future of these technologies wherein the need for ethical scrutiny will likely not diminish.

Introduction

Stem cells are biological products derived from various sources, including aborted fetal brains, umbilical cord blood, spinal cord tissue, hematopoetic cells, immortalized stem cell lines (derived from human teratocarcinoma), adipose tissue, autologous cells (derived from bone marrow and adipose tissue), and human embryos created in laboratories or left over in clinics performing in vitro fertilization [1-3]. Their interest to contemporary clinical research cannot be exaggerated in light of their combined "pluripotent" and longevity properties, ie, their ability to change from undifferentiated to differentiated cells and proliferate in the 3 germ layers, ie, the ectoderm (regulating skin and the nervous system), the mesoderm (affecting bone and muscle formation), and the endoderm (affecting organs like the lungs and digestive system). The therapeutic and regenerative possibilities stem cells represent for repairing damaged or nonfunctional tissue are breathtaking. Clinicians anticipate that the future of stem cell technologies will improve or restore function in potentially all major organ systems while in 2013, stem cell transplantation research was already in phase 3 trials for Crohn disease, bone marrow transplant procedures, congestive heart failure, limb and myocardial ischemia, liver failure, leg ulcers, leukemia and lymphoma, retinitis pigmentosa, and cartilage disorders and defects [4,5].

Although not anywhere as advanced, stem cell research for orthopedic conditions such as for bone fracture and cartilage and tendon repair have been underway for some time [3]. Unlike human embryonic stem cells, the cells used in these studies are adult, *multipotent* cells that have limited ability to differentiate into preferred cell types in contrast to pluripotent cells [2]. Found in the bone marrow, hair follicles, adipose tissue, and the intestinal villus crypt, these cells nevertheless show a remarkable affinity for differentiating into cartilage, adipose tissue, and bone cells (thus their interest from the orthopedics community). Mesenchymal stem cells harvested from bone marrow have especially shown excellent osteogenic differentiation in animal studies, are known to home in on the kinds of injured tissue typical in fractures, and exhibit paracrine-based mechanisms of tissue healing marked by a reduction of inflammation without immune rejection [3].

Presently, no stem cell trials aimed at improving neurologic or orthopedic functioning have received

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approval from the Food and Drug Administration (FDA), because the challenges of these kinds of research are daunting [6]. Not only must researchers solve the problems of delivering and engrafting the cells to the correct anatomical site, but the cells must be "coaxed" to differentiate, proliferate, and, most importantly, result in the organism's exhibiting a meaningful and empirically measureable structural improvement or functional change. As discussed herein, the entire research trajectory—from the moment of securing stem cells for implantation, through the translational and first-in-humans process, and then proceeding through clinical trials culminating in product launch—is fraught with unpredictability and ethical challenges. What follows is a brief overview and discussion of some of the more salient ones.

Stem Cells and Moral Status

Anyone even modestly familiar with ethical dilemmas surrounding stem cell research is probably aware of the most familiar one: strident moral objections to the creation of human embryos from which stem cells are derived and used. Opponents of stem cell research that uses human embryos understand the human embryo to have "moral status" upon its creation and argue that it must be accorded fundamental human rights from the moment of its conception. As such, the removal of the embryo's stem cells at the blastocyst stage (around the third to fifth day of embryogenesis), resulting in embryonic death constitutes, to them, a frank homicide [7]. Indeed, the National Institutes of Health (NIH) will not fund stem cell research wherein the cells are derived from human embryos created specifically for research purposes [8]. NIH-funded researchers who use human embryonic cells must secure these cells either from the NIH Registry or from clinics or facilities where the cells were intended originally for reproductive purposes and are no longer needed [8]. Consequently, even if one hesitates to confer "moral status" at the blastocyst stage, positions like the NIH's resonate with the "symbolic significance" of the human embryo, given its potential for eventually attaining inarguable moral status along with the fact that all of human life begins with a fertilized ovum that proceeds through the expression of its embryonic genes [9].

In 2006, Takahashi and Yamanaka [10] discovered how to develop human induced pluripotent stem cells (iPSCs). iPSCs are derived from adult skin cells, which Yamanaka and his colleagues discovered how to genetically manipulate and alter to behave like human embryonic stem cells. Because they do not require the creation of a human being, ie, embryo, and exert no compelling claim to moral status, many (especially conservative) ethicists hailed the technological discovery and pronounced the problem of moral status resolved [11].

Unfortunately, that scientific enthusiasm and moral relief turned out to be premature. Some scientists pointed out that small, still poorly understood differences—which can nevertheless have colossal clinical repercussions—are known to occur in gene-expressed patterns of iPSCs. They may not behave enough like human embryonic stem cells and may ultimately yield clinically disappointing results. Other, albeit preliminary studies, have suggested that iPSCs retain some "epigenetic memories" of their original somatic cells that could interfere with their differentiating into preferred cell types [12]. Still other researchers point to the amount of manipulation required in creating iPSCs and worry that those manipulations can cause undesirable and harmful mutations in resulting cells [11].

Only time will tell whether iPSCs represent therapeutically realistic alternatives to human embryonic stem cells, and we will probably witness trials comparing results from the 2 for quite some time. It nevertheless seems a virtual certainty that any ethical resolution of the more fundamental ideological debate regarding when to ascribe moral status is unlikely anytime soon. Obviously, the question isn't an empirical or factual one that can be scientifically settled but rather a valuative one to which different people will bring different points of view. Because those points of view are themselves nested in and informed by larger and even deeper networks of fundamental moral beliefs, feelings, and intuitions that resist scientific proof, the debate may go on endlessly [13].

Interestingly, the use of mesenchymal stem cells for orthopedic conditions may avert these ethical worries because they are adult (often autologously donated) cells; do not require the creation of an embryo; and, hence, have no claim on moral status. Because their ability to differentiate is not as elaborate as pluripotent, embryonic cells, however, only time will tell whether they can deliver satisfying, clinical outcomes. Some investigators, for example, have derived mesenchymal cells or "chondrogenically committed cells" from human embryonic cells for cartilage tissue regeneration [14,15]. If that technique consistently delivers functional outcomes that prove vastly superior to the use of only adult stem cells, it will reintroduce the violation of moral status controversy in orthopedic stem cell research. Alternatively, if adult stem cells can stand on their own without the supplementation of ethically controversial materials, the moral status question surrounding stem cells will seemingly be overcome.

Research Risks and Methodology

Informed Consent

If significant ideological differences revolve around whether the use of human embryonic stem cells in neurologic research is or is not ethical, shouldn't

investigators consider those differences in formulating their informed-consent processes? Some patients who consider enrolling in trials might be concerned and perhaps decline treatment upon learning that they will receive biological products resulting from the intentional destruction of human embryos, whereas some clinicians might not wish to participate in research dependent on those materials. Consequently, ethicists urge that participants be informed of the origins of the transplanted materials [16].

Furthermore, a number of stem cell investigations of neurologic conditions have been launched, including for stoke, Parkinson, amyotrophic lateral sclerosis, pediatric neurodegenerative disease, and brain trauma [17]. Because a great deal of this research remains in early, phase 1 trials, however, research participants need to understand the nature and magnitude of risk that is present, especially given the difficulty of translating animal research to humans [18]. The literature on research risks typically observes that once stem cells (regardless of their origins) are implanted, they cannot be explanted; they might migrate to undesired and undesirable anatomical sites; the risk of oncogenesis cannot be discounted because of the use of immunosuppressive medications and the possibility of cellular mutation; and complications such as seizures, pain, and worsened disability have been known to occur [16].

Reviewing a stem cell study of 7 patients with spinal cord injury in China, neurologists from the United States noted that inappropriate sites were injected; that one patient suffered life-threatening complications, including posttransplant meningitis, pneumonia, and gastrointestinal bleeding; and that no significant functional improvements could be detected in any of the patients [19]. Another case study involving a child who had gone to a Moscow stem cell clinic reported that the child developed numerous tumors in his brain and spinal cord after receiving the transplants [20]. Obviously, these kinds of risks are especially real and "more than minimal," prompting ethicists to call for multiple layers of research protections that will be discussed in this article.

Safety Risk in Orthopedic Research Using Mesenchymal Stem Cells

Because many stem cell trials in orthopedics not only use adult stem cells but autologous (self-donated) ones, much of the worrisome risk profile described previously is increasingly thought to be eliminated. Indeed, various researchers reporting their experience with culture-expanded, adult stem cells have described an exceedingly positive safety profile.

Perhaps most compelling is the 2013 report by Hernigou et al [21], who followed 1873 patients treated from 1990 to 2006 with autologous bone marrow cell concentrate. The mean follow-up time was 12.5 years, and the study used magnetic resonance imaging and radiography to determine the appearance of cancer at the treatment site or elsewhere. The investigators found no tumor formation at the site of implantation. Although 53 cancers were diagnosed in other sites, it is unlikely that those tumors were related to treatment, especially because that number was considerably less than what the expected number would be for patients of the age and gender distribution of the research participants.

Likewise, Centeno et al [22] found no neoplastic complications among 227 patients who were treated for various orthopedic conditions with autologous, mesenchymal cells. This is not to say, however, that no adverse events occur in such procedures, as Centeno et al reported 7 instances of probable procedure-related complications and 3 cases of possible stem cell complications. Yet, all turned out to be self-limiting or were treated with simple therapeutic measures. Perhaps this is not surprising, because these cells are self-donated and thus less likely to result in the formation of tumors. We might additionally mention that some types of mesenchymal cells appear to exert a tropic effect on other cells in the environment that is believed to promote tissue repair [2]. Also, autologous cells are manipulated considerably less than iPSCs, such that the likelihood of contamination via procedure is probably dramatically reduced.

Nevertheless, and as attested to by other articles in this issue, many details regarding the use of these stem cells are unknown and need to be perfected, including choosing the best source for deriving them (which might vary depending on the pathology being treated), standardizing the optimum numbers of cells to inject and timing the injections, standardizing protocols for extracting and expanding stem cells from their original cellular environments, and standardizing the injection protocols themselves [23,24].

The Reasonable Person Standard

A popular standard that ethicists have urged for determining the scope and content of informed consent communications is the "reasonable person" standard, meaning that disclosure of information should include what a "reasonable and prudent" person would wish to know, especially as that information might affect his or her decision to undergo some kind of treatment [25]. Because research trials with humans typically do not hold out therapeutic promise or value in their early stages but rather begin with determining safety without promising benefit, however, the informed consent process in research tends to be more scrupulous than it does in clinical care [26]. As in any research trial, because human participants are being *used as a means* to gain generalizable knowledge rather than being treated as ends in themselves, the professional's duty to

protect their autonomy is pronounced, especially given the inherent uncertainty of the research undertaking. Ethicists have pointed out that if the likely harms from participating in a stem cell trial are similar to the outcomes of the disease process itself, then the information gained from trial participation would have to be immensely useful to justify enrollment; otherwise, the trial should not proceed [26].

Of course and in clinical research in general, reasonable steps need to be taken to ameliorate the possibility of "therapeutic misconception," where participants might misconstrue a clinical trial as holding out a therapeutic benefit when it does not. Table 1 lists various items that are recommended in informed consent discussions with research participants in stem cell trials; yet and as will be discussed herein, the specifics of an informed consent discussion will be heavily dependent on the contextual specifics and aims of the research trial itself [8,11,27].

Whom to Recruit and When to Intervene?

Because the possibility of serious harm befalling research participants in stem cell trials is well-recognized but because the probability and magnitude of that harm might not be well known—often because of a wide "translational gap" between nonhuman and human stem cell studies [28]—clinical researchers may find themselves with a number of vexing decisions regarding their selection of subjects in phase 1 trials. For example, some ethicists have urged that early phase 1 stem cell trials only enroll participants for whom no current treatments are available, primarily because those trials pose the possibility of serious risk materialization that cannot be justified if some therapeutic remedy is available [26]. The problem with that suggestion, however, is that in the process of exhausting the spectrum of standard clinical treatments, a patient's disease and its underlying pathophysiology can become more entrenched and resistant to intervention. Pascale Hess has reported on just such a scenario involving stem cell interventions among children with Batten diseases (infantile or late-infantile neuronal ceroid-lipofuscinoses) [29]. Although the study's best-case scenario would witness a child's disease process being stabilized, a final report on the study noted that no degree of efficacy could be measured, largely because the disease had decimated the participant's brain cells, leaving only a limited number of cells left to protect [30].

Another problem associated with exhausting available clinical remedies is that the disease process might ultimately compromise the individual's capacity to give informed consent. Although some study protocols might accept the consent of a legally authorized person to serve as a proxy for the individual, other studies might be required by their institutional research boards (IRBs) to only proceed with participant consent [31].

Alternatively, individuals who are in the earlier stages of a neurologic disease might not be ideal candidates if their symptoms are not severe. Research ethicists commonly hold that the risk/benefit ratio of a risky trial requires enrolling sicker patients who are thought to have less to lose in the event of serious complications [29]. Yet, if a particular disease is aggressive and ultimately fatal (such as the Batten diseases), then an earlier rather than later intervention would seem reasonable—an observation that only confirms the recommendation of adjusting enrollment, interventional timing, and informed consent per the contextual parameters of a study's focus and objectives.

Given the interest of this issue of the *Journal* on orthopedic interventions, it is worth pointing out that participant recruitment in orthopedic trials using stem cells can be controversial as well. Other authors in this issue have noted that decisions over the use of autologous versus allogeneic cells can be difficult, given the (1) age and biological condition of patients; (2) their presenting conditions; and (3) the likely (or unpredictable) clinical course of their injuries or diseases. Furthermore, orthopedic pathologies can be enormously heterogeneous—ranging from modest tissue injury to extremely serious disease like osteogenica imperfecta—not to mention the biogenetic uniqueness of each

Table 1
Informed consent elements in stem cell research [8,11,27]

Investigators should:
• Insure the participant's capacity to make decisions and voluntariness regarding trial participation
• Describe the source or origin of the cells that will be used
• Confess uncertainty about the "fate" of the cells posttransplant, ie, regarding the possibility of tissue rejection, undesirable cellular proliferation and migration, and tumor formation
• Describe other risks associated with the intervention, such as are typically disclosed in neurosurgery
• Explain that the undertaking is experimental, ie, intended to gain knowledge rather than intended to produce a therapeutic benefit
• Go over and explain the consent form's wording and vocabulary
• Characterize the intervention itself, explain its rationale, and admit that its long-term health effects are unknown
• Describe how "quality of outcome" is understood and will be measured
• Describe the study's adverse event reporting process
• Discuss the participant's likely need of long-term, invasive follow-up but that participants have the right to withdraw participation
• Note the uncertainty of long-term efficacy, even if a favorable outcome initially occurs
• Admit that the majority of stem cell participants have thus far not received a therapeutic benefit from their trial participation
• Note that if the intervention is in early phase 1 trials, that it has never been used among persons, or it has been used in only a few
• Inform participants of the availability of participant advocates, clinical trial coordinators, and other personnel involved in the study
• Assess what the participants have understood, perhaps via a post-consent quiz or extended conversation

patient and how that uniqueness affects long-term outcomes [23,24].

In timing a stem cell research intervention, all of these considerations would need to be taken into account, which only illustrates the importance of continuing research informing weighty ethical decisions at least involving a patient's disease severity, its projected rate of progression, and the participant's quality of life and life expectancy [29].

Efficacy Testing in Phase 1 Trials?

Given these decidedly risk-laden considerations that recall the fundamental and non-negotiable duty of protecting research participants from harm, some ethicists have recommended that phase 1 trials not only test for safety but for efficacy as well [29,32]. This would mean that these phase 1 trials would instantiate *clinical* end points along with safety end points as part of the protocol's outcome measures. Of course, efficacy must be present in studies that present "more than minimal risk" to children [33].

A recommendation of combining efficacy testing with safety testing would require that studies in animals show compelling and meaningful clinical end points that better "close" the translational gap between nonhuman and first in human studies [28]. Indeed, the Guidelines for the Clinical Translation of Stem Cells drafted by the International Society for Stem Cell Research emphasize that efficacy and safety after delivery of the cells need to have been previously demonstrated in appropriate animal models [8]. Furthermore, the validity of any stem cell trial would be in doubt if it fails to provide an adequate scientific rationale; has insufficient preclinical evidence of efficacy and safety; fails to describe and justify the characteristics of the cells that will be delivered; and fails to describe the mode of cell delivery and clinical follow-up [11].

Still and for those insisting on closing the translational gap between animals and humans, it remains the case that the tissue morphology is different in humans than in animal models; disease and healing mechanisms are different; and the neural circuitries are different. Furthermore, laboratory-induced injury in animal models tends to be much more anatomically uniform and precise than the myriad of orthopedic and neurologic injuries (and their underlying pathophysiologies) which humans present, and healing and recovery rates are different in humans and animals. For example, rats have been known to show a much greater degree of spontaneous recovery from neurologic injury, especially spinal cord injury, than humans, whose degree of axonal regeneration required for functional improvement is considerably greater. Last, objectively comparing, assessing, and translating *functional* recovery from animal models to humans—considering that animal species evolved their functionalities in an environment of survival challenges much different from humans—might require Solomonic wisdom [26].

The "Tragedy of Translation"

These factors have prompted some scholars to characterize "first in humans" use in embryonic stem cell research as a "tragedy of translation" [18]. Not only do we have a "leap into the dark" with first in humans trials because of the translation gap, but investigators may import their subjective and inevitably self-interested judgments in assessing the degree of harm probability and magnitude present in a trial. For example, a diagnosis of amyotrophic lateral sclerosis may seem a death sentence and prompt patients and their research investigators to recklessly pursue dangerous or unprecedented trials, such as the aforementioned instances of "stem cell tourism" illustrate. Yet, that decision could turn out to aggravate these patients' conditions with other maladies and make them worse off than had they done nothing.

In light of these conundrums and the fact that functional recovery in humans enrolling in stem cell trials would probably not be evident for months or even years, some ethicists have recommended a duty of "fidelity" from the research community [18]. Such a duty would entail an abiding relationship, akin to the kind witnessed in prolonged courses of clinical treatment, that would be extended to research participants. Adding a duty of fidelity to the extant duty of nonmaleficence would alter the traditional understanding of research participants being "used as a means" to confirm a hypothesis or gaining generalizable knowledge to treating participants as ends in themselves who require a degree of understanding, care, and empathy that extends beyond the traditional investigator-participant relationship.

Sham Surgery?

A very interesting problem in designing stem cell trials in both neurologic and orthopedic research concerns the search for a realistic placebo, given the dramatic nature of these interventions. Some researchers oppose a sham surgery placebo (where burr holes or incisions are made into the body) as unnecessary and a needless invitation to increased risk, especially because functional recovery from stem cell implantation requires a much longer time than placebo-related benefits typically last [27]. Other scholars argue that a placebo control nevertheless heightens the rigor of the study, especially if participants are receiving or undergoing other interventions such as exercise [16]. They worry that the absence of placebo controls would invite an unacceptably high risk of false-positive findings not to mention, of course, that double blinding would be impossible [34].

The issue is of particular interest in orthopedics. In a review of sham surgery in orthopedics, Mehta et al [35] favored a sham intervention if skepticism existed over the therapeutic value of a treatment (especially versus a placebo); the benefits of the intervention might be attributable to the "experience of surgery" or to post-operative care; no superior therapy was available; and the risks of sham surgery were reduced as much as possible. These observations recall Sihvonen et al's study [36] of 146 patients 35-65 years of age who had knee symptoms consistent with a degenerative medial meniscus tear and no knee osteoarthritis. The patients were assigned randomly to arthroscopic partial meniscectomy or sham surgery. The investigators reported that the outcomes after arthroscopic partial meniscectomy were no better than those after a sham surgical procedure. Of course, research participants enrolled in a trial that includes a sham surgery arm must be informed of such, so it is somewhat reassuring that at least one study of patients with Parkinson disease reported that the majority were willing to participate in such a trial [37].

In any event, implementing a sham surgery control will require as much minimization of risk as possible, which would primarily focus on reducing infection and anesthesia risks. Prudence might additionally dictate that phase 1 and 2 studies use the best medical therapy available in control groups, whereas phase 3 trials incorporate placebo surgery. Hurst [38] has raised interesting questions as to whether a (placebo) intracranial injection might itself affect the natural course of certain neurologic disorders like Parkinson. Nevertheless, she believes that the degenerative but prolonged course of certain diseases like Parkinson seems to argue for a late stage, phase 3 sham surgery so as to decisively counter concerns over controlling for a placebo effect and for effects from other treatments that patients will likely be having.

Hype and Monitoring Stem Cell Trials

Hype

Investigators conducting stem cell research face critical ethical responsibilities deriving from the fact that such trials are highly innovative, little research experience among humans exists, and patients are sometimes enrolled with serious, untreatable disease who are desperate to try anything. Yet and despite the "frontier" quality of this research [26], commentators have complained that phase 1 trials in gene-transfer research—another frontier technology—have sometimes used misleading language that conveyed a hope of therapeutic benefit to prospective participants, eg, "In this study, a team of physicians, and scientists will treat your [disease] by delivery of a pair of genes to your [organ]" [39] or "The investigators hope that gene therapy will be an effective treatment for your disease" [40]. Of course, in neither instance was the clinical treatment of the research participant's disease the fundamental object of research concern. The phenomenon of "stem cell tourism" is particularly on point in that at least one study described how many of these clinics exaggerate the benefits of their therapies and dismiss associated risks [41]. Perhaps not surprisingly, none of these clinics volunteered to an adequate peer review of their products' scientific rationale, safety, or efficacy [11].

Although clinical investigators may have learned to confine their reports to precisely what they have discovered and can scientifically demonstrate, innovative research can witness additional voices that don't always exhibit such restraint. Venture capitalists, for-profit technology development centers, disability advocates, and especially journalists might misunderstand, exaggerate, or distort investigators' findings that then shape public opinion. Given the likelihood that some desperate orthopedic and neurologic patients may fall prey to reports that exaggerate research findings, investigators should take pains to explain their findings precisely and anticipate and correct misunderstandings. To the extent that scientific hype goes unaddressed, one can only expect a diminished trust in the scientific enterprise and an erosion in its claim to integrity.

Monitoring

An appropriate review and monitoring of neurologic stem cell trials is ethically required to protect participants, assure the integrity of data, and protect institutions involved in the research. Investigators performing stem cell research, whether it is publicly or privately funded, are encouraged and sometimes required by their institution's IRB board to have their proposals reviewed and approved by a stem cell research oversight committee [8]. Such committees usually comprise an interdisciplinary team of professionals,including scientists, ethicists, legal experts, and community members. Not only do such committees pay considerable attention to the quality of the informed consent process, but they also examine and assess safety issues such as cell processing and manufacture, standards for preclinical testing using animal models, fair and transparent enrollment procedures, the scientific rationale of the protocol, the translatability of in vitro and in vivo preclinical studies, and the risk of unexpected cell function, migration, proliferation, and tumorigenesis [11,42]. Obviously, committee members need to boast considerable expertise in stem cell trials and, as much as possible, be immune from conflicts of interest.

A significant monitoring problem concerns the co-ordination of monitoring sites, which can include an institution's IRB, a stem cell research oversight

committee, and the FDA. Furthermore, some institutions might insist on additional and more refined reviews that, for example, will scrutinize a proposal's ethical implications and conflict of interest dimensions. Lo and Parham [16] have suggested that institutions might consider a stem cell monitoring model akin to the Recombinant DNA Advisory Committee (RAC) that the NIH developed for gene transfer research. RAC review is required by the NIH for investigators who use NIH funding or vectors or transgenes developed with NIH funding. They are comprised of national experts in relevant scientific fields and occur in addition to IRB and FDA review. The emphasis of the RAC review is typically on the protection of research subjects, including their selection, dose escalation, and selection of safety end points [16].

Another monitoring model is the Centralized IRB Initiative (CIRB), developed by the National Cancer Institute. CIRBs typically review multisite oncology trials and provide facilitated reviews. IRBs can approach CIRBs for such a review and use it to inform how they will proceed, eg, require a full IRB review or accept the CIRB review. The goal is to avoid duplicative reviews that can delay IRB approval. Furthermore, a centralized review entity, like the CIRB, can provide a highly reliable, consistent review; have greater transparency than local, individual IRBs; and especially deploy the benefits of an institutional memory of prior proposals, their strategies, challenges, resolutions, and follow-up considerations [16].

Innovative Stem Cell Therapies Outside of Clinical Trials

Securing an ethically and institutionally adequate system of monitoring is heightened by FDA changes permitting a "compassionate use" and off-label prescribing of FDA approved stem cell products [43]. The FDA has enacted these allowances to improve access to investigational drugs for patients with serious life-threatening disease who lack therapeutic options. Physicians can request FDA permission to administer stem cell products as long as they are being tested elsewhere in a clinical trial and as long as such use will not interfere with research investigations. Importantly for monitoring purposes, however, is that physicians requesting expanded access must submit an application that describes the rationale for intended use, patient selection criteria, a description of the manufacturing facility, the method of administration to the patient, toxicology information, and assurance of IRB approval [43].

Notice that the intention in either compassionate use or off-label prescribing is a therapeutic one and is not considered research, even though the FDA requires IRB approval. Ethicists therefore worry as to whether local IRBs will have the expertise to perform such reviews, especially as the interventions involve the administration of innovative therapies. Obviously, the basic activity of an IRB is to evaluate and assure sound research, not patient care. Consequently, additional levels and varieties of review seem to be required in instances of stem cell interventions outside of the parameters of clinical trials, given the host of ethical vagaries stem cell interventions present. In their article [6] in this issue of the *Journal*, Centeno and Bashir describe some of the ethical and regulatory challenges that, almost inevitably, beset frontier research in ways that blur the definitions of what is or isn't a "drug," medical practice versus research, and off-label or compassionate use prescribing.

Conflict of Interest

It would be extraordinarily naïve to think that investigators who are developing stem cell research technologies are blissfully unaware of the intellectual property rights their inventions and discoveries represent, along with the marketplace valuations their technologies or deliverables might attract. Because the last half-century has witnessed the emergence of the entrepreneurial scientist, massive (and, many think, oppressive) regulatory measures have been implemented by institutions conducting such research to insure that investigators' "conflicts of interest" are managed in ethically acceptable ways.

"Conflict of interest" is a term of art that characterizes a situation wherein a professional's secondary interests may compromise his or her primary interests [44]. Although these secondary interests can include friendship considerations, career advancement, or funding competition, they usually involve the potential promise of significant financial gain that can mar or obscure an individual's primarily obligations [45]. In matters of research, those primary obligations at least include protecting the welfare of research participants, the integrity of research data, and the integrity and reputation of the investigator's institution [46].

Imagine the kinds of conflicts a clinician-researcher who is evolving a novel drug or device that has enormous market potential might encounter. The urge to present his or her data, discoveries, or inventions in the best light possible might be immense, such that the investigator might be tempted to enroll only those participants who will likely exhibit the best outcomes; fail to inform those participants about the risks inherent in trial participation so as to ensure their enrollment; fail to disclose his or her potential for economic gain; "torture" (or, worse, falsify or fabricate) data such that they impress with remarkably compelling findings; or simply overstate what the data actually show, reminiscent of the aforementioned discussion on hype.

Although a treatment of these issues exceeds the scope of this article, we can note that institutions typically implement a number of management strategies when such conflicts are perceived. Usually, these strategies are calibrated according to the intersection of the investigator's potential material gain, the investigator's proximity to and involvement in the research activity itself, and the stage or maturity of the project's development [46]. Thus, a clinician-scientist who owns a substantial equity in a stem cell startup company might become tremendously wealthy from a successful product, but if he or she is entirely removed from the research endeavor itself, there is no conflict to be managed. Conversely, the investigator who resides in the research trenches and is enrolling subjects, doing informed consents, collecting and analyzing data, etc, but who has no financial interest whatsoever in the outcome would likewise have no conflict. Also, an investigator who has much to gain from a research project in which he or she has an substantial financial interest but is engaged in very basic (or "immature") research that must proceed well into the future before anything of marketplace value materializes would be deemed to have only a modest conflict, if any. Consequently, only when the potential of personal or material gain significantly intersects with the researcher's performance of his or her research responsibilities will a formal or institutional concern about a conflict of interest arise [46].

The most common regulatory practices an institution imposes on conflicted scientists include requiring the latter to declare their conflict of interest to participants and on publications. Sometimes, conflict of interest committees might limit (or prohibit) the investigator's role in enrolling or consenting patients, gathering or interpreting data, or writing up research findings. Also, it is not uncommon for academic institutions to appoint independent reviewers to oversee a research project whose investigators might witness conflicts of interest, whereas in the most pronounced cases, an institution might insist that an investigator place his or her equity in escrow, take a leave of absence to do the research, divest his or her corporate interest, or even sever involvement with that conflict originating corporation [46]. Although researchers are known to bristle at such regulatory measures—because they typically deny the possibility of succumbing to any influences that would compromise their scientific objectivity or their duty to protect research participants—there is an abundance of literature attesting to the power of such variables to compromise one's objectivity [47]. The best response from investigators is to manage their conflicts in a regulatory-compliant fashion and, perhaps and paradoxically, take a certain amount of pride in those conflicts as indicative of a career that represents both scientific as well as material success.

Conclusion: Chimeras, Social Justice, and Living Forever

Although the aforementioned article provides an overview of the more salient dimensions of ethical considerations in clinical stem cell trials, many other problems persist whose discussion exceeds the scope of this article. For example, although the aforementioned sections mention the pressing problem of closing the translational gap such that we should only undertake first in human trials upon securing "adequate" scientific and methodologic confidence from animal research, it nevertheless omits the "animal rights" argument as to whether animals should be used *at all in any* kind of research. Furthermore, research that combines stem cell with genetic transfer research resulting in "chimeras" poses unprecedented ethical problems wherein animals may acquire human traits or capacities that raises the possibility of their acquiring moral status [7].

There is also a clutch of justice problems attaching to stem cell research, which are shared with other types of innovative research that promise enormous benefit. For example and especially when stem cell interventions evolve into standard therapies, will a disturbingly large number of persons be denied access to these technologies based on their cost? Will certain groups of persons having access to these technologies exploit them and create a wider gap between the functional haves and have nots? Will that seeming injustice also translate into a marketplace developing around "choice" embryonic cells, especially affecting women who can donate their eggs? Notwithstanding the aforementioned concerns over the moral repugnance directed at creating human embryos solely for research purposes, possible harms to women who may be tempted by the income potential of egg donation include risks associated with ovarian hyperstimulation, the long-term risks of cancer caused by repeated ovulation attempts, and the risks of surgical retrieval [48].

Of course, it is hardly beyond the pale that as stem cell therapies evolve for the treatment of lost, diminished, or declining function, they will also be used for the enhancement of "normal" functioning. These technologies will be functionally regenerative or enhancing in the sense of enabling optimal, possibly staggering, functional performance for an indefinite, perhaps limitless, period of time. Stem cells may ultimately serve as a "parts replacement" if not "refinement" technology where, as mentioned in the introduction of this essay, virtually any organ system can be restored to a reasonable if not astonishing functional level. And when the day comes that stem cell interventions can be combined with gene transfer or gene-modification therapies, not only living without end becomes theoretically possible, but so too does enjoying functional levels that one's original DNA could not provide.

These will be among the ethical challenges confronting future generations. Presently, stem cell research is in its infancy and, if we have learned anything from gene transfer research, these kinds of innovative technologies require more labor, thoughtful ethical analyses, patience, and financial investment than was originally supposed. It also seems likely that "frontier" research in the 21st century will be depressingly slow, highly multidisciplinary, and technically difficult to do well. Yet, it seems preposterous to think that once certain kinds of stem cell interventions yield significant and meaningful functional results, humans won't exert a relentless and unstoppable demand for them, regardless of their cost and ethical complexity. At that point, we can only hope that clinicians and potential stem cell consumers will be able to exercise a sufficient degree of rationality and ethics in the use of stem cell therapies, lest they invite even greater problems and burdens than anyone could ever imagine.

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