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Cellular Therapies for Heart Disease: Unveiling the Ethical and Public Policy Challenges

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Abstract

Cellular therapies have emerged as a potential revolutionary treatment for cardiovascular disease. Promising pre-clinical results have resulted in a flurry of basic research activity and spawned multiple clinical trials world-wide. However, the optimal cell type and delivery mode have not been determined for target patient populations. Nor has the mechanisms of benefit for the range of cellular interventions been clearly defined. Experiences to date have unveiled a myriad of ethical and public policy challenges which will affect the way researchers and clinicians make decisions for both basic and clinical research. Stem cells derived from embryos are at the forefront of the ethical and political debate, raising issues of which derivation methods are morally and socially permissible to pursue, as much as which are technically feasible. Adult stem cells are less controversial; however, important challenges exist in determining study design, cell processing, delivery mode, and target patient population. Pathways to successful commercialization and hence broad accessibility of cellular therapies for heart disease are only beginning to be explored. Comprehensive, multi-disciplinary and collaborative networks involving basic researchers, clinicians, regulatory officials and policymakers are required to share information, develop research, regulatory and policy standards and enable rational and ethical cell-based treatment approaches.

Introduction

Investigational, cell-based therapies for cardiovascular disease are being launched at an explosive pace throughout the world. This activity is fueled by the urgency to find effective and safe therapies for a range of cardiovascular diseases and by highly promising preclinical results. The translation from the discovery of the treatment potential of adult progenitor cells in 1997[1] to the first human trial in 2001[2] outpaced the development of most cardiovascular therapies. This has led some investigators to argue that human trials are premature, and that too little is known about mechanisms and interactions of progenitor cells.[3] Others counter that there is sufficient safety data available to proceed with responsible and carefully planned human trials.[4] In the context of increasing patient needs and great expectations for cell-based solutions, the tradition of careful progression from “bench to bedside” is shifting to a pattern

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of rapid translation from basic research to clinical trials, with observations from trials looping back for re-evaluation at the pre-clinical level for retesting and optimization.

This “bench to bedside and back again” approach raises ethical and policy challenges that are exacerbated by the fact that the cells being studied are controversial in both scientific and public arenas. The challenges associated with isolating, rigorously characterizing, and delivering well defined populations of cells are significant. Stem cell research—particularly involving cells derived from human embryos—raises unique and sensitive issues, and thus has been the subject of more public and political debate than most other scientific endeavors. This has changed the public policy landscape internationally for funding, research practice guidelines, oversight and what is considered morally permissible research.

We begin by highlighting important issues in basic research, particularly regarding cell source and selection, followed by issues unique to cell therapy trials, including trial design, patient selection criteria and potential risk implications of using cell-based rather than pharmaceutical therapies. Finally, we provide an overview of current efforts to standardize processes for stem cells and oversight guidance primarily from a US perspective.

Cell Sources – Practical and Ethical Concerns

Multiple cell sources have been considered for cardiovascular cell therapy. These sources range from autologous (derived from the patient’s own tissues) to allogeneic (not from self). Other articles in this issue and previous reviews compare and contrast these sources.[5–7] We will focus on the practical and ethical issues associated with the different cell sources. It is essential to appreciate that the complexity of living cells is tremendous and that understanding the detailed phenotypic properties of a cell preparation is a far greater challenge than characterizing the chemical properties and purity of a pharmaceutical agent.

Autologous cell sources have generally undergone the most rapid translation to clinical trials in part based on limited concern about immune rejection and decades of experience with bone marrow transplantation. Initial trials have varied tremendously in the processing and selection of cells from simply isolating a mononuclear fraction from bone marrow cells and rapidly delivering them back to the heart to isolation of myoblasts from a muscle biopsy followed by several weeks of culture expansion before delivery.[2,8] If there is limited processing of cells, then the possibility for unanticipated events appears to be minimal. However, the more the autologous cells are processed and/or expanded, the greater the likelihood of potential problems including microbial contamination, aberrant cellular phenotypes, and tumorigenicity. Another complicating factor is that autologous cells can vary tremendously from patient to patient. Significant variation in progenitor cell availability among adults with coronary artery disease exists,[9] and the functional ability of the cells can vary between a healthy normal volunteer and, for example, a patient with diabetes and severe systemic atherosclerosis.[10] Autologous cell sources used to date have generated little in the way of ethical concerns and have not been the subject of major public policy debate.

Allogeneic cell sources are also actively being investigated. Mesenchymal stem cells (MSCs) obtained from bone marrow can be greatly expanded in culture and allogeneic MSCs are being tested in a Phase I clinical trial post-MI. MSCs are obtained from adult tissues and have raised few ethical concerns, in contrast to the other major sources of allogeneic stem cells under investigation such as embryonic stem cells (ESCs). Wide application of allogeneic cell therapy may be limited by institutional variability in cell processing, expense and reduced viability due to prolonged storage, and immune rejection.

ESCs are cells derived from the inner cell mass of the preimplantation blastocysts, which are very early stage embryos. These blastocysts may come from surplus, unused embryos created

for *in vitro* fertilization procedures. Most often these are frozen, stored embryos, and are obtained with informed consent of the embryo donors with the stated purpose of being used for research.¹ However, derivation of the ESCs results in destruction of the embryo which raises ethical concerns regarding:

- The moral status of early forms of life (embryos)
- Taxpayer complicity in funding the destruction of early embryos
- The protection of human subjects, which for some people includes the embryo
- Research and academic freedoms to pursue research deemed to have merit
- Protections and rights of donors of gamete tissue or embryos

A wide diversity of opinions exists regarding these fundamental questions, which has resulted in highly divergent research policies around the world. The inner cell mass of the preimplantation blastocysts used for isolation of human ESC lines contains only undifferentiated, pluripotent cells that have not begun the process of organogenesis. No neural cells are present in the inner cell mass and thus there is no form of consciousness. Opponents of human ESC research argue that these embryos have genetic completeness and the potential to develop into a child, and these properties afford embryos the same moral status and legal protections as any human being. Proponents of human ESC research counter that all cells in the body have genetic completeness yet are not given such status. For example, somatic cell nuclear transfer, in which a nucleus from a fibroblast or other somatic cell can be transferred to an enucleated oocyte to create ESCs, challenges notions that developmental potential is specific to blastocysts. Arguments about potentiality have been central to debates about the moral status of embryos, and have led some to propose alternative derivation techniques intended to circumvent the possibility that a blastocyst from which cells are derived could have further developed into a human.[11]² Additionally, derivation of human ESCs from a single blastomere biopsy without destroying the embryo has been suggested as another strategy to isolate ethically acceptable human ESC lines.[14] However, this argument assumes that a single blastomere is not capable of generating a viable embryo, but this is not the case for certain species and unknown for humans.[15] Thus the question remains as to what pluripotent cells if any require special status and protection. For example, recent studies have demonstrated that overexpression of several specific genes in mouse fibroblasts can result in generation of pluripotent stem cells that share many properties of ESCs including the ability to form chimeric animals when injected into a blastocyst.[16,17] Additionally, stem cell lines have been isolated from mouse spermatogonial stem cells which share many features of ESCs.[18] The moral status of the embryo and pluripotent stem cells will continue to be the subject of debate, and will have a significant effect on political, legislative and funding decisions .[19,20] Readers are referred to extensive discussions in other sources (see Table)

¹There has been considerable discussion over whether to obtain permission for research purposes in general, or to name the derivation of stem cells in particular. Some bioethicists argue that donors might regard research for fertility differently than embryonic stem cell research. For now, consent is being left to individual institutions and their Institutional Review Boards and Embryonic Stem Cell Review & Oversight (ESCRO) committees. Additionally, the question of whether to consent gamete donors specifically for human ESC research was raised in the process of devising the National Academy of Sciences Guidelines.

² The so-called “altered nuclear transfer” technique is posited on the theory that a human cell could be genetically manipulated *in vitro* to mutate the Cdx2 gene which is necessary for creation of a trophectoderm.[12] The cell with the mutated gene would then be used in nuclear transfer to create a blastocyst that would never fully develop and thus, according to this technique’s proponents, would not have the potential to become a human being. Researchers challenge this claim on its assumptions that mouse genetics will translate to humans and that the mutation would also affect development of the blastocyst, forming a “mutated” embryo from which normal ES cells may not be obtained.[13] Bioethicists also argue that this technique not only does not solve the potentiality problem, it actually creates “disabled” embryos, possibly more offensive than creating normal ones.

Current U.S. Public Policy Regarding Human Embryonic Stem Cells

Given the divergence of moral opinions regarding human ESC research, it is not surprising that the U.S. and other countries have struggled to develop relevant legislation and research policy. President Bush set current US policy by declaring that federal funding for studies of human ESCs lines derived before August 9, 2001 were permitted, but no federal funding could be used to derive new human ESC lines or to perform research on lines derived after this date (see NIH Human Embryonic Stem Cell Registry, <http://escr.nih.gov>). Although this compromise position allowed research on existing human ESC lines, with the passage of time, investigators have expressed concerns that the original cell lines were developed using mouse feeder cells and animal products in the culture media which raises concerns about infectious agents and other contaminants. These concerns could dramatically limit the eventual clinical utility of these original lines. Furthermore, techniques for the derivation and propagation of human ESCs continue to improve, so investigators are concerned that older lines may be technically inferior. Interestingly, federal oversight only applies to federally-funded research. This has encouraged some commercial entities to pursue non-approved lines or to derive new lines, knowing that there are no restrictions on privately funded research.

Importantly, the current state of U.S. policy has resulted in fragmentation of efforts, with several states creating their own legislative and funding mechanisms, either supporting less restrictive research. California is the most prominent example, with the establishment of the California Institute of Regenerative Medicine and its taxpayer supported \$3 billion, ten year budget, and its own set of regulations and guidelines for funding and ethical oversight. In contrast, a few states have passed legislation placing further restrictions on ESC research. Thus the regulatory policy for the derivation and study of ESCs is highly heterogeneous across the U.S. leading to confusion and conflicting policies.[21] Public policy also varies greatly around the world ranging from some countries strongly supporting this research to other countries completely prohibiting it. Attempts to collaborate on research across U.S. states or internationally becomes extremely problematic due to varying rules for derivation, consenting donors, sharing materials and funding.³

Ethical Oversight of Human Embryonic Stem Cell Research and Applications

In the absence of coherent national and international legislation or authoritative guidance for ethical practice related to human ESCs, a number of scientific organizations and professional associations have stepped in to create guidelines. The aim is to provide a uniform set of practices and mechanisms to ensure transparent, ethical, and responsible performance of scientific experiments. Most notable for the U.S. are the guidelines set forth by the National Academies of Science (NAS).[22] These are *voluntary* guidelines recommended for institutions planning to conduct human ESC research. They focus on research protocols, not derivation methods. The guidelines call for the creation of local ESC review and oversight committees (ESCRO) to review human ESC protocols, working in conjunction with established local Institutional Review Boards (IRBs). The guidelines are posted online at http://www.nap.edu/catalog.php?record_id=11278.

At the global level, the International Society for Stem Cell Research's guidelines share many of the elements found in the NAS guidelines, with a few key differences. For example, International Society for Stem Cell Research guidelines are more permissive regarding research with human-nonhuman chimeras whereas the NAS places limits on the kinds of experiments

³This has been addressed by an interdisciplinary group of ethicists and scientists (The Hinxton Group), which has written recommendations that include an interdiction against countries with restrictive laws discriminating against or restricting investigators from the freedom to travel and work collaboratively across national borders.

that may be done. Additionally, the United Kingdom has written a code of practice for use of cells from the UK stem cell bank (www.hfea.gov.uk/cps/rde/xchg/hfea). Reproductive cloning (nuclear transfer to create a living human being) is prohibited by governments in almost all countries and international organizations, while regulations regarding somatic cell nuclear transfer for therapy varies widely across societies, with some being extremely permissive and others restrictive.

While most of the guidelines from NAS and other groups are relatively straightforward, some are controversial, raising the question of whether individual institutions may modify or ignore some items. In particular, the NAS guidelines recommending obtaining consent from potential donors, including gamete donors, and prohibiting financial payments to donors (of both embryos and gametes) may be difficult to mandate. Also, the guidelines cover U.S. researchers only: material acquired from non-U.S. sources may or may not abide by the same rules, and it may be difficult to find out if the cells were acquired and lines derived in a way that aligns with U.S. guidelines. The oversight process will continue to evolve as new challenges arise from scientific advances, but at least a beginning groundwork for oversight has been laid.

Animal Models for the Development of Cardiac Cell Therapy

One of the major practical challenges in preclinical research related to cardiac cell therapy is the choice of animal model(s). Many early proof-of-principal studies have been done in rodent models based on cost and convenience considerations, but such rodent models have obvious limitations in extrapolating to human therapies. One challenge in relating animal studies to human clinical applications is related to the source of the cell preparation relative to the animal model used. The tested cell preparation is most commonly from the same species and strain as the recipient animals in order to minimize immune rejection. Thus one would like to be able to obtain identical cell populations in different species including humans, but this is not always possible. Progenitor cells are identified by their unique cell surface antigens, and unfortunately, the cell surface antigens can differ across species. Also, reagents to identify those surface antigens are not available in all cases. An alternative approach is to xenotransplant human progenitors into immunocompromised animal models to demonstrate safety, engraftment or functional recovery. It is not clear that this approach will predict treatment response in humans.

Additionally, animal cardiovascular disease models often do not mimic the highly complex nature of human disease, and therefore, cell behavior in humans is not easily predicted. For example, a myocardial infarction that has been surgically induced in a rat manifests different pathology compared to stuttering, thrombotic, multi-segment, occlusive coronary artery disease in humans where infarct zones are patchy and may not be transmural. Finally, the issue of small animal models compared to larger animal models is of major importance in translating the findings to humans. Typically larger animal models have been most reliable and predictive for translating therapies to humans. For example, cell loss in a murine heart post-myocardial infarction, is perhaps 5 million cardiomyocytes, compared to a human heart which may lose 500 million or more cardiomyocytes. Pig or dog models would demonstrate cell loss closer to the human scale. For the development of allogeneic solid organ transplantation, nonhuman primate models have been particularly useful given their more comparable immune systems to man. At this stage, there is no predominant model system, and studies have been done in a wide range of animal species with and without immune suppression making it difficult to compare results. Regardless, animal models will play an essential role in the optimization of cardiac cell-based therapies by providing critical data defining mechanisms of benefit, refinement of delivery approaches, and understanding safety concerns.

Preclinical Approval for Cardiovascular Cellular Therapies

Every cardiac cell therapy clinical trial in the U.S. requires an Investigational New Drug (IND) application to the Food and Drug Administration (FDA). The FDA's Center for Biologics Evaluation and Research (CBER) is tasked with regulating potential biologic and cell-based treatments in the U.S. Importantly, a small degree of risk imposed by a potential cell product must be tempered by the severity of the patient's condition, the magnitude of the benefit expected, and the alternatives available. Assuming biological relevance has been provided from studies in animal models, from a safety and regulatory standpoint, two main issues must be addressed prior to human testing, which can be broadly categorized as 1) cell-specific issues, and 2) delivery mode.

Cell-specific issues

The source, method of collection and use must be well-defined. Is the trial to test autologous or allogeneic transplantation? "Homologous" implantation implies that cells are obtained from a particular organ such as bone-marrow, *ex-vivo* expanded or modified and re-injected back into that same organ. "Non-homologous" implantation implies that cells are injected back into a *different* organ such as cardiac tissue. Non-homologous delivery may prompt increased regulatory scrutiny since cell behavior unique to a certain organ system may not be predicted in a different organ system. Making inferential errors from one organ system to another or from animal to human are a potential source of harm to humans. Additional issues exist for allogeneic transplantation such as immunocompatibility.

Expansion of cells in culture raises multiple questions. How many doubling times have occurred? There is considerable concern about chromosomal changes that have been demonstrated in culture with successive passages.[23] Cells also adapt to local culture conditions, raising the question of whether the cells which remain after several passages are the ones the investigator wanted, or if it is different cells that are being selected for in those particular culture conditions. Abnormalities can become amplified as researchers scale up for clinical trials. Have tumorigenic mutations occurred? Have the cells been modified in any way, either intentionally or unintentionally? Are animal byproducts used in the culture conditions? While animal products exist in a number of medical products (e.g. vaccines), the use of murine feeder cells in most existing ESC lines has raised concern about the ability to use these lines--intended for basic research—for testing in humans. From a regulatory standpoint, no clear correct answers yet exist for these questions; however, these are questions that will trigger closer scrutiny. In the mean time, the proposed cell product and methods must be evaluated on a case-by-case basis.

Delivery Mode

Prior to human trials, not only do the cells themselves require evaluation, the method of administering cells must also be considered safe. Various local and systemic delivery modes have been tested, and advantages and disadvantages exist with all approaches. Direct surgical intramuscular administration may offer excellent visualization and cell retention rate; however, these procedures are also highly invasive. Coupling therapeutic progenitor cell therapy with another procedure such as coronary artery bypass surgery may be more acceptable. Alternatively, minimally invasive strategies such as intracoronary infusion and endomyocardial injections are appealing but may suffer from reduced cell retention and inaccurate targeting. Systemic approaches such as intravenous or cytokine mobilization strategies are least invasive; however, these techniques rely on intact and robust "homing" ability of the target organ to achieve adequate cell numbers locally. Before initiating human trials, pre-clinical bench top testing of delivery catheters, syringes and needles must be performed to ensure preservation of cell number and viability through passage through the

device. In addition, image guidance systems must be tested and validated to ensure safety and accuracy of targeting.

In summary, several key steps are required prior to initiation of human cell therapy trials for cardiovascular disease. First, the proposed cell product must have some biologic rationale to offer benefit. Second, the methods of harvesting and enriching the cells must be well characterized and storage and ex-vivo expansion must be safe, reliable, free of toxins, and reproducible. Third, the delivery mode must be validated to be safe, and ensure preservation of cell number and viability via passage through the catheters, syringes, and needles used.

Clinical trials

A highly communicative, collaborative, and multi-disciplinary environment is required to facilitate clinical trials for cell-based therapies, which are far more complex than typical pharmaceutical trials. Designing and executing clinical trials for cell therapy in patients with cardiovascular disease is particularly challenging. Notably, nearly all stem cells tested in animal models of cardiovascular disease have shown benefits. Yet mechanisms underlying these observations are poorly understood, and optimal cell type, cell dose, target population, and delivery mode remain unknown. The high expectations of benefit in humans must be managed to prevent undue hope and hype that may be misleading to clinicians and patients.

The three main disease states being targeted for novel cell therapy approaches are acute myocardial infarction, chronic myocardial ischemia and congestive heart failure. Both technical and ethical challenges regarding trial design and patient selection exist with each.

Trial Design

Cardiovascular disease patients often have heterogeneous symptoms, varying degrees to which their disease is a burden and prognoses that are difficult to predict. Patients often reduce their daily activities or become completely sedentary to avoid symptoms and paradoxically appear well compensated. More objective test measures such as stress perfusion imaging may be preferred over subjective self-reporting of symptoms, particularly in early stage, small scale safety and feasibility trials.

Dose escalation studies are commonly performed with pharmaceuticals, but may not be appropriate for cell therapy, especially if autologous administration is anticipated. For example, patients with cardiovascular disease mobilize progenitors from the bone-marrow to the peripheral circulation poorly when cytokines are administered, so there may be too few cells available to make comparative generalizations.[24] Furthermore, cell losses can occur unpredictably during cell harvest (i.e., apheresis or bone marrow aspirate), during enrichment and during local administration. For these reasons, traditional dose escalation studies testing optimal cell dose may not be appropriate for autologous cell therapy trials. These issues may be less of a concern with allogeneic transplantation, assuming healthy, young donors are used and cells are easily expanded.

Early human cardiovascular cell therapy trials focused on safety are encouraged to be designed double-blinded and randomized-controlled. This is prompted in part by the high rate of serious adverse events intrinsic to the disease state being investigated. Additionally, trials must be designed to demonstrate incremental benefit on top of that expected from the “placebo effect.” The potential for placebo effects is high in cardiovascular patients, which may account for up to 40% of the benefit observed in control groups.[25]

Patient selection and recruitment

The inclusion or exclusion of patients for cell-based interventions may affect the trial outcome, but is also a significant concern for the ethical treatment of patients. Cardiovascular disease patients being considered for cell-based therapies have sometimes failed all other conventional options. This being the case, should one select the sickest, no-option patients who will likely die anyway? In reality, these patients are often chosen for novel investigational therapies as seemingly, the patients have little to lose. Most patients and their families understand that the prognosis is usually poor: heart failure associated with severely reduced left ventricular function has a prognosis worse than most forms of cancers. These patients and their families are particularly desperate, and therefore vulnerable to considering alternative therapies, however scientifically misguided. Healthier patients would likely do better with investigational cell-based therapy and would have the best chance of recovery if there is a problem. However, deferring proven therapies in the course of a trial may result in long-term harm if the cell treatments fail.

Specific situations warrant special mention. Chronic, severe congestive heart failure trials are problematic as patients may be potential candidates for heart transplantation. The unpredictable timing of transplantation may result in the interruption of mid to long-term efficacy results from cell therapy. Additionally, transplant recipient candidates who receive therapeutic allogeneic progenitor cells may become sensitized to cell donor antigens and potentially compromise their transplantation immunophenotype status. However, if cell therapy patients do undergo heart transplantation, it can provide an excellent opportunity to obtain human heart tissue from the explanted heart to critically evaluate the impact of cell therapy at the tissue level.

Recruiting patients for trials of experimental therapies is always challenging, but there are additional considerations for cell therapies. Cell therapy trial design can involve recruitment of cardiovascular disease patients who are in treatment with maximal conventional therapy and who have no further options such as refractory angina patients or end-stage heart failure patients. Under these conditions, the screening rates of potential participants may be high, but enrollment rates are usually poor. Patients may not enroll if they fear being assigned to a placebo group, or may assume they will get treatment even they are in this group. Exclusion criteria are used to create as much of a homogeneous sample population as possible. Cardiovascular patients likely often have serious co-morbidities, such as diabetes, which can complicate any sort of treatment. Yet, to exclude the many people who are suffering from the possibility of gaining benefit is difficult to explain to patients and their families.

Cardiovascular disease is increasingly prevalent in the elderly. Elderly patients tend to be more resigned in their fate and may be less willing to consider investigational therapeutic approaches. In trials for myocardial infarction, patients often have had little time to adjust to their illness and may therefore find investigational treatments unappealing. More significantly, there may be little time for patients and their families to carefully weigh the risks and benefits of participating in a trial, particularly those which must be initiated soon after injury. Concepts such as “randomization,” “blinding,” and “placebo group,” as well as the explanation of procedural risks may be hard for patients to fully comprehend under stressed conditions. Truly “informed” consent in these cases is difficult to achieve. One option may be surrogate consent, if a family member is available to consent on behalf of the patient, or deferred consent, which was employed in studies of calcium channel blockers and thrombolytic agents.[26,27] In this case, consent may be presumed if the probability of benefit is high and the likelihood of consent from the patient would have been high as well. Both types of alternate consent have been used in other trials for which a treatment must be initiated within a very short time of diagnosis.

While some of these are issues faced with any kind of novel treatment, other questions arise that are more specific to cellular treatments. Some have to do with balancing the need for proper evidence with reasonable care for patients. For example, with autologous cell sources, patient-to-patient variability will be greater than pharmaceutical treatments because the cells used will be differentially impacted by each patient's unique set of co-morbidities, genetic background, age and cardiovascular disease severity. Thus making comparisons and providing proof of efficacy will be more difficult. Likewise, the endpoints used in Phase I and Phase II trials for cardiovascular treatments can be subjective (angina, dyspnea) or not clearly predictive of long-term outcome such as small incremental improvements in ejection fraction. To have adequate statistical power for hard endpoints such as survival, large Phase III trials will be needed, but funding of such trials as well as logistics of standardized cell preparations and delivery remain a formidable challenge for the future. In an era of evidence-based medicine, slightly incremental improvements may be enough to satisfy the FDA that a treatment can be used in humans, but may not be enough to warrant acceptance by public or private payers, particularly when safe, conventional standard-of-care therapies exist.

What is the proper duration of a cell-based trial and how long patients should be followed afterward? Tissue remodels over time, and in the short-term, investigators may just be measuring more acute effects from the paracrine actions of the cells and modulation of the inflammatory response in post-MI trials.[28,29] Yet there may be a tradeoff of accuracy of results with the health care needs of the patients if trials endure too long. If longer study times are used, should the study remain blinded for seriously ill patients with heart disease? What if another therapy emerges to become part of mainstream standard of care, *prior* to the completion of your investigational cell treatment? How does the heterogeneous application of these proven alternative therapies confound the results of long-term studies? Also, if further procedures are needed in a longer duration trial, will participants need to be reconsented, and if so, how? For example, a trial design may designate a single delivery of cells in a heart failure population, but what if evidence emerges that multiple deliveries may be more beneficial.

Commercialization of Cardiac Cell Therapies

Bringing cardiac cell therapies to widespread clinical applications will require the active participation by industry, but the pathways for commercialization are only beginning to be explored. In contrast to the well worn paradigm of drug development for heart disease, commercial success with cardiac cellular therapy remains to be proven. Nevertheless, clear commercial opportunities exist with regard to unique cell sources, cell processing procedures/devices, and cell delivery equipment. For allogeneic cell sources the development of off the shelf cellular products may provide an economically viable option, although overcoming the potential problems of immune rejection of the cells will be necessary. Mesenchymal stem cells have been expanded in culture and represent the first allogeneic cell source to be tested in Phase I cardiac cell therapy trials. In the long-term, it is likely a variety of other potential allogeneic cell sources will be advanced such as various derivatives of human ESCs. Intellectual property associated with certain cell sources such as human ESCs has been controversial, but such intellectual property may be essential for the timely development and commercialization of this biotechnology. Proprietary methods for sorting and selecting autologous cell populations also exist and are being evaluated for cardiac cell therapies. Optimal cellular delivery approaches are spawning the development of new catheter types and new advances in imaging technology to allow highly localized and controlled cell delivery. However, the investments by industry at this early stage of therapy development are relatively small and cautious, and thus there is a strong need for publicly funded developmental trials to move this field forward at the present time. Finally, given the potential promise and media attention to cell therapies for heart disease, there have also been some questionable for-profit clinical applications. Internationally, some companies and clinics offer stem cell treatments for cardiovascular

disease, outside of randomized and blinded research trials. . Despite minimal clinical trial data, some companies have proceeded to perform autologous cell treatments, often for a substantial fee. Proponents argue that there is sufficient safety information, at least in the short-term, and that this treatment offers hope to those desperate no-option patients. The lure to potential patient clients is that these treatments are readily available, in comparison to some countries which limit stem cell treatments, and because the therapies are outside of clinical trials, there is no risk of receiving a placebo. In some instances, this has already resulted in a recruitment competition with well-designed trials exploring the potential therapeutic effect of similar progenitor cells. In all such cases to date, the cells being promoted have not undergone rigorous scientific testing for both safety and efficacy.

The Way Forward – Optimization, Standardization, Collaboration

With the variety of techniques and cell types being tested and the rush to clinical trials but with inconsistent results, there are important policy questions regarding oversight as well as the development of reliable and reproducible methods for cell processing, culture and expansion. Developing robust applications of these new therapies that can be broadly applied represents a major challenge. Only by establishing agreed upon standards for cell sources, reagents utilized, and delivery techniques will the field be able to make the scientific advances that will enable these therapies to become established. With regard to the uniform characterization of cell sources, for human ESCs, an effort at coordination comes from the International Stem Cell Forum, which is attempting to facilitate collaborative, transparent international research by establishing a centralized human ESC database.[30] In particular their focus is providing standardized global criteria for the derivation, characterization and maintenance of stem cell lines. Phase I work on characterization is complete and Phase II work on standardizing culture media is underway.[31] An effort to provide detailed characterization and comparison of the NIH-approved stem cell lines is likewise underway in the U.S. at the National Stem Cell Bank (<http://www.nationalstemcellbank.org>) which also provides broad distribution of the available lines. The UK also has formed a bank for human ESC lines as a standard repository (<http://www.ukstemcellbank.org.uk/index.html>). In the long-range, cell banking will likely provide a useful tool in therapeutic cardiac applications as has been the case for bone marrow transplantation therapies.

Recognizing that the obstacles faced for establishing new cell-based therapies exceed the expertise and resources of any one laboratory or institution, networks of stem cell researchers, clinical investigators, biotechnology experts, ethicists, and regulatory experts have been established both nationally and internationally. The Stem Cell Network in Canada is a good example of engaging a broad range of expertise from academic researcher to industry representatives with the goal of addressing the critical pre-clinical issues that will enable translation of the promise of stem cells to clinical applications (<http://www.stemcellnetwork.ca>). Likewise, an International Consortium of Stem Cell Networks has been established to provide a forum for exchange of best practices and development of international equivalents of national initiatives as well as fostering international communication.

For cardiac cell therapies, in the U.S. the NIH National Heart, Lung and Blood Institute (NHBLI) established a working group and implemented a multi-institutional clinical cell therapy network.[32] The aim is to centralize and standardize cell processing and identify the most informative trial protocols for the different centers to use in common for short duration phase I and II trials. By using agreed-upon protocols and processing methods, consistency and reliability should be enhanced. In addition, a data coordinating center and regulatory support will strengthen the network. Establishing this network is intended to aggressively move clinical cardiac cell therapies applications forward. Unfortunately, support and organization of the

basic and preclinical research for cardiac regenerative medicine has not yet been similarly supported in the U.S. Thus the foundation of understanding upon which clinical trials are built remains tenuous with major questions regarding mechanism of benefit and optimal cell sources. Ultimately, interactive networks and collaborations which span from the basic laboratory to clinical trials will be needed to optimally advance this promising avenue for cardiac therapies.

Conclusions

In summary, several interesting and important challenges remain before cell-based therapies for heart disease achieve wide acceptance. Scientific investigators need to still convincingly demonstrate treatment effectiveness in broad populations with cardiovascular disease. At the same time, regulatory oversight will be essential. Institutions need to maintain flexibility and adapt to novel technologies and at the same time ensure the safety of patients, a concern shared by all. Collaborative scientific networks within and between institutions are key to share expertise, and avoid duplication of resources. Finally, policy makers need to develop informed and consistent legislation to provide assurances and resources to scientists, industry and society that will enable cell technologies.

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TABLE

Additional online resources regarding ethics, regulation, and policy of human ESC research

Source	URL
California Institute for Regenerative Medicine Regulations	http://www.cirm.ca.gov/laws/default.asp .
The Hinxton Group Recommendations for Ethical Research with Embryonic Stem Cells	http://www.hinxtongroup.org/au_cs.html
International Stem Cell Forum	http://www.stemcellforum.org.uk/about_stem_cell_research/policy_on_stem_cell_research/ethics.cfm
International Society for Stem Cell Research: Guidelines for Human Embryonic Stem Cell Research	http://www.isscr.org/guidelines/index.htm
National Academies of Science Guidelines for Human Embryonic Stem Cell Research	http://www.nap.edu/catalog.php?record_id=11278
NIH general information about stem cells	http://stemcells.nih.gov/info/basics/defaultpage.asp
NIH guidelines for Research Using Human Pluripotent Stem Cells	http://stemcells.nih.gov/research/registry/eligibilityCriteria.asp
NIH National Stem Cell Bank	http://nationalstemcellbank.org
U.K. Human Fertilisation and Embryology Authority	http://www.hfea.gov.uk/cps/rde/xchg/hfea