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Ethical Aspects of Tissue Engineering: A Review

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Tissue engineering (TE) is a promising new field of medical technology. However, like other new technologies, it is not free of ethical challenges. Identifying these ethical questions at an early stage is not only part of science's responsibility toward society, but also in the interest of the field itself. In this review, we map which ethical issues related to TE have already been documented in the scientific literature. The issues that turn out to dominate the debate are the use of human embryonic stem cells and therapeutic cloning. Nevertheless, a variety of other ethical aspects are mentioned, which relate to different phases in the development of the field. In addition, we discuss a number of ethical issues that have not yet been raised in the literature.

Introduction

Tissue engineering* (TE) is a promising new field of medical technology. If further developed, it might diminish suffering caused by tissue or organ damage and thereby lead to longer and healthier lives.[1] However, like other new technologies, TE is not free of ethical challenges. Identifying these ethical questions at an early stage is not only part of science's responsibility toward society, but also in the interest of the field itself: it enables the field to flourish by preventing it from investing time and money in directions that are likely to lack societal support.

Despite high hopes, TE is still in its infancy. There are as yet only a few clinical applications, mainly for skin, cartilage, and bone.[2,3] However, even though the field is still largely focused on research, it is moving ever more closely to clinical practice. The number of clinical trials is steadily rising. Now, therefore, seems a suitable moment to reflect on the moral implications of this technology: the field has developed far enough to have a sufficiently clear view of the directions in which it is heading and has not yet developed too far, so that there is still opportunity to steer clear of undesirable directions and effects.

TE has not figured prominently in public debates, with the notable exception of research involving the use of human embryonic stem cells (hESCs). In this review, we map which ethical questions related to TE have already been documented in the scientific literature. Further, we discuss which other issues might be raised and which issues require closer attention.

Methods

To find articles that explicitly pay attention to ethical issues raised by or directly related to TE,† the databases PubMed, EMBASE, and Web of Science were searched using the following combinations of terms: "tissue engineering" & ethic*, "tissue engineered" & ethic*, "regenerative medicine" & ethic*, "tissue engineering" & moral, "tissue engineered" & moral, and "regenerative medicine" & moral. The search was limited by date (published before 01-01-2008) and language (English). Papers in which ethic* referred to the product name Ethicon were excluded, as well as papers that contained one of the above-mentioned combinations of search terms, but in which the ethical issues discussed did not pertain to tissue engineering/regenerative medicine. Further, the most important journals in the field of tissue engineering and regenerative medicine—*Tissue Engineering*, *Biomaterials*, *Journal of Tissue Engineering and Regenerative Medicine*, *Regenerative Medicine*, and *the Journal of Regenerative Medicine*—were searched using the keywords ethic* and moral. These searches combined yielded 203

*We use "tissue engineering" (TE) in the sense of *ex vivo* TE. An *ex vivo* tissue-engineering product typically consists of three elements: cells (human, either autologous or allogeneic, or xenogeneic), a supporting structure (e.g., an extracellular matrix or scaffold), and biomolecules (e.g., growth factors). Moreover, these elements are combined *in vitro* before the construct is implanted in the body.

†Authors may have a different or broader conception of TE than we do, but we take their remarks about the ethical aspects of TE into account insofar as they apply to TE in the restricted sense in which we use the term.

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papers.[‡] These papers were studied and classified according to the ethical aspects of TE mentioned and to the type of journal in which they appeared.

Results

Papers classified according to issue

Table 1 shows the 10 ethical issues[§] related to TE that are most frequently mentioned or discussed in the scientific literature. The ethical question that dominates is the use of hESCs. About 70% of the selected articles refer to the moral problems raised by these cells. These articles range from ethical or ethically oriented papers extensively discussing issues like the moral status of human embryos (e.g., Refs.[4–18]) via scientific reviews that describe the moral opposition evoked by hESCs as one of the disadvantages of using these cells (e.g., Refs.[19–44]) to research papers that present alternative sources of stem cells—for example, stem cells derived from adult bone marrow,[45–49] amniotic fluid,[50–52] placenta,[50,53–56] or umbilical cord (blood)[57–62] or acquired through reprogramming of differentiated cells[63–66]—or ways to acquire hESCs without destroying (viable) embryos.[67–72]

A closely related topic that is also often discussed or mentioned is therapeutic or research cloning. About 20% of the selected articles refer to the moral problems involved in therapeutic cloning. Some articles merely mention that cloning is considered by many to be morally problematic (e.g., Refs.[8,15,35,37,40,42,63,65,68,69,73–75]); other papers elaborate on the ethical objections to this technique. The objections most often discussed are the objection that the creation of a human embryo specifically for research purposes and its subsequent destruction contravene its moral status,[4,6,9,17,20,43,76,77] the objection that permitting therapeutic cloning will inevitably put us on a slippery slope toward reproductive cloning,[4,9,17,20,29,43,76–78] and ethical questions related to paid egg donation. These latter questions include (1) the risks involved in hyperstimulation of the ovaries and the surgical or transvaginal recovery of oocytes for women who will not directly profit from the donation and (2) the commodification of both oocytes and women.[8,17,20,76,77,79,80]

But the use of hESCs and therapeutic cloning are not the only ethical issues mentioned in the literature. A variety of other questions are discussed, which relate to different phases in the development of the field of TE.

Papers classified according to phase in development

Classified according to the phase in the development of (the field of) TE to which they seem most relevant, the following ethical issues beyond the use of hESCs and therapeutic cloning are mentioned or discussed.

Fundamental and preclinical research. Four clusters of ethical issues associated with this early phase in the development of TE can be distinguished: issues related to (1) the source of cells (to be) used in TE products, (2) the donation of cells, (3) the use of (laboratory) animals, and (4) morally problematic "techniques."

(1) Embryonic stem cells are not the only cells that are considered morally problematic because of their origin. First, several arguments are brought forward against the use of fetal cells,[6,17,37,50,73,81–83] in particular embryonic germ cells: the primary source of these cells is induced abortion, which is in itself a morally controversial intervention;[37,50,73] some argue that using fetal tissue from elective abortion is a way of legitimizing abortion and this will encourage institutions to increase the number of abortions;[6,73] some fear that women might conceive specifically to obtain fetal cells via abortion.[6]

Also controversial is the use of xenogeneic cells or materials for TE purposes. The main arguments mentioned are the risk of introducing pathogenic agents (bacteria, viruses, or other infectious agents) into humans,[24,83–94] the serious immunological problems xenogeneic cells may cause if they are not genetically altered or physically isolated,[24,83,87,88,91] and the public acceptability of using animal cells/tissue.[87,88,91] Some people object to the introduction of animal cells/tissue into the human body as such; others reject the use of material from specific animal species on the basis of religious precepts (e.g., reservations of Muslims and Jews regarding the use of porcine cells/tissue).[85]

Finally, even though the use of allogeneic cells is generally considered to be less problematic than the use of xenogeneic cells, the immunological problems involved in the use of these cells[24,90,91,95] and the risk of disease transmission[24,90,95] are sometimes mentioned as reasons against the use of this type of cell.

(2) A second cluster of moral issues pertains to the donation/collection of cells for TE. The requirement of obtaining informed consent is often stressed: donors should be informed as fully as possible about future uses of their tissue/cells, and no tissue/cells may be used without the consent of the donor.[4,16,81,96–103] Similarly, the importance of protecting the privacy of the donor is pointed out, for example through the anonymization of samples used in scientific research.[16,96–98,101–105] Further, many au-

Table 1. Ten Ethical Issues Most Frequently Mentioned

Ethical issue	*Number of papers*[a]
Use of hESCs	140
Therapeutic cloning	43
Donation: altruism vs. transfer of property rights	16
Use of xenogeneic cells/tissue	14
Informed consent of cell donor	11
Privacy of cell donor	9
Contribution of TE to life extension	9
Ethical aspects of clinical trails	8
Private banking of umbilical cord blood	8
Use of fetal cells	8

[a]Total number of selected papers: 203. Papers referring to more than one issue are grouped under each of these issues.

[‡]The References section does not show all 203 articles. We were particularly interested in ethical aspects of TE beyond the use of embryonic stem cells and therapeutic cloning. Of the papers that address one of these latter two issues only a selection is therefore presented, namely, those papers in which these issues are not only mentioned but also, to some extent, discussed.

[§]The objections/arguments described hereafter are not necessarily endorsed by the authors who mention them in their paper.

thors indicate that free and unpaid donation is or should be the ideal behind policy/legislation regulating the collection of cells/tissues for research in regenerative medicine.[84,86,90,98,102,103,105,106]

A closely related issue is the question of the ownership of the human body and its parts.[13,76,81,95,99–102,104,106] This question is sometimes interpreted as a question of who has authority over the use of collected cells/tissue,[99,101] but more often as a question of whether the human body can be subject to property rights. Acknowledging these rights seems a necessary condition for allowing paid donation and the patenting not only of processes involving human (stem) cells, but also of these cells themselves.[13,16,90,102,107–109] The reasons most often mentioned against granting property rights are that it would violate human dignity and that it could lead to exploitation of poor people.[13,81,95,106]

Moreover, there is considerable debate about the most desirable mode of banking of umbilical cord blood.[54,99,104,110–114] Stem cells from this blood might in the future be used for regenerative purposes. Several ethical arguments are advanced for preferring public banks to private, commercial banks that collect cord blood for autologous use. A number of authors stress that at present it is doubtful whether cord blood stem cells will ever be used for autologous transplantation. To claim that cord blood banking is a way to save the key components for future medical treatment of your child is therefore to create false hope.[99,104,110–112] This is especially problematic because the promotional materials of these commercial banks are targeted at prospective parents at a vulnerable time.[104,110–112] Moreover, private banks may take cord blood out of circulation that might have been collected by public banks for allogeneic transplantation in unrelated recipients. Donating to private banks therefore conflicts with the principle of solidarity.[99,104,112]

(3) A small number of papers pay attention to the moral justifiability of using animals either as a source of cells or for TE research.[88,115,116] Laboratory animals are used to study the fundamental processes involved in TE, and they function as models of human disease for testing new products. As several authors[115,116] stress, these animals can experience substantial discomfort, and experiments should therefore only be performed when no alternatives are available and when the benefit of the experiment outweighs the animals' suffering. On the other hand, several other papers point to the prospects of using human cell cultures and TE products like artificial skin as alternatives for laboratory animals in safety testing or drug discovery.[97,117–119]

(4) Besides objections to therapeutic cloning, moral reservations regarding certain other "techniques" are mentioned, notably regarding the genetic engineering of cells for TE products[90,120,121] and the mixing of human and animal cells or genetic material (e.g., the use of interspecies nuclear transfer or the engrafting of human ES cells into a mouse blastocyst).[74,83,122,123]

Clinical trials. Although an integral analysis of the ethical aspects of clinical trials with TE products is lacking, a number of issues are discussed. Most important among these are the requirement of informed consent of the participant,[16,124,125] the importance of and difficulties involved in risk–benefit analysis,[16,91,124] the need for clear criteria of efficacy and safety,[38,86,91,126,127] and the desirability of long-term posttrial follow-up including the establishment of a registry.[126]

Clinical practice (short-term). The following issues mentioned in the literature seem to be particularly relevant when TE products are introduced in clinical practice: the informed consent of patients, especially if the product contains xenogeneic material;[85,88,93,102] in view of public health, the necessity of complying with the regulations of Good Manufacturing & Laboratory Practice[38,86,91,98,105] and justice in the distribution of treatments with TE products, both among different groups within Western societies and between these societies and developing countries.[84,124,128]

Advanced clinical application (long-term). Besides the issues previously described, a number of more philosophical questions about TE are raised. The first question can be concisely described by slightly adapting the title of one of the papers about stem cells[31]—TE: immortality or a healthy old age? In other words, should TE only or primarily be used to fight the negative effects of ageing or may it also be deployed in the extension of the human lifespan?[15,18,31,90,95,128–132] Second, is it morally desirable to use TE to enhance human capabilities?[124,128,133] And how will TE affect our view of and attitude toward our body?[5,81,90,128,132]

Distribution among phases. In conclusion, and taking a more quantitative perspective, the preclinical phase is dominant not only in terms of the number of issues associated with it, but also in terms of the number of articles that pay attention to issues most relevant to this phase (Table 2). Even if papers referring to the use of hESCs and therapeutic cloning are not included, more papers pertain to the preclinical phase than to all three later phases combined.

Papers classified according to type of journal

A large majority of the selected papers are published in scientific/biomedical journals; only a small minority can be found in journals in the domain of (medical) ethics, social science, or the humanities (Table 3). Not all articles in the biomedical journals are purely scientific; some are of a more reflective nature. Nevertheless, by far most authors have a scientific/biomedical affiliation.

Discussion

Even though the use of hESCs and the closely related topic of therapeutic cloning dominate the scientific literature dealing with the ethical aspects of TE, that does not mean

Table 2. Papers Classified According to Phase in Development TE

Phase development TE	*Number of papers*[a]
Preclinical research	55[b]
Clinical trials	8
Clinical practice	12
Advanced clinical application	14

[a]Total number of selected papers: 203. Papers referring to more than one issue are grouped under each of these issues.
[b]Papers referring to hESCs and/or cloning are not included.

Table 3. Papers Classified According to Type of Journal

Type of journal	Number of papers
Biomedical journal	190
Other (ethics, social science, and humanities)	13

that these issues are at present most relevant from an ethical point of view. Current applications of TE are not yet using cells derived from hESCs, and it is unlikely that they will do so in the near future[134] (although research in this direction is being carried out[135–137]). Moreover, even if TE products based on hESCs will be developed, still many TE products will contain other types of (stem) cells. And although there are strong indications that it is in principle possible to acquire human blastocysts through somatic cell nuclear transfer,[138] it is as yet far from evident that it will be possible to obtain in a safe and efficient way differentiated cells, let alone tissues or organs, derived from hESCs acquired via therapeutic cloning.[20,139,140] In other words, the strong focus of the debate on the issues of hESCs and therapeutic cloning is not warranted.

Although, apart from hESCs and therapeutic cloning, a large number of ethical issues relevant to the development of TE are already being mentioned in the literature, we believe that there are significant issues that are not yet covered or did not get the attention they deserve (cf. Refs.[141–143]). Some of these issues have been discussed in relation to other new medical technologies like cell and gene therapy, but we consider it important that they be explicitly discussed in the context of TE.

First, the need for obtaining informed consent from a cell donor is greatly stressed. However, the problems involved in meeting the ideals of informed consent are hardly discussed: Is it possible to provide all relevant information regarding future uses and tests? If not, will general information suffice?** Will the donor be able to (fully) understand the detailed and scientific information given? If not, what is his/her consent worth?††

Second, although the need for animal models that more closely resemble human diseases is noted,[115,123,148–150] the significance of this fact for the justifiability of animal experiments is largely ignored. Further, since the TE products that are being developed as alternatives to laboratory animals are not primarily intended to replace experiments for TE research, it is still an open question whether the development of TE will lead to an overall reduction of the number of laboratory animals used.

Third, more attention needs to be paid to the ethical issues involved in clinical trials,‡‡ in particular to the significance of the complexity of TE products for dealing with these issues. TE products are complex in at least the following three respects: (1) TE products show a certain amount of variability because they contain metabolically active cells in the dynamic environment of the extracellular scaffolds; (2) implanting a TE product initiates an ongoing interaction between the product and the recipient's body, which also varies to some extent; (3) implanting a TE product is an irreversible process—once the process of integration and regeneration is initiated, it is impossible to reverse it completely.[143] This complexity seems to have consequences for the possibility of meeting the requirements of informed consent (cf. consent cell donation), of making an accurate risk–benefit analysis, for the generalizability of the results of trials and for the necessity of a long-term posttrial follow-up. Moreover, since TE is claimed to be part of a new medical paradigm, namely, that of regenerative medicine, it would seem that the goal of a trial testing the efficacy of a TE product should be to demonstrate not only that the treatment is as effective as current treatments, but also that there is in fact regeneration in the body.

Fourth, given that TE products will likely be rather expensive, broad access to these products will be dependent on reimbursement. However, the lack of standards for clinical trials and persisting uncertainty whether treatments with TE products will not only be safe but also more effective than current treatments decrease the likelihood that they will be refunded. But if reimbursement were not provided, application of these products would be the privilege of the happy few, and all the fruits of publicly funded research would be reaped by private hands.

Fifth, two groups of people are likely to benefit especially from TE: young people with congenital diseases, for whom TE might provide a long-term solution superior to any therapy currently available, and the elderly, who suffer more than average from degenerative diseases. In the light of the limited budgets for health care, who should profit most? Apart from the issue of just allocation—which group is most entitled to these treatments?—a number of other considerations seem to be relevant for answering this question.§§ Thus, although application for elderly people could significantly increase their quality of life, this application also raises anthropological and socioeconomic questions. Would large-scale application to the problems of the elderly lead to a medicalization of ageing; that is, would ageing increasingly be regarded as a medical problem to be treated rather than as a natural physiological condition?*** And would application to the elderly aggravate the socioeconomic problems of an ageing society?††† Pediatric applications, on the other hand, raise their own set of problems, for example, regarding the long-term safety and efficacy as well as the validity of the substituted consent given by the parents.‡‡‡

**For a similar discussion of the amount of information that is required or desirable for informed consent regarding the collection of tissue samples, see, for example, Refs.[144,145]

††For a discussion of similar problems in the context of informed consent for clinical trials, see, for example, Refs.[146,147]

‡‡For a general discussion of the ethical issues in clinical trials, see Ref.[151]

§§Acknowledging that these considerations are of diverse ethical nature and deserve attention in their own right, we here focus on how they might bear on the question of who should profit most from TE products.

***The issue of the status of the ageing process has been mainly discussed in the context of research into the extension of the maximum human lifespan, see, for example, Refs.[152,153]

†††For a general discussion of the economics and ethics of anti-ageing interventions, see, for example, Ref.[154]

‡‡‡For a general discussion of the ethical issues in neonatal surgery, see, for example, Ref.[155]

Sixth, even though a few authors[128,133] mention ethical issues involved in using TE for enhancing the human body, the examples they use (extending the range of our senses or improving cognitive function for healthy individuals through cell-based therapies) are unlikely to be realized in the near future. An application beyond therapy that will probably be available much sooner is the use of TE products for cosmetic purposes (e.g., more natural breast implants; cf. Refs.[156,157]). The question of the desirability of such non-medical applications of TE needs to be addressed.[§§§]

Although all the above-mentioned issues are relevant for an ethical assessment of TE, they are not equally urgent. We would argue that special attention should presently be devoted to the ethical questions related to clinical trials, because of the stage of development of the field of TE—on the verge from preclinical research to clinical trials—and because of the relatively scarce attention paid to this phase so far. Moreover, the ethical issues involved in the collection of cells (informed consent, privacy/confidentiality, and altruistic vs. paid donation) should remain a focus of reflection, for without an ethically satisfactory regulation of cell donation even preclinical research would/should come to a halt.

The fact that so many papers in scientific/biomedical journals pay attention to potential ethical issues related to TE clearly indicates that tissue engineers already reflect on the ethical aspects of their work. The involvement of professional ethicists, on the other hand, still seems relatively low. We would argue that, to ensure an adequate identification and analysis of the ethical aspects of TE, ethicists should become more engaged in the ethical debate on TE. However, to prevent the ethical reflections from becoming too abstract or irrelevant in the light of scientific developments, close collaboration with scientists in the field of TE is of vital importance. Combining the intellectual capacities of scientists and ethicists should lead to ethical considerations that have both reflective depth and practical relevance.

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