Chapter 34

Ethical and Policy Issues in Practices of Regenerative Medicine for the Treatment of Chronic Pain

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1.0 INTRODUCTION

There is building evidence to support the use of select techniques of 'regenerative medicine' in the treatment of certain forms of chronic pain. For example, chronic pain conditions can be mitigated through the use of injected biologics, in the form of cells, components of cells, extracellular fluids such as blood plasma, and other kinds of protein molecules such as collagen and growth factors. These materials can fortify physiological processes of repair and regeneration (i.e., to reduce inflammation, prevent further tissue deterioration, regrow tissues, and restore structural and functional integrity). Applied alone or in conjunction with other modes of treatment, such approaches offer promise for relieving both signs/symptoms as well as causes of chronic pain.

Biologics may be manipulated and modified before they are introduced into the patient. Technological modification is often required to 1) obtain biologics in quantities sufficient for effective treatment, 2) prepare the biologics for regenerative action/effect at the target site, and 3) ensure that these biologics do not incur deleterious side effects. The regenerative use of biologics is frequently described as a "natural" form of therapy, since it is unlike pharmacologics, surgical procedures, or transplants from nonhuman animals (i.e., xenotransplants). Such naturality should not obscure the fact that highly advanced technologies are involved in the development, manipulation and cultivation of regenerative biologics. This is true for stem cells, as well. Attaching the label of "natural" to a stem cell can distract attention from a number of relevant technical, medical and ethical issues and concerns, which must be balanced against the medical and social urgency to provide safe and effective relief from chronic pain. This urgency is all the more heightened as the search for alternatives to addictive opioid drugs become an increasing scientific, clinical, social, and legal priority.

Most commonly, studies addressing applications of regenerative approaches to chronic pain focus on joint degeneration, intervertebral disc degeneration, and neuropathic conditions (1). A majority of these studies target pain incurred by osteoarthroses of the major joints (knee, hip, and shoulder), and treatments for these disorders and resultant pain most frequently involves the use of platelet-rich plasma (PRP). In this technique, plasma of a patient's own blood is separated (from its red blood cells) to afford an injectate concentrated with leuokocytes, platelets, and platelet-secreted growth factors. PRP has been deemed as a safe treatment for particular forms of chronic pain, and is approved as an "off label" application by the United States Food and Drug Administration (FDA), 21 CFR 1271 (2). As well, there is growing evidence to support PRP's superiority over corticosteroids for mild to moderate osteoarthritic pain, and the effectiveness of PRP treatment in conjunction with physical rehabilitation. Although large studies of PRP alleviation of joint pain are lacking, surveying small randomized controlled trials demonstrates that significant pain relief can be achieved (3,4).

2.0 STEM CELLS

Another common method of regenerative medicine involves injection of mesenchymal stem cells (MSC) that are taken from the patient's body. Like PRP, stem cells stimulate physiological mechanisms of recovery and repair, yet further contribute structural component (i.e. - cells) as well. The use of MSC has been shown to produce clinically significant alleviation of pain of arthro- and/or chondro-degenerative conditions (4-7). However, MSC therapy incurs issues as focal to the use of stem cells. Mesenchymal stem cells are "multipotent", and therefore have a limited ability to differentiate into a constrained variety of connective tissues (such as cartilage or tendon). They are derived from bone marrow; similar types of stem cells are derived from adipose tissue. Stromal vascular fraction (SVF, which contains stem cells) and adult pluripotent stem cells (APSC) are among the more common methods of regenerative medicine used for treating chronic pain conditions. Studies employing these methods, while relatively few in number, have provided evidence of moderate control of arthro-degenerative pain (8). Given that the source is the patient's own body, such cells are autologous in nature. Because autologous cells characteristically do not evoke an immune response (and rejection) by the host, such cells are generally preferred to allogeneic stem cells that have been obtained from another human source.

Autologous stem cells are also regarded as "ethically preferable" in that they are "adult" cells, as opposed to stem cells from an allogeneic embryonic source, which although could be derived from umbilical cord tissue and blood, and/or amniotic fluid, can also be taken directly from embryonic tissues that are obtained upon termination of pregnancy. Ethical issues relevant to, and reflective of differing cultural and religious perspectives regarding the moral status of the embryo have fostered tensions toward certain governmental policies and legal rulings in America and Europe (9-11). Research involving ESCs is regulated with special restrictions in the United States, UK, and several other countries, due in large part to these moral sensitivities (12).

While there is no US federal law criminalizing research on stem cells or embryos, there are some state laws prohibiting such research due to anti-abortion sentiments. To meet National Institutes of Health (NIH) ethics, and thus to be considered for subsequent FDA approval, ESC research must use tissues that have already been legally created and destroyed. Most embryos used for federally- or private foundation-funded stem cell research are obtained from fertility facilities. Embryos are created and stored for in vitro fertilization procedures, but many are never used, so surplus embryos that would ordinarily be destroyed can instead be donated for research purposes with the consent of the fertility patients. In the United States, much of Europe, and some Asian countries, governmental funds cannot be used to subsidize research involving embryos beyond the early stages of development (13). This limitation does not affect the typical harvesting of stem cells from embryos during the 4-6 day period of the blastocyst stage, but does inhibit investigations of cellular development and transformation during later stages of embryonic growth.

The use of ESCs stands as an ethical demarcation line. On one side, the source of these cells makes human ESCs morally tainted for those who believe that human life begins at conception. Nevertheless, since IVF will remain legal, and the disposal of surplus embryos will likewise remain legal and morally tolerable (at least to some; with emphatic note of opposing religious views), research on embryos destined for destruction appears to remain politically palatable. On the other side, only destroyable IVF-derived embryos seem to be morally legitimate sources in the contemporary political context. Such ethical debates – and perspectival dissonance – have both constrained the value and experimental use of ESCs, and at the same time, prompted research to explore methods of increasing the potency of APSCs. Attaining the pluripotent characteristics of ESCs by other means that avoid the destruction of embryos has proven to be difficult, either because of unpromising results, or due to impediments in governmental approval and support (in the United States and Europe). Yet, such challenges have also served to compel researchers to pursue alternative sources and procedures of stem cell acquisition. Perhaps most significant in this regard has been development of technologies and methods to genet-

ically re-program autologous cells, so as to enable cultivation of directed cell lines of specific tissues (e.g., neurons, glia, etc.) in accord with Good Manufacturing Practice (GMP) standards. While reprogrammed autologous cell lines are not without current – and potential –problem(s), these methods are iteratively improving, with increasing specificity, selectivity and efficiency as demonstrable hallmarks of enhanced scientific, engineering and manufacturing capability (NB: a complete discussion of these methods and developments in the field is beyond the scope of the present chapter, for overview see (14).

3.0 ETHICAL ISSUES

While it is important to acknowledge and regard moral concerns about ESCs, simply avoiding their use does not fully abate both general and more specific ethical and legal issues evoked by the use of stem cells; a listing of which is provided in Table 1 (15-17).

These can be categorized as being: (1) inherent to scientific/technical aspects, and (2) generated by social factors, circumstances, and concerns (16), and are not mutually exclusive, but rather are interactive (Fig. 1). Issues inherent to the science and technology are focal to safety, efficacy, clinical effectiveness and cost. Safety is also a prime social concern and consideration as regards veridicality of claims (about relative benefits, burdens and risks) that are important to sustain the probity of informed consent. As well, safety, efficacy/effectiveness and costs contribute to the viability of any scientific, technological and/or medical approach in practice (as a social good), which in turn both reflects and contributes to the relative value of the approach(es) in question. Costs and value also contribute to and reflect need, demand, and provision (i.e., which patients will receive these state-of-the-art technologies, and the methods with which such questions about the allocation of resources can/should be addressed and resolved) (18). And while justice characteristically refers to ethical integrity in the of provision of goods, the concept of "justice-as-lawfulness", and questions of the ways that legal claims could, and should be handled when dealing with cutting edge technologies (for which a casuistic approach might not be viable) must also be acknowledged (17,19,20).

Table 1. Domains of neuroethico-legal issues.

Science and/or Technology Inherent
- ▷ Uncertainties of New, or Novel Applications of Science and Technology[1,2,3]
  - • Lack of prior application/durable use-in-practice/exemplars
- ▷ Unknown Mechanisms of Action and/or Interaction(s)[1,2]
- ▷ Known Burden or Risk Factors/Effects[1,2,3]
- ▷ Unknown and/or Unanticipated Effects (inclusive of side- and/or adverse-effects)[1,2]
  - • Differing efficacy and effectiveness
- ▷ Costs of Development, Manufacture and/or Distribution[2,3]

Societally Derived
- ▷ Misperception/Misinterpretation of Capabilities, Limits and/or Meaning/Value[1,2,3]
- ▷ Inappropriate Use/ Misuse in Practice[1,2,3]
  - • Can lead to over- or under-use
- ▷ Economic Inequalities and/or Cost Manipulation[2,3]
  - • Can lead to misuse
- ▷ Provision/Distribution of Resources[2,3]
  - • Based upon economics and/or political direction (and economic factors, as above)
- ▷ Cultural Difference(s) in Needs, Values, Use and/or Access[2,3]
  - • Inclusive of philosophical views and ethical perspectives and practices; and political influence
- ▷ Vulnerability of particular individuals and/or populations[1,2,3]
- ▷ Legal liabilities[1,2,3]

Legend:
1 = Influences/affects or affected by safety
2 = Influences/affects viability of use-in-practice
3 = Influences/affects or affected by costs

Adapted from Giordano et al (15-17).

To be sure, there are persistent concerns about known risks, and possible unknown risks (intermediate and/or longer-term) effects) of stem cells. Such risks include: 1) local tissue and/or systemic

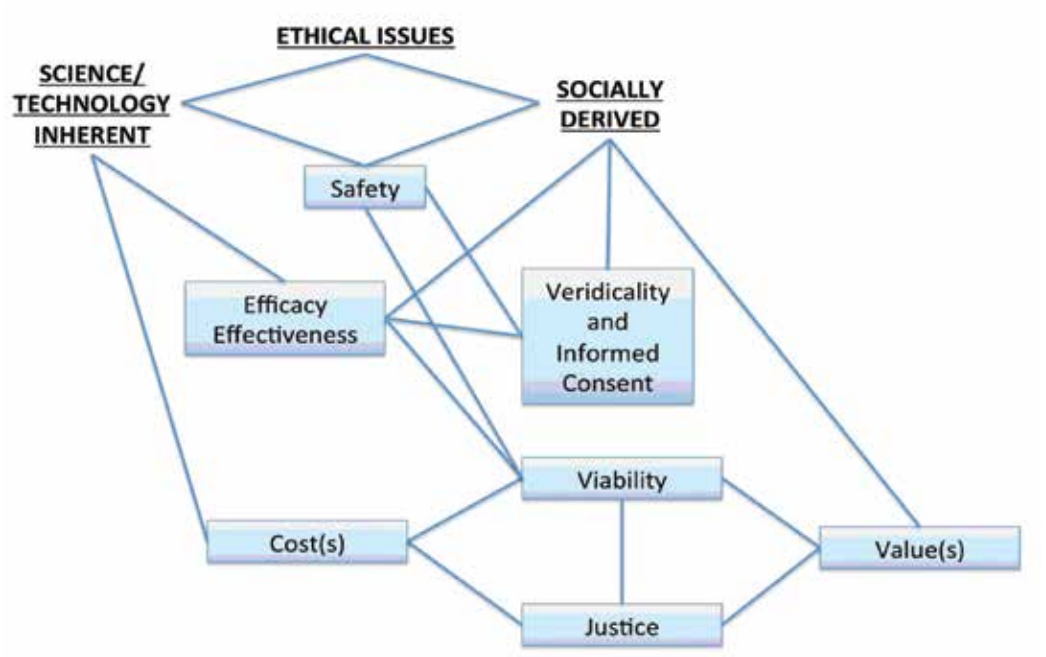

Fig. 1. Interactive domains of ethical issues as inherent to scientific/technical aspects, and fostered by social factors, circumstances, and concerns, as presented in Table 1.

responses to implanted tissues; 2) mutagenicity; 3) aberrant alteration of the local geno- and phenotype – and resultant function - of the nervous system, which could incur) induction of (perhaps previously unknown) mechanisms of non-local neural network activity (17). And while autologous ASPCs may reduce if not negate risk of immunological reactions, these cells must also be monitored for consistent differentiation, stability and tumorigenicity (21,22) for overview of intersecting technical and ethical concerns, see also (23). Ongoing research is focused upon methods to assure full pluripotency, and to concomitantly avert such adverse effects remains a focus of ongoing research (24-26).

Given that stem cell-based therapeutics remain experimental, both the acquisition and use of stem cells of every sort should be governed by ethical standards that protect the rights and interests of research participants. Obtaining fully informed consent of autologous stem cell donors/recipients should detail the experimental plan, as well as the type of stem cells to be used, the source of those cells, the intended use of those cells, the probability (and/or likelihood) of benefits and risks, and mechanisms for, and assurance of continuity of clinical care (19,20,27). Donors of tissues for use in others (e.g., embryo donors) should be informed about whether cells are destined for a specific research or clinical project, or for indefinite use as a stem cell line. Some ethical questions remain unresolved, such as whether donors should be asked for unrestricted future use of cells in advance (or be subject to re-consent rules), and whether donors could receive some form of financial compensation (28,29).

4.0 POLICY ISSUES

The transition from preclinical laboratory studies to "first-in-human" clinical trials must satisfy requisite assessments of preclinical benchmarks for the functional integrity, stability and purity of biolog-

ics, and reasonable expectations about effectiveness in vivo based on animal models. In addition, there are particular difficulties with testing the safety and efficacy of stem cells that are somewhat unlike the rigors typical for drug testing. For example, in the United States, navigating the three phases for FDA approval toward marketable stem cell treatments generates particular challenges where stem cells are concerned (30,31). The FDA has not approved SVF for marketing and consumer use, asserting that SVF and other stem cell procedures require premarket review because stem cell transfer involves "significant manufacturing", and stem cells are not performing "the same basic functions" (as the inherent biological cells/tissues) (32). Moreover, while the FDA can expedite review of experimental stem cell therapies via the Regenerative Medicine Advanced Therapy (RMAT) designation, to date no stem cell therapy has yet received FDA approval through that route. At this writing, the FDA has only approved one widely-used stem cell treatment, for bone marrow transplantation.

Any and all research and clinical trials of MSC, SVF, APSC, and ESC require advance approval to reach phase I, II, or III study because the biological structure and/or function of those tissues is modified before application; thus such research falls under the same regulations as biologic drugs (32). This "modification" is understood by the FDA to include the multiplication of stem cells cultured in vitro, even if the cells are from the patient and retain their structure and multipotency while multiplying. The FDA has therefore strictly enforced the regulation of autologous (and allogeneic) stem cell research in the same manner as manufactured drugs (32,33). Certain states, however, such as California, have liberalized and funded stem cell research (34), and although many European countries have roughly equivalent standards, less restrictive rules about the development and use of autologous and allogeneic stem cell therapies are typical in a number of countries, including Australia, India, and China (35,36).

Phase III trials of stem cell therapies for pain have been rare, although a few have been completed or are currently underway. An appreciable number of randomized controlled studies have not accompanied even the most common use of autologous adipose SVF for orthopedic conditions; case reports and small cohort studies that primarily assess safety and feasibility comprise the preponderance of research. It is important to note that even early stages trials are susceptible to unintentionally or intentionally conveying unreasonable therapeutic expectations (37). Despite lack of FDA approval or many phase III studies, over three hundred business enterprises are developing or offering stem cell interventions (almost all MSC/SVF) in the United States alone. Their advertisements typically suggest that authentic medical treatments for diseases, degenerative conditions, and pain relief are being provided (38,39).

5.0 CURRENT AND FUTURE VISTAS

Like many other domains of neurotechnological development, stem cell research, its translation toward clinical application(s), and markets of engagement are becoming ever more international enterprises (40,41). Indeed, a recent study of websites of over four hundred clinics located around the world reveals how typical marketing tends to pronounce far-reaching claims of successful treatments for a host of health problems, while providing fewer specifics or verifiable facts about the origin and quality of stem cells, academic legitimacy or certified legality (42). There are legitimate concerns that fundamental expectations for safety and efficacy are not being sufficiently satisfied in this emerging arena of stem cell marketing. Scrutiny of, and consternation about the unethicality or illegality of stem cell products will only intensify when stem cells developed/produced in and by less-regulated nations enter the market with increasing regularity and numbers. The ethical failures accompanying this growing international business of "stem cell tourism" are not just mirages due to failures to appreciate cultural differences, although it is true that the economics of medicine is hardly the same around the world (43), and the values, needs and ethics that guide the economics, research and therapeutics of medicine in various countries and cultures may differ that well.

Appreciating such differences does not imply that medical experimentation and care should descend into scientific or moral relativism; nor should the ethics that guide such efforts assume an imperialist stance (44,45). In this light, we have

proposed that both a cosmopolitan palette, and more particular communitarian constructs may be of value in establishing an internationally relevant neuroethics, at very least as a preliminary, tentative concept from which to advance both discourse and practice (46). Important to any such effort are issues of (in)equality, (in)equities and economic and political power dynamics of allocation, provision and sustainability of the resources, goods and resources of biomedicine that each and all must be recognized, acknowledged and addressed (17,47,48). Stem cell patients anywhere have the right to be well-informed about treatment options, benefits, and associated risks, and clinicians have a responsibility to protect and benefit patients by promulgating professional standards for stem cell therapeutics at both domestic and international levels (49). Guidance provided by the International Society for Stem Cell Research could be instrumental in this regard (50-52).

But, such guidance cannot and should not be static, nor should it ascribe to a "wait and see" approach. Any efforts to shape brain research and its uses must apprehend and the accelerating pace and widening scope of international endeavors and (public, professional, commercial and political) interest in neuroscience and technology. The defined and intended "good" of such enterprises (i.e., to reduce the burden of disease and illness, inclusive of chronic pain) is evident; yet none the less obvious are the ethico-legal issues that such novel science and technological means generate within the social sphere. Furthermore, ethical deliberation and discourse must inform policy, which tends to be formulated somewhat more slowly, and in some cases may be more reactive than proactive (27,41,53). As we have stated before (17,19,27,44-46,54-56), and reiterate here, addressing such issues need not impede neuroscientific and neurotechnological progress, but instead should serve more clearly elucidate: 1) those ways that applications of science and its tools could affect particular patients - and society; 2) the utility of current ethical systems, guidelines and policies; and 3) what types of new ethical and policy formulations might be needed to best direct research and use of neuroscience and technology.

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PART SIX

REGENERATIVE MEDICINE

PRACTICE MANAGEMENT