

From lab to clinic
Ethical aspects of soft tissue engineering

For reasons of consistency within this thesis, some terms have been standardized throughout the text. As a consequence the text may differ in this respect from the articles that have been published.

The research presented in this thesis was conducted at the Scientific Institute for Quality of Healthcare (IQ healthcare). This institute is part of the Nijmegen Centre for Evidence Based Practice (NCEBP), one of the approved research institutes of the Radboud University Medical Center.

The research in this thesis was financially supported by EU-FP6 project EuroSTEC (Soft tissue engineering for congenital birth defects in children: contract: LSHB-CT-2006-037409).

Financial support by the Scientific Institute for Quality of Healthcare (IQ healthcare) for the publication of this thesis is gratefully acknowledged.

ISBN: 978-90-76316-857

Nijmegen, 2013

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Chapter 6 Springer Science and Business Media

Cover: Alexander Calder, *Trois feuilles noires* (detail), 1956
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Lay-out: Jolanda van Haren/Anke Oerlemans

Print: GVO drukkers en vormgevers B.V. | Ponsen & Looijen, Ede

From lab to clinic

Ethical aspects of soft tissue engineering

Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. mr. S.C.J.J. Kortmann,
volgens besluit van het college van decanen
in het openbaar te verdedigen op woensdag 4 december 2013
om 16.30 uur precies

door Anke Johanna Maria Oerlemans

geboren te Nijmegen op 26 januari 1983

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1

Introduction

1

What is tissue engineering?

"A salamander can grow back its leg, why can't a human do the same?"
Anthony Atala, New York Times¹

The second half of the twentieth century saw developments in the replacement of failing tissues and organs by medical devices or donor organs, or substitutive therapy. Organ transplantation, surgical reconstruction with foreign tissue, artificial prostheses and artificial administration of metabolic products are all interventions attempting to treat organ and tissue damage.² Although they are life-saving, cost-effective and safe, these therapies have several drawbacks. Devices or donor organs are not fully incorporated into a patient's body, they require invasive surgery and their lifespan is limited. In addition, there is a chronic shortage of donor organs and many substitutive therapies, such as dialysis, have a significant negative impact on the quality of a patient's life. For these reasons, scientists have been looking for alternatives. Tissue engineering is presented as a field of medicine dedicated to increasing the therapeutic options available for the treatment of tissue damage and organ failure.

The term "tissue engineering" (TE) was first mentioned at a meeting sponsored by the National Science Foundation in California in 1988. This meeting discussed efforts to manipulate existing tissues or combine them with prosthetic materials.³ Nowadays, the term is used for the actual generation of tissue, by using engineered scaffolds, possibly with living cells. The interdisciplinary field of TE aims to replace, repair and/or regenerate tissues and organs. As Langer and Vacanti put it in their classical analysis in *Science*:

*"Tissue engineering applies the principles of biology and engineering to the development of functional substitutes for damaged tissue."*⁴

TE is generally understood to be one of several different biomedical approaches — together with, for instance, somatic cell therapy and immunomodulation therapy — that are part of the field of regenerative medicine. This emerging medical field is defined as follows:

*Regenerative medicine is the process of creating living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage, or congenital defects.*⁵

TE treatments promise a more complete recovery with significantly fewer side effects or risk of complications, compared to conventional treatments. A TE application that has proven to be of clinical benefit is TE skin, which can be used for skin replacement or temporary wound cover for burns, and as a treatment for diabetic ulcers. TE may also be used for the induction of bone and connective tissue growth, to guide long bone regeneration, and to replace damaged cartilage. In the future, TE grafts could potentially be used in cardiac bypass

surgery. And somewhat further away, TE research may yield solid organ transplantation, treatments for spinal cord injury, and insulin-producing pancreatic islets that could be regenerated by the body to cure diabetes.⁵⁻⁸

Although the focus in the scientific literature is on clinical applications, TE may be used for other purposes as well. For example, TE constructs can serve as simulations of biological systems, or as disease models in research.⁹⁻¹⁷ They can be used as alternatives for animal testing, such as a TE skin substitute to test the toxicity of certain chemicals.^{18,19} TE products can also be used as biological and chemical sensors.^{20,21} Some laboratories are working on the creation of consumable meat products (“*in vitro* meat”) made from TE animal muscle cell constructs.^{22,23} Finally, a possible application is so-called bio-jewelry, such as a wedding ring made from TE bone of your partner.²⁴

TE attracted public interest in 1997 when a BBC documentary showed what is now known as the “Vacanti mouse”. Vacanti’s paper showed how the cartilaginous part of a 3-year-old child’s ear was regenerated.²⁵ The media upheaval was not so much caused by the experiment, as by the spectacular sight of a nude mouse with a human ear on its back.²⁶

Hopeful statements in the early years of TE caused considerable excitement and promised patients quick cures. The field was not able to deliver those promises, however. In spite of significant scientific progress, there are as of yet few examples of clinical applications. Some tissue-engineered products are clinically available, but most TE applications are still in pre-clinical phase, making TE still very much an emerging technology.^{7,8,27-29}

The ATMP regulation

In the past, medical products were regulated as either medicinal products or medical devices. Human tissue-engineered products (HTEPs) fell between these two categories: in some ways, an HTEP is an active implantable medical device, but there is also a significant role for pharmaceuticals.⁶ Additionally, an HTEP may contain viable cells.³⁰ In addition to HTEPs, other cell therapy medicinal products fell between the existing categories as well. This prompted the European Union to create a new class of medical products: Advanced Therapy Medicinal Products or ATMPs.

An ATMP is either (1) a gene therapy medicinal product, (2) a somatic cell therapy medicinal product, or (3) a tissue-engineered product (see Table 1). Regulation No 1394/2007 requires those planning to market an ATMP within the European Union to seek authorization from the European Medicines Agency (EMA).³¹ In the United States, articles containing or consisting of human cells or tissues intended for transplantation, implantation, infusion, or transfer to a human recipient are regulated by the Food and Drug Administration (FDA) as human cells, tissues, and cellular and tissue-based products (or HCT/Ps).³²⁻³⁵ The level of regulation depends on the characteristics of the product, but good tissue practices (or GTPs) are required regardless of the specific characteristics. GTPs describe the methods,

facilities, and controls used in the manufacturing of HTEPs to prevent infectious disease transmission and cross-contamination.³²⁻³⁵

Table 1. Definition of a tissue-engineered product according to EMA regulation No 1394/2007

According to the definition used in the regulation, a tissue-engineered product has the following characteristics:

- It contains or consists of engineered cells or tissues;
- Is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue;
- Cells or tissues shall be considered 'engineered' if they fulfill at least one of the following conditions: the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved;
- The cells or tissue are not intended to be used for the same essential function or functions in the recipient as in the donor.

The EuroSTEC project

The research in this thesis took place within the context of the EuroSTEC project^a (Soft tissue engineering for congenital birth defects in children: from biomatrix — cell interaction — model system to clinical trials). This was an integrated project funded by the European Commission under the Sixth Framework Program. The project commenced on January 1st, 2007 and ended on December 31st, 2011. EuroSTEC united fifteen partner organizations (ten research institutes and five companies) from nine European countries.

The aim of this project was the development of treatments for structural disorders such as spina bifida, bladder exstrophy, diaphragmatic hernia and esophageal atresia, to be used either in maternal-fetal surgery or surgical intervention after birth. Usually, these closure defects are first diagnosed during routine prenatal ultrasound screening. In case of, for example, spina bifida and diaphragmatic hernia, many pregnant women (parents) may decide to terminate the pregnancy. In other cases, the child will be operated on some time after birth and — depending on the kind and severity of the defect — will require surgery and/or other treatments throughout childhood and even into adulthood. Closure defects are associated with a varying range of morbidity and decreased quality of life.

The EuroSTEC project focused on both maternal-fetal (or in utero) as well as neonatal interventions using HTEPs. Part of the EuroSTEC project design was an extensive ethical analysis, which focused on all three phases of the project — fundamental or in vitro research, animal experiments and clinical trials — and would also look ahead to the application of soft TE in clinical practice. The previously published thesis of Catarina Rodrigues described the ethical reflection on maternal-fetal interventions.³⁶ The research in this thesis is the product of the ethical analysis of the development and application of neonatal interventions using TE products.

^a The EuroSTEC project, www.eurostec.eu (last accessed April 1, 2013).

Ethics of tissue engineering

Like other new technologies, TE is not free of ethical challenges. The application of HTEPs in children, as was the case in the EuroSTEC project, adds a further layer of complications to the mix. To be able to respond adequately and timely to possible future moral issues, a prospective and anticipatory ethical analysis is paramount. Confronting 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.

Even though the field of TE is still largely focused on research, it is moving toward application in clinical practice. The number of clinical trials is rising steadily.^{7,8,29} 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.

Objectives of this thesis

- To map which ethical questions related to TE have already been discussed in the scientific literature;
- To identify what ethical issues the experts involved in research on soft TE for closure defects expect to occur during the different phases of the EuroSTEC project;
- To further explore TE experts' views on the topics of donation and the source of cells used in TE;
- To identify the ethical challenges in clinical testing of HTEPs for pediatric urological conditions;
- To consider whether all relevant issues are present in the discussion of TE, and argue what aspects we think ought to be a part of a rich and high-quality debate of TE;
- To consider in what way the concept of "hype" plays a role in the TE discourse.

Outline of this thesis

Chapter 2 maps 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.

To obtain a first survey of ethical issues that might arise during the different phases of the EuroSTEC project, a Delphi method was used. The professionals directly involved in the EuroSTEC project were questioned about their views on possible ethical issues. *Chapter 3* reports on the first two rounds of this Delphi study. The first round yielded 27 ethical issues, which the respondents were asked to prioritize in the second round.

On the basis of the results of two previous rounds of questionnaires, two topics were selected for discussion in focus groups: ethical issues associated with (1) source of cells and (2) donation. *Chapter 4* reports on the results of these focus groups.

The use of HTEPs to treat children with congenital structural defects poses challenges in the clinical testing phase. Taking TE-based treatments for children with congenital urogenital defects as an example, in *chapter 5* we highlight the challenges to clinical testing of HTEPs in general. We aim to identify the ethical road blocks in the clinical evaluation of HTEPs under the European Medicines Agency and Food and Drug Administration regulations for pediatric urological conditions and, ultimately, to recommend strategies to overcome them.

Finally, we survey the discourse surrounding TE. *Chapter 6* takes Swierstra and Rip's NEST-ethics structure as a starting point to consider the debate about TE, and argues what aspects we think ought to be a part of a rich and high-quality debate of TE. In *chapter 7*, we identify the promissory narratives present in the discourse on TE, and consider in what way the concept of "hype" plays a role in discussions of this technology.

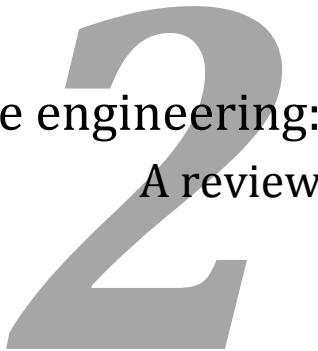
Chapter 8 discusses the implications of the work reported on in this thesis.

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Ethical aspects of tissue engineering: A review



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Abstract

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^a (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^b, 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 TE/regenerative medicine. Further, the most important journals in the field of TE 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

^a We use "tissue engineering" (TE) in the sense of ex vivo TE. An ex vivo TE 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.

^b 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.

yielded 203 papers^c. 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^d 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.,⁴⁻¹⁸) via scientific reviews that describe the moral opposition evoked by hESCs as one of the disadvantages of using these cells (e.g.,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 cells⁶³⁻⁶⁶ — or ways to acquire hESCs without destroying (viable) embryos.⁶⁷⁻⁷²

Table 1. Ten ethical issues most frequently mentioned

Ethical issue	Number of papers*
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 cells donor	9
Contribution of TE to life extension	9
Ethical aspects of clinical trials	8
Private banking of umbilical cord blood	8
Use of fetal cells	8

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

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.,^{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

^c 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.

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

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 authors 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 longterm 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 cells³¹ — 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.

Table 2. Papers classified according to phase in development TE

Phase development TE	Number of papers*
Preclinical research	55#
Clinical trials	8
Clinical practice	12
Advanced clinical application	14

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

Papers referring to hESCs and/or cloning are not included

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.

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

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 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 future¹³⁴ (although research in this direction is being carried out¹³⁵⁻¹³⁷). 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.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?^e Will the donor be able to (fully) understand the detailed and scientific information given? If not, what is his/her consent worth?^f

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

^e 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,^{144,145}

^f For a discussion of similar problems in the context of informed consent for clinical trials, see, for example,^{146,147}

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^g, 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^h. 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

^g For a general discussion of the ethical issues in clinical trials, see ¹⁵¹

^h 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.

physiological condition?ⁱ And would application to the elderly aggravate the socioeconomic problems of an ageing society?^j Pediatric applications, on the other hand, raise their own set of problems, for example, regarding the longterm safety and efficacy as well as the validity of the substituted consent given by the parents.^k

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.^{156,157}). The question of the desirability of such nonmedical applications of TE needs to be addressed.^l

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.

ⁱ 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,^{152,153}

^j For a general discussion of the economics and ethics of antiageing interventions, see, for example,¹⁵⁴

^k For a general discussion of the ethical issues in neonatal surgery, see, for example.¹⁵

^l For a general discussion of the ethics of cosmetic interventions, see, for example,^{158,159}

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Ethical aspects of soft tissue engineering for congenital birth defects in children— What do experts in the field say?

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Tissue Engineering Part B: Reviews 2010; 16(4): 397-403.

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Abstract

This article is part of the EuroSTEC project, which aims at developing tissue engineering-based treatments for structural disorders present at birth. EuroSTEC is positioned at the intersection of three areas with their own ethical issues: (1) regenerative medicine, (2) research with pregnant women and fetuses, and (3) research with neonates. Because of the overlap of these three areas in this project, we can expect to be confronted with new ethical challenges. To be able to respond adequately and timely to current and possible future ethical issues, a prospective and anticipatory ethical analysis is essential. To obtain a first survey of ethical issues that might arise during the different phases of the project, the Delphi method was used. The professionals directly involved in the EuroSTEC project were questioned about their views on possible ethical issues. The first round yielded 27 ethical issues, which the respondents were asked to prioritize in the second round. For the fundamental research phase, issues deemed most important were privacy and informed consent of the tissue donor. For the animal experimentation phase, three issues were mentioned (in order of decreasing priority): the suffering of animals, the use of animals as means to an end, and the limited adequacy of the animal models. Issues that were deemed most important during the clinical (trial) phase pertained to the problem of weighing risks and benefits for the fetus/child and the pregnant woman.

Introduction

EuroSTEC is an Integrated Project on “Soft tissue engineering for congenital birth defects in children.” Funded by the European Commission under the Sixth Framework Program, it commenced on January 1, 2007. The project unites 15 partner organizations (10 research institutes and 5 companies) from nine European countries.¹

Modern tissue engineering (TE) approaches will be used to treat children with congenital structural disorders, such as spina bifida, urogenital defects, gastroschisis, diaphragmatic hernia, and esophageal atresia. Usually, these closure defects are first diagnosed during routine prenatal ultrasound screening. In case of, for example, spina bifida and diaphragmatic hernia, many pregnant women (parents) may decide to terminate the pregnancy. In other cases, the child will be operated on some time after birth and — depending on the kind and severity of the defect — will require surgery and/or other treatments throughout childhood and even into adulthood. Closure defects are associated with a varying range of morbidity and decreased quality of life.² In the last two decades, *in utero* fetal therapy has been performed to reduce long-term morbidity of the child. At present, a multicenter randomized clinical trial (RCT) is being performed in the United States to study maternal–fetal surgery for spina bifida.³ In short, modest advances have been made in the field of maternal–fetal surgery for certain structural defects, although these interventions remain experimental.^{4–6}

The EuroSTEC project focuses on both maternal–fetal (or *in utero*) as well as neonatal interventions using human tissue-engineered products (HTEPs). Part of the EuroSTEC project design is an extensive ethical analysis, which will focus on all three phases of the project — fundamental or *in vitro* research (which, for the purposes of this article, will be referred to as “fundamental research”), animal experiments, and clinical trials — and will also look ahead to the application of soft TE in clinical practice.

The ethics of the clinical applicability of TE has so far received little attention. Issues that receive a relatively large amount of attention within the broader context of TE are the use of human embryonic stem cells and therapeutic cloning.⁷ The EuroSTEC project is positioned at the intersection of three fields: (1) regenerative medicine, (2) research with pregnant women and fetuses, and (3) research with neonates. All three areas have their own ethical issues, but because of their overlap in this project, the combination of these issues may lead us to be confronted with new ethical challenges. To be able to respond adequately and timely to possible future moral issues, a prospective and anticipatory ethical analysis is paramount.⁸

In this article, we survey experts’ views on ethical issues raised by the development of a clinical application of TE. From the perspective of an empirically based ethics, the views of these professionals — all involved in the EuroSTEC project — are expressly relevant because they have practical experience of the day-to-day (research on the) clinical application of TE. This unique feature may lead them to identify ethical issues that are difficult to recognize for those who are not directly involved in the process. The central objective of this empirical

study was to identify what ethical issues that the experts involved in research on soft TE for closure defects expect to occur during the different phases of the EuroSTEC project.

Methods

Data collection and analysis

A modified Delphi study was deemed the most suitable method to survey the ethical issues that the EuroSTEC professionals expect to occur during the course of the project. The Delphi method is a standardized research method. However, it is common to modify a Delphi study and restrict the number of rounds to ensure a high response rate throughout the multiple rounds.^{9–11} The Delphi method is a systematic, iterative forecasting method used to collect and distill knowledge from a group of experts.¹² Characteristic of this qualitative research method is that it takes place over several rounds, with the answers of one round being used to formulate questions for the next rounds.

In this case, the first round consisted of a questionnaire with two sections: (1) six short questions asked for certain personal information, such as sex, nationality, and role in the project (respondents were not asked to include their name), and (2) four open-ended questions. Each of these questions invited the respondents to list the ethical issues that they expect to occur during a specific phase of the project (fundamental research, animal experimentation, clinical trials, and clinical practice). For the latter two phases, respondents were asked to answer for maternal-fetal and neonatal interventions separately.

The research population consisted of all persons involved in one or more research areas of the EuroSTEC project (which includes, among others, pediatric urologists, fetal and neonatal surgery specialists, obstetricians/gynecologists, animal research experts, and researchers in the fields of biochemistry, biopolymer synthesis, molecular biology, and bioengineering). All professionals involved in the project were invited to participate in the first round. The questionnaire was sent to the research population by email several days before a central research meeting in November 2007. Respondents had the opportunity to return it by email or in hard copy at the meeting itself.

The results of the first round were initially analyzed by the primary analyst (AO) and subsequently reviewed by the second analyst (WD). Respondents' answers referring to the same issue were given the same code label. Subsequently, similar ethical issues were grouped in a category. In June 2008, the results were presented to the participants. As is customary in a Delphi study, the results of the first round were used to develop the questionnaire for the second round.

This second questionnaire consisted of (1) the same six short questions as in the first questionnaire and (2) a list of ethical issues distilled from the first round, grouped by research phase. For each ethical issue in the list, respondents were asked to indicate on a 5-point Likert scale how important they thought this issue would be during the project (1 labeled "not important," 5 labeled "very important"). Again, the entire group of professionals was invited to participate, regardless of whether they had responded to the first-round questionnaire. The second Delphi round was conducted during a central research

meeting in November 2008; the questionnaire was sent to the research population several days in advance, and respondents had the opportunity to return it by email or in hard copy at the meeting itself. The results were described and analyzed in the final months of 2008 by calculating the average score per item (on a scale of 1 to 5) using SPSS 16.0 software. Product of round 2 was a list of ethical issues, ranked in order of importance.

Results

Response

The first round saw a response of 29 out of a total of 48 (60.4%). The response rate of the second round was 67.9% (or 38 of 56). There is a discrepancy in total number of addressees between these rounds, because eight people were added to the EuroSTEC project between rounds 1 and 2 (for respondent characteristics, see Table 1).

Table 1. Respondent characteristics

		Round one (n=29)	Round two (n=38)
Gender (% male)		20 (69.0)	28 (73.7)
Nationality	<i>Austrian</i>	-	4
	<i>Dutch</i>	11	13
	<i>French</i>	1	2
	<i>German</i>	3	3
	<i>Swedish</i>	3	4
	<i>Swiss</i>	7	6
	<i>Other</i>	4	4
Educational background (%)	<i>Sciences</i>	16 (55.2)	24 (63.2)
	<i>Medicine</i>	8 (27.6)	13 (34.2)
	<i>Other</i>	5 (17.2)	1 (2.6)
Involved in* (%)	<i>Fundamental research</i>	22 (75.9)	27 (71.1)
	<i>Animal experimentation</i>	6 (20.7)	14 (36.8)
	<i>Clinical (trial) phase</i>	4 (13.8)	5 (13.2)
Place of work (%)	<i>University/hospital</i>	25 (86.2)	33 (86.8)
	<i>Industry</i>	4 (13.8)	5 (13.2)

* Some respondents are involved in multiple research phases.

The first round yielded a total of 27 ethical issues. During this first round, the questions were divided into four phases: the fundamental research phase, the animal experimentation phase, the clinical trial phase, and the clinical practice phase. However, answers pertaining to the last two phases appeared to be very similar. With exception of certain issues in the field of research ethics, all pertain to both clinical trials as well as eventual implementation of TE in clinical practice. Therefore, these phases were combined in the second-round questionnaire (and renamed the “clinical [trial] phase”).

The scores given to the 27 issues in round 2 (on a scale of 1 to 5) ranged from 2.54 to 4.59 (see also Table 5).

Results by research phase

Fundamental research

For the fundamental research phase, the first round yielded two main categories, named “source” and “donation,” with a total of 10 issues mentioned (Table 2).

Table 2. Results – Fundamental research phase

Category	Issue	Rank*
Source	• The use of fetal cells	14
	• The use of cells from neonates	15
	• The use of fetal stem cells	19
	• The use of excess tissue obtained through abortion	24
	• The use of embryonic stem cells	25
	• The use of umbilical cord stem cells	26
Donation	• Privacy of the donor of tissue	4
	• Informed consent of the donor of tissue	5
	• The possible invasiveness of the procedure through which tissue is obtained	11
	• Unclarity about the ownership of donated tissue	20

* Out of a total of 27 ethical issues.

SOURCE: Six different issues all refer to the source of cells used in the fundamental research phase. The origin of these cells appears to be morally problematic or at least morally relevant to the respondents.

DONATION: The second category within this research phase (entitled “donation”) contains four issues that all refer to some part of the donating process; material received from a person and used for research or development of an HTEP. Often mentioned in this respect were the protection of the privacy and the need for informed consent of the tissue donor. Also mentioned, although much less often, was the possible invasiveness of the procedure through which tissue is obtained. An example of this, mentioned by a respondent, is the possible risks involved in collecting amniotic fluid from a pregnant woman for the purposes of research.

In terms of ranking by importance, issues directly related to the tissue donor (privacy and informed consent of the donor and the invasiveness of the procedure) ranked highly, taking the 4th, 5th, and 11th place in the overall ranking (of 27 issues in total). The use of excess tissue obtained through abortion and the use of embryonic and umbilical cord stem cells were among the lowest ranked (at places 24, 25, and 26, respectively). The other five issues ranked between places 14 and 20 (see also Table 5).

Animal experimentation

For the animal experimentation phase the answers given could be brought back to three issues, grouped under the category of “use of animals” (Table 3). First, as mentioned by almost all respondents, is the suffering of the animals during experiments, which ranked

highest among the three (and ranked 7th overall). Second, the instrumental use of animals — as means to an end — to improve the health of human beings was mentioned. Last, the limited adequacy of the animal models was pointed out, although this was mentioned far less frequently than the first two. The latter two ranked at numbers 18 and 21, respectively.

Table 3. Results – Animal experimentation phase

Category	Issue	Rank*
Use of animals	• The suffering of animals	7
	• The use of animals as means to an end	18
	• The limited adequacy/extrapolation of the animal models	21

* Out of a total of 27 ethical issues

Clinical (trial) phase

The clinical (trial) phase yielded the largest amount of issues (14), more than the fundamental and animal experimentation phase combined. The list of issues could be clustered into five different categories, namely risk–benefit ratio, parents, material, intervention, and miscellaneous (Table 4).

Table 4. Results – Clinical phase

Category	Ethical issues	Rank*
Risk-benefit ratio	• Weighing risks for the mother against possible benefits for the unborn child	2
	• Weighing risks for the fetus/neonate against possible benefits for the fetus/neonate	3
	• Weighing the possible risks and benefits of a maternal-fetal intervention against those of a neonatal intervention	6
Parents	• The possible pressure or discomfort parents experience during the decision-making process concerning the participation of their child in a clinical trial	9
	• The impossibility of fully informing parents of the risks involved in trials/clinical applications of tissue engineering	13
	• Respecting parents' religious beliefs	23
Material	• The "mixing" of animals and humans through the introduction of animal material into the human body	22
	• Religious objections to the use of animal material inside the human body	27
Intervention	• The dilemma of choosing between terminating the pregnancy on the one hand and surgical intervention with poor long-term quality of life prospects for the child on the other hand	1
	• Weighing the possible risks and benefits of early intervention during pregnancy against those of intervention later in pregnancy	8
	• Difficulty of determining how severe a defect should be for a surgical intervention to be required/unavoidable	10
Miscellaneous	• Determining the right moment to cease clinical research and implement the intervention in clinical practice	12
	• Rights of the fetus	16
	• Distributive justice	17

* Out of a total of 27 issues.

RISK–BENEFIT RATIO: A category of issues mentioned by virtually all respondents was difficulties surrounding the risk–benefit ratio. In the EuroSTEC project, the “risk” can be divided into different types of risk. In the case of a maternal–fetal (or *in utero*) intervention, there are risks for both pregnant woman and fetus. As explained by respondents, for the pregnant woman, this means the negative consequences of a surgical intervention, without actually experiencing any physical benefits herself. These risks include miscarriage and preterm delivery after the procedure, and the risk of bodily injury associated with any surgical intervention. The risks for the fetus include, again, spontaneous abortion or preterm delivery, with associated consequences of severe morbidity or death of the fetus, and the risk of bodily injury.

In addition to risks associated with the surgical intervention, respondents indicated that the materials used carry certain risks with them. The collagen used, derived from bovine tendon, may lead to infection with certain viruses. In addition, there appear to be some questions as to whether the use of certain cells could give rise to the development of tumors later in life.

However, the maternal–fetal intervention has numerous possible benefits, both for the future child and the pregnant woman. As pointed out by several respondents, the future child may need fewer or no more surgical procedures later in life, or may even survive where it would have died with conventional treatment. Benefits for the pregnant woman include, for example, an improved psychological well-being due to having a healthier child. As pointed out by the respondents, the ethical question is how we balance the risks against the benefits, especially because so little is known about some of the risks.

PARENTS: The category we called “parents” comprises three different issues all somewhat related to the parents’ involvement in decision making regarding participation of their fetus or child in clinical research or consenting to treatment of this child. Respondents indicated that parents may experience discomfort or feel pressured by the researcher and/or physician (ranked 9th). Also mentioned was the impossibility of fully informing the parents of the risks involved in procedures using HTEPs (number 13 on the ranking list), because the technology is complex and difficult to understand, especially for lay people, and particularly at a time of intense pressure. Mentioned only once was the matter of respecting parents’ religious beliefs when dealing with their views about the use of certain materials (from animal sources) in their (unborn) child (ranked 23rd).

MATERIAL: Two issues were grouped under “material,” both initially mentioned by only a few respondents. First, the use of animal material inside the human body or, as one respondent put it, the “mixing of humans and animals” was identified as an ethical issue. Second, one respondent mentioned possible objections against the use of animal material (or rather, material from certain specific types of animals) for religious reasons. Incidentally, these two issues were ranked low compared with the other issues, placing at positions 22 and 27 of the ranking list, respectively.

INTERVENTION: A fourth category of ethical issues refers to difficulties surrounding the determination of the right time of intervention. Although it may seem like a medical-technical question, it does have a moral layer, as discussions about the right timing of an intervention are related to the moral status of the fetus and the idea that it is gradual and dependent on viability. In the discussion we will return to the respondents' phrasing of the ethical issues.

An issue that came up repeatedly — and was deemed the most important issue during the second round — was the dilemma of choosing between termination of pregnancy and surgical intervention with poor long-term quality-of-life prospects for the child.

Several professionals involved in clinical research and/or clinical practice mentioned the issue of determining the right timing of a maternal-fetal intervention. This in effect is related to weighing risks and benefits of the two options — respondents named the example of spina bifida, in which early intervention (i.e., covering of the defect) diminishes secondary damage to the spinal cord due to prolonged exposure of the neuronal tissue to amniotic fluid, but which in turn might lead to delivery before the fetus is viable. If one were to intervene later in the pregnancy, even when the fetus has a chance of survival if born prematurely, secondary damage to the spinal cord would have already occurred.

Another issue mentioned is the difficulty of determining how severe a defect should be for a surgical intervention to be required. In some cases, the defect is nonlethal but comes with considerable morbidity. Respondents questioned whether we should then take the risk of intervening in utero, with a possibly better long-term quality-of-life prospect, but also with the risks of infection and premature delivery associated with a maternal-fetal intervention. In other words, if a neonatal intervention is an option, should we still want to perform a maternal-fetal intervention?

All three issues ranked relatively highly, at numbers 1, 8, and 10, respectively.

MISCELLANEOUS: Several uncategorized issues were grouped under "miscellaneous." An issue mentioned once was distributive justice or, as the respondent put it, "will this only be available to the richest, or is it for everyone?" (ranked 17th). Mentioned more frequently were the so-called "rights of the fetus" (ranking at number 16).

An issue that pertains specifically to clinical trials is deciding on the right moment to cease clinical research and implement the intervention in clinical practice. As several respondents indicated, this should not be done too early, because enough evidence of the risks and benefits associated with the treatment should be available. On the other hand, it would be a shame to wait too long, because it would delay the potential good that can be done.

Table 5. Round two results – Overall ranking

Rank	Ethical issue	Average score*
1	The dilemma of choosing between terminating the pregnancy on the one hand and surgical intervention with poor long-term quality of life prospects for the child on the other hand	4.59
2	Weighing risks for the mother against possible benefits for the unborn child	4.49
3	Weighing risks for the fetus/neonate against possible benefits for the fetus/neonate	4.47
4	Privacy of the donor of tissue	4.38
5	Informed consent of the donor of tissue	4.34
6	Weighing the possible risks and benefits of a maternal-fetal intervention against those of a neonatal intervention	4.22
7	The suffering of animals	4.21
8	Weighing the possible risks and benefits of early intervention during pregnancy against those of intervention later in pregnancy	4.21
9	The possible pressure or discomfort parents experience during the decision-making process concerning the participation of their child in a clinical trial	4.20
10	Difficulty of determining how severe a defect should be for a surgical intervention to be required/unavoidable	4.19
11	The possible invasiveness of the procedure through which tissue is obtained	4.11
12	Determining the right moment to cease clinical research and implement the intervention in clinical practice	4.11
13	The impossibility of fully informing parents of the risks involved in trials/clinical applications of tissue engineering	4.09
14	The use of fetal cells	4.08
15	The use of cells from neonates	4.06
16	The rights of the fetus	4.00
17	The problem of distributive justice; to whom should treatment be offered?	3.97
18	The use of animals as means to an end	3.92
19	The use of fetal stem cells	3.89
20	Unclarity about the ownership of donated tissue	3.63
21	The limited adequacy/extrapolation of the animal models	3.62
22	The “mixing” of animals and humans through the introduction of animal material into the human body	3.49
23	Respecting parents’ religious beliefs	3.47
24	The use of excess tissue obtained through abortion	3.39
25	The use of embryonic stem cells	3.34
26	The use of umbilical cord stem cells	2.97
27	Religious objections to the use of animal material inside the human body	2.54

* On a scale from 1 to 5, with 1 labelled “not important” and 5 labelled “very important”.

Discussion

Our Delphi study yielded a total of 27 ethical issues (see table 5). Some issues were rather nonspecific, such as “informed consent of tissue donor” for the fundamental research phase or “the suffering of animals” for the animal experimentation phase. Others — like many of the 14 mentioned for the clinical phase — more specifically related to the EuroSTEC project, because they pertained to either TE research, or research with fetuses or neonates (or a combination of both). As mentioned previously, the project is positioned at the intersection of different fields with their own ethical issues. It is interesting to note that the issues deemed most important are not specific to TE research, but to research with pregnant women and fetuses and neonates.

Some of the issues mentioned were more in the realm of morally relevant facts and problems than true ethical issues. An example is “the possible invasiveness of the procedure through which tissue is obtained”: although the implications of risks associated with a procedure do inform the moral judgments about the acceptability of the procedure, the invasiveness itself is not an ethical issue in the strict sense of the word. Our participants were not ethicists and may have had some trouble identifying ethical issues in their practice and phrasing them in the questionnaire. In addition, the fact that we used a questionnaire as method of data collection most likely had some influence: written questionnaire answers are usually somewhat concise (more concise than, e.g., during a face-to-face interview). This may have caused participants to phrase their answers as morally relevant facts and problems, whereas if they were to elaborate further, the underlying ethical issue would become more explicit. Therefore, we did include these morally relevant items in our analysis.

In a previous literature study focusing on ethical aspects of TE,⁷ an overwhelming majority of papers was found to focus solely on the use of human embryonic stem cells or therapeutic cloning, while other ethical issues received little attention. It was argued that the most pressing matter at this time were ethical questions related to clinical trials, because of the current stage of development of the field of TE. Trommelmans et al.^{13,14} too argued that these issues have so far received relatively little attention.

A recent publication by Trommelmans et al. reported on a survey conducted among participants of a consortium of universities and enterprises focusing on TE of skin, cartilage, bone, and viscera.¹⁵ Participants were asked for their opinion on the need for development of ethical guidance and were presented with statements concerning clinical trials. Our study took a more bottom-up approach: we started by asking the participants to name ethical issues, instead of presenting them with a fixed list. Based on their study, Trommelmans et al. argued that clinical trial issues are in need of more profound reflection, a conclusion we endorse based on our own research.

As evidenced by our priority list — issues more or less related to clinical trials were in the top half of this list — TE professionals too consider these issues to be of great importance. Both previously cited articles and our participants note that the complexity of HTEPs poses challenges to meeting the requirements of informed consent (for donors as well as recipients of tissue/HTEPs) and making an accurate risk–benefit analysis. We believe that the ethical challenges in clinical trials are in most immediate need of attention, both from tissue engineers and ethicists.

It might be objected that knowledge gained from the two Delphi rounds was — by nature of those rounds — more broad than deep. However, this was our explicit objective, to give an initial survey of the full range of ethical issues expected by people with experience in TE research. The mere wording of some of the respondents’ answers request further explanation in face-to-face conversations. An example of this would be the issue “the rights of the fetus.” Although it may seem a rather straightforward concept, by using the term “right” in combination with “fetus,” a certain interpretation of the entity “fetus” as a subject

with rights is implied. Future research — in the form of focus groups — will aim to deepen this knowledge and explore the issues further.

Our research population consisted of a diverse group of TE professionals: participants were involved in fundamental research, animal experiments, and/or clinical research, and many different countries, nationalities, occupations, and institutions were represented. In future empirical research, we wish to extend the target population to include other groups, such as TE experts outside of the EuroSTEC project. Additionally, the views of ethicists and of prospective patients and/or their parents are lacking in this study. It is our explicit intention to include them in future research.

Ethics of TE and regenerative medicine remain a relatively small field. This study was one of the first to feature a survey of TE professionals' views on ethical aspects of a clinical application of TE. Although the participants of this Delphi study were recruited from one specific project, we feel the relevance of our results is not limited to this project. Numerous parallels can be drawn between the project at hand and any other (pre)clinical study in the field of TE. The full list of ethical issues is unique to the research of EuroSTEC, but, for example, issues pertaining to animal experiments with TE products will be of interest to those conducting these types of experiments. Those involved in clinical trials in this field will find the ethical issues that refer to this phase relevant to their own research. Therefore, we feel our study will be of relevance to research on applications of TE in general.

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Ethical issues regarding the donation and source of cells for tissue engineering: A European focus group study

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Tissue Engineering Part B: Reviews 2011; 17(4): 229-234.

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Abstract

This article is part of the EuroSTEC project, which aims at developing tissue engineering-based treatments for structural disorders present at birth. EuroSTEC is positioned at the intersection of three areas with their own ethical issues: (1) regenerative medicine, (2) research with pregnant women and fetuses, and (3) research with neonates. Because of the link between these three areas in this project, one can expect to be confronted with new ethical challenges. To be able to respond adequately and timely to current and possible future ethical issues, a prospective and anticipatory ethical analysis is essential. To obtain a first impression of the ethical issues that might arise during the different phases of the project, a Delphi method was used. On the basis of the results of two previous rounds of questionnaires, two topics were selected for discussion in focus groups: ethical issues associated with (1) source of cells and (2) donation. The results could be divided into three clusters: Tissue, Donor, and Scientist. Where the former two clusters roughly coincide with the results of the previous rounds, the third subject was entirely new but discussed by both groups: the role of the scientist in the tissue engineering process.

Introduction

EuroSTEC is an integrated project on “Soft tissue engineering for congenital birth defects in children.” Funded by the European Commission under the Sixth Framework Programme (FP6), it commenced on January 1, 2007. The project unites 15 partner organizations (10 research institutes and 5 companies) from nine European countries.¹

Recent developments in tissue engineering (TE) will be used to treat children with congenital structural disorders, such as spina bifida, urogenital defects, gastroschisis, diaphragmatic hernia, and esophageal atresia. The EuroSTEC project focuses on both maternal-fetal (or *in utero*) as well as neonatal interventions using tissue-engineered products. Part of the EuroSTEC project design is an extensive ethical analysis, which will focus on all three phases of the project — (1) fundamental (*in vitro*) research, (2) animal experiments, and (3) clinical trials — and will also look ahead to the application of soft TE in clinical practice.

In a previous study we conducted a survey of ethical issues that might arise during the course of the project.² A modified Delphi study — a systematic forecasting method consisting of multiple rounds — was used to question professionals who are directly involved in preclinical or clinical research on TE for congenital birth defects. Their views on possible moral issues throughout the course of the project were surveyed as a starting point. As is commonly done, we modified the Delphi method and restricted the number of rounds to ensure a high response rate throughout the multiple rounds.³⁻⁵ The first two rounds yielded a number of ethical issues² that demanded further exploration.

For the fundamental research phase, two dominant categories of ethical issues emerged: ethical issues associated (1) with the donation and (2) with the source of the cells used (see Table 1 for a list of the ethical issues identified by Delphi participants).

Table 1. Ethical issues in the fundamental research phase as identified by Delphi participants

Category	Issue
Source	<ul style="list-style-type: none">• The use of fetal cells• The use of cells from neonates• The use of fetal stem cells• The use of excess tissue obtained through abortion• The use of embryonic stem cells• The use of umbilical cord stem cells
Donation	<ul style="list-style-type: none">• Privacy of the donor of tissue• Informed consent of the donor of tissue• The possible invasiveness of the procedure through which tissue is obtained• Unclarity about the ownership of donated tissue

Previous literature research⁶ also identified these two clusters of ethical issues for fundamental research in TE. However, research on tissue engineers’ own perspective on these issues was lacking. From the perspective of an empirically based ethics, the views of these professionals — all involved in the EuroSTEC project — are expressly relevant because they have practical experience in the day-to-day routine of TE research and carry

responsibility for that practice. The central objective of this empirical study was to further explore TE experts' views on the two topics.

Materials and methods

Participants

Two groups of experts working in fundamental research within the EuroSTEC project were formed, with attention paid to equal distribution of gender, country, and place of work (for group characteristics, see Table 2).

Table 2. Participant characteristics

		Focus group 1 Donation (n = 10)	Focus group 2 Source of cells (n = 11)
Gender (% male)		7 (70.0)	7 (63.6)
Working in country	<i>Austria</i>	2	3
	<i>The Netherlands</i>	2	5
	<i>France</i>	1	-
	<i>Germany</i>	2	1
	<i>Sweden</i>	3	2
Place of work (%)	<i>University/hospital</i>	7 (70.0)	8 (72.7)
	<i>Industry</i>	3 (30.0)	3 (27.3)

Focus group sessions

As a result of the first two rounds of the Delphi study, two dominant categories were identified with regard to the fundamental research phase: "donation" and "source of cells." The first Delphi round focused on the identification of ethical issues by the participants and round two asked them to indicate the importance of the issues identified. The focus groups in the third round aimed at exploring why these issues were mentioned and deemed more or less important. Focus groups are a form of group interview that uses communication between research participants to its advantage in order to generate research data; the group interaction during the process is explicitly used as part of the method. The idea behind the method is that a group process enables participants to explore and clarify their views in ways that would be more difficult during a one on one interview.⁷

The sessions were held in April 2009. General methodology and procedure were first explained in a plenary session, after which both groups went to separate rooms. A hand out with the ethical issues previously mentioned and ranked in order of importance was distributed to the participants of each specific group. As an opening question, the focus group leader asked the focus group participants for their opinion on the ranking of the ethical issues. The discussion was led by two senior researchers (WD and PvdB) and lasted approximately one hour. The sessions were recorded with the consent of the participants to allow qualitative analysis.

Analysis

The recordings were transcribed and entered into Atlas-ti 5.2. The transcripts were coded using a grounded theory approach, in which the codes and codebook emerge from the data (as opposed to previously formulated hypotheses which are “tested” against data).⁸ The transcripts were coded by a primary analyst (AO), whereas a secondary analyst (WD) reviewed the transcripts with the assigned codes and the code book. Codes were then grouped into themes (or “families”), and subsequently grouped in clusters.

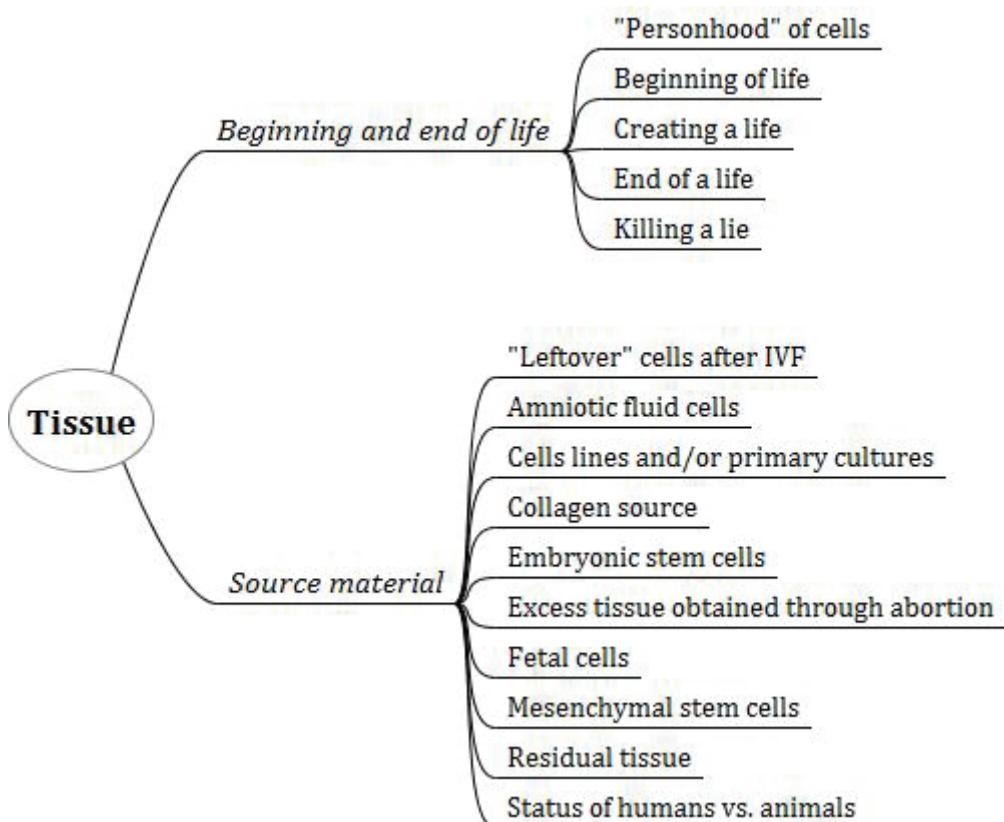
Results

The qualitative analysis yielded 58 codes, which were grouped into eight themes and subsequently clustered in three clusters: (1) Tissue (16 codes in two themes), (2) Donor (22 codes in three themes), and (3) Scientist (20 codes in three themes).

Cluster 1: Tissue

This cluster encompasses two themes: (a) Beginning and end of life and (b) Source material (Figure 1).

Figure 1. Themes and codes for cluster “Tissue.”



Beginning and end of life

The theme of beginning of life was addressed in focus group 2 (discussing the source of cells). The group agreed that the main question in judging the moral acceptability of experimenting with certain cell types centers on the question of "what do we consider life?" Within this context, the group mainly delved into the differences in moral status of human embryonic stem cells (hESCs) and fetal cells. In the literature on ethical issues in TE, the use of hESCs is the ethical issue most frequently discussed.⁶ Still, only one participant had moral qualms about working with hESCs. That participant would decline working with hESCs personally, but did not have problems with others working with these cells.

Some participants referred to the use of hESCs as "killing a life," with one person explicitly referring to Catholic doctrine on the topic, others held a different view. In the words of one of the other participants: "[Y]ou can't [say] that they die because they never lived." Most of the participants seemed to consider the use of fetal cells ethically more problematic, referring to the possibility of injuring a fetus when taking a tissue sample. As one person put it: "[P]eople don't necessarily think that embryonic stem cells [...] would have the possibility of developing into an adult while fetal cells [...] come from the fetus which can potentially survive to be something."

Another participant referred to a difference in views between scientists and the general public, citing that where a scientist might view leftover embryos of in vitro fertilization (IVF) as a mere clump of cells, the general public sees it as new life and might judge their moral value differently.

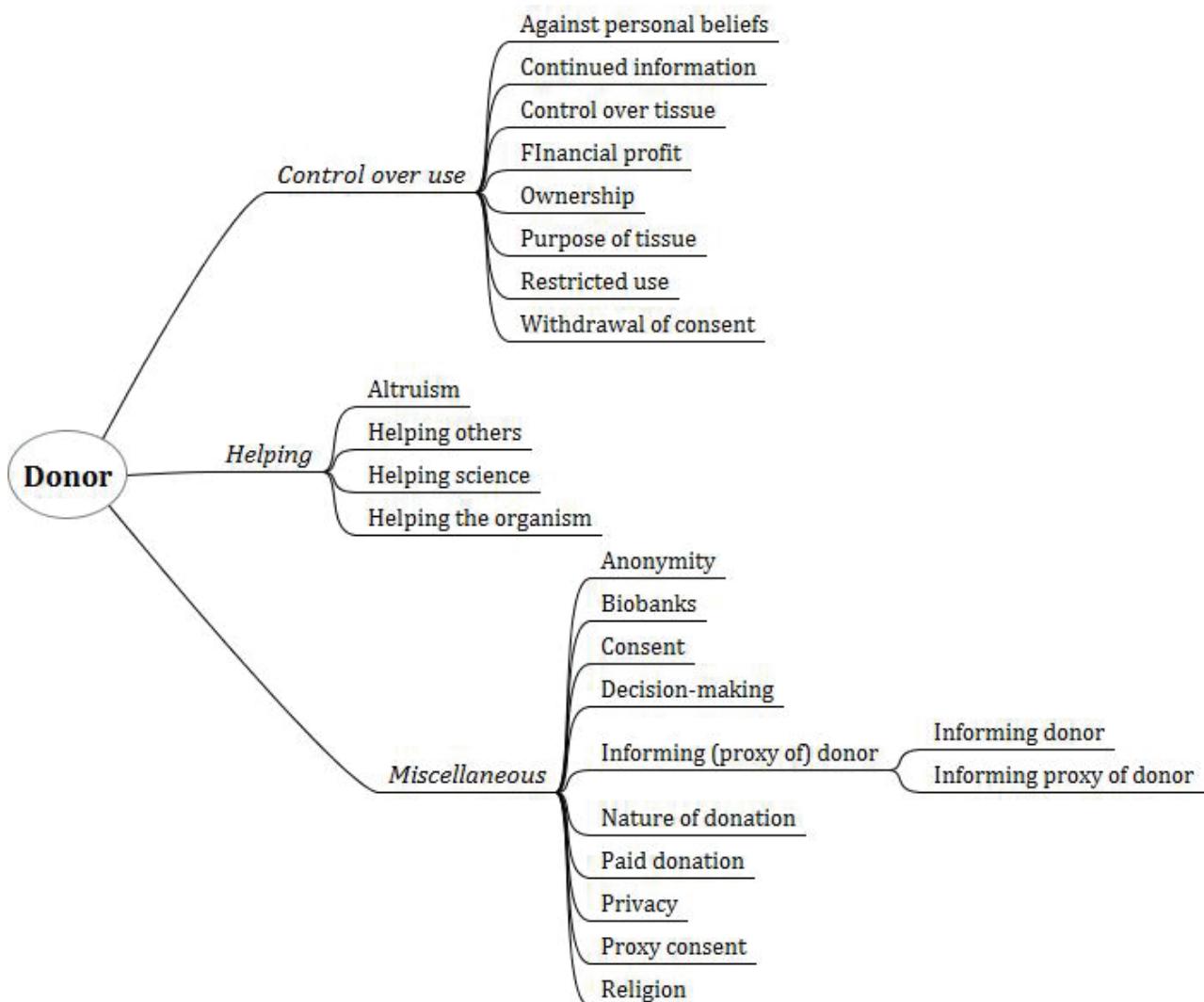
Source material

The discussion of this theme overlapped with the previously discussed theme of the beginning of life. In discussing the complex issues of different sources of TE material, the deciding factor for most participants seemed to be the consequences for the donor of the sampled tissue, not necessarily the moral status of the source of the tissue. One of the participants noted it was not actually the nature of the cells that determined his moral judgment, but he instead considered the consequences of the "harvesting" of the cells in question the deciding factor in how ethically problematic the use of this tissue would be. For example, according to this argument cells that remained after IVF ("leftover") were less problematic than cells taken from a fetus, living in utero, through biopsy. He argued that he would have to look at the consequences ("what I am endangering") to make a final judgment on a case-by-case basis.

Cluster 2: Donor

This cluster was divided into three subthemes: (a) Control over use, (b) Helping, and (c) Miscellaneous (Figure 2).

Figure 2. Themes and codes for cluster “Donor.”



Control over use

All participants deemed control, or some say over their donated material, important for donors, especially when the purpose of its use is considered. According to the participants, the donated material should not be used for “bad” purposes without the donor’s knowing; if a donor is told their material will be used for “good” research, their material should indeed be used for the purpose they were informed about and agreed to. As one participant put it: “Let’s say if you agree to, with my donated tissue, to help children in need [...] then you want to know that this helped children in need. The specific child that is [...] helped might not be that important to you, but it could be that, okay, this is not for developing cosmetics for this cosmetics industry.” Another said: “Suppose that the military would [want] to use it, to see the effect of some kind of bomb or whatever. I would definitely not like to have my skin be used for that.”

An added difficulty is the removal of tissue from incompetent subjects and their inability to give consent. Several participants indicated that if they were to give proxy consent for the use of tissue from their children, they would restrict their consent solely to autologous use. Only when the child in question would reach the age of consent the material could be used for other purposes, and only if the child agreed. One participant was quite adamant about the question of ownership in this context: "This belongs to the child. 'Cause [...] for me there's no question of ownership. There's a fingerprint on the material that has been donated [by] the child. [I] as a parent just gave the opportunity [...] to donate, but what has been donated is not my property, even though I [gave] the permission."

Should donors be able to withdraw their consent? One participant said that that would not be a problem, and he would simply "go to my fridge, I would take his sample, I would take his slides, I would [...] discard the data from my Excel file and it's done." Others, however, saw this as a near impossibility; for instance, what should be done if data have already been published based on the material this person donated?

The question of the extent to which a donor should and can be informed about the future use of their donated sample was thoroughly discussed. The way in which a scientist frames the question might heavily influence the likelihood of a prospective donor consenting. As one participant put it: "Are you willing to help people with cancer? Who wouldn't say yes to that question? But if they knew that this helping people with cancer would really be taking the cells, isolating the cells, cryopreserving them and multiplying them and spreading them all over the world, maybe they wouldn't be so helpful." Another participant added that it would be very difficult to specify exactly what donated tissue would be used for, because it often happens in TE, that the exact purpose is still unknown when one takes the sample.

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Helping

Keeping in mind the difficulties that surround the process of donation as discussed in the context of the previous theme, the main motivation for donation was addressed: being able to help, be this helping oneself (in autologous donation), helping others, or being of benefit to science in general. In spite of possible obstacles or problems involved in donation, all participants agreed altruism is required to keep the scientific process of TE going. As one participant indicated, if there were no parents who gave consent to use their child's tissue, a large part of the research of this very project could not be done.

Miscellaneous

In addition to the two broader themes that were donor-related, several smaller topics received attention.

The achievability of full anonymity, one of the staples of the donating process, was questioned by the group; after all, in order to do research on a sample, characteristics like gender, race, and possible diseases are known to the researcher, which means that the sample might be traceable to a certain donor. Additionally, the balance between anonymity/privacy on the one hand and the previously discussed control over tissue on the

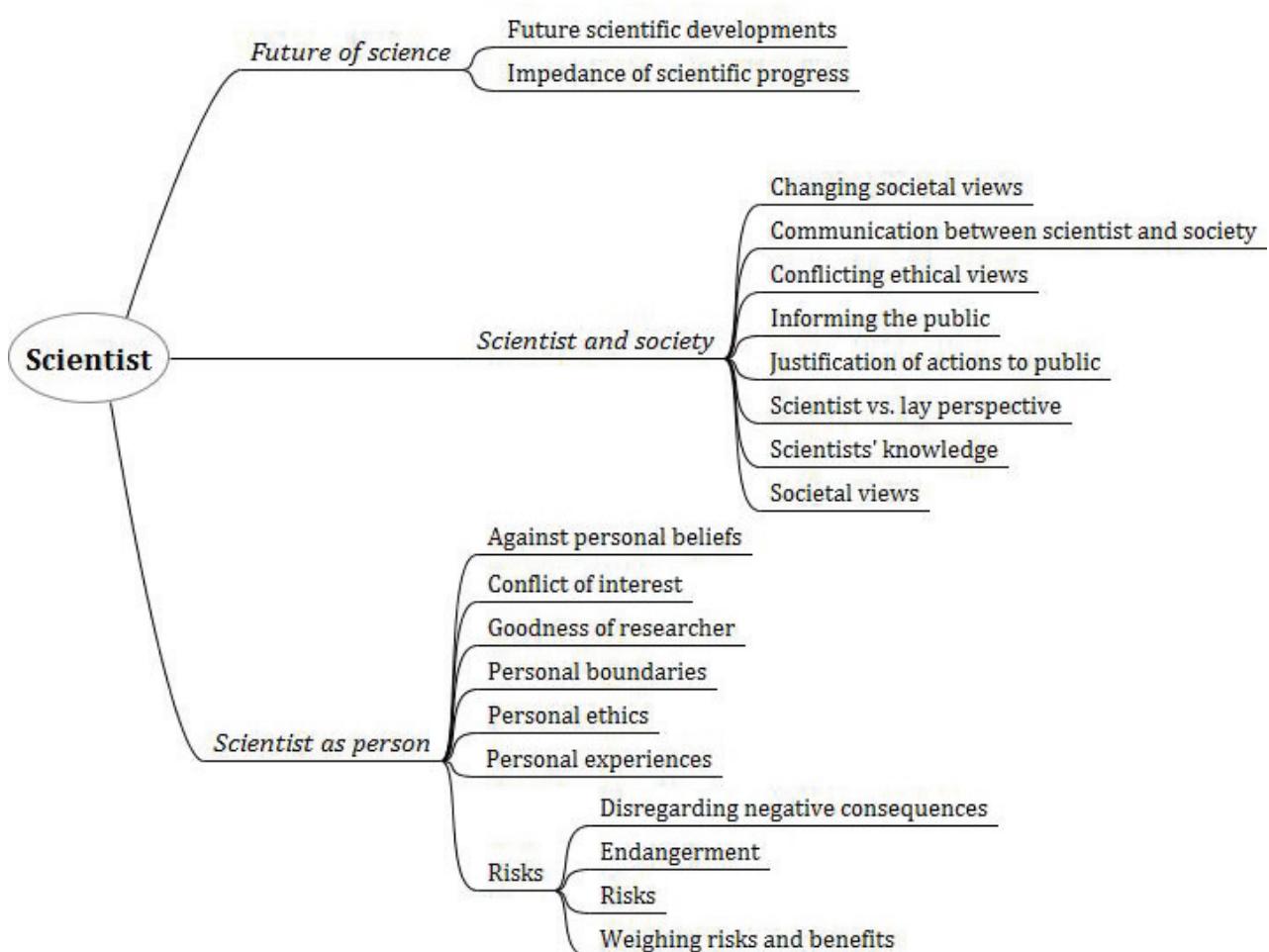
other was deemed problematic. If one would be required to continue to supply a donor with information about the purposes of the use of parts of their material, then the repeated information requires that name and contact information would have to be known to someone, thereby encroaching on the ideal of anonymity and privacy.

In discussing possible motivations for donating, the topic of financial compensation came up. Several participants were adamant about their opposition to paid donation. One explained: "I would oppose it 100%. [...] It can induce all kinds of strange situations [in which people] are trying to make money if [they're] poor, [...] doing things that are very unhealthy. So to protect people from themselves, I would say, I would oppose it."

Cluster 3: Scientist

The cluster "Scientist" consists of three themes: (a) Future of science, (b) Scientist and society, and (c) Scientist as person (Figure 3).

Figure 3. Themes and codes for cluster "Scientist."



Future of science

In discussing problems associated with the (proxy) consent process, several participants predicted that a stricter, more rigorous process might cause the number of parents that donate their children's tissue to decrease. They conjectured a decrease in number of donated tissues might seriously impede scientific progress. One participant, a university teacher, used the analogy of using animals to benefit human beings through research: "[N]ot everyone understands the implications of not giving away tissue samples for research. I would like to [use] the example of my teaching where I say 'animal trials' and students stand up and say 'no, why do you use animals? [...] we're totally against the use of any animals for anything.' And I say, 'Okay, please sign this paper, we will not use any of the treatments that have been developed using animals on you and your family.' They say, 'Uh oh, no, no, I'm [in favor of] animal...use of animals,' so the implications of not being able to use human tissue in research means that you don't have a cure for diseases and the coupling there is not maybe obvious for people. It's not even obvious for my university students."

Scientist and society

The relationship between a scientist and society, especially the role of communication, was discussed extensively. The risk of popular media picking up wildly negative stories about certain technologies was viewed by all as a real threat. According to the participants, the influence of the media on popular opinion about technology should not be underestimated. Therefore, scientists should tell the public about their work, although explaining the details of the TE process to a largely lay audience remains a challenge.

One participant described the responsibility of a scientist as follows: "[S]cientists tend to only see the good side of stem cell biology, and we often forget that there is a general public which has an opinion about the consequences of different research and scientists have a tendency to think; oh, this...this works for this particular application while there's a huge amount of consequences that maybe we're not thinking about. [...] Before you jump on a new train you have to test that it's safe and that, for instance, if we use embryonic stem cells there are all sort of different cancers and new diseases that can be introduced. Maybe not right away, but maybe in 50 years, and this is gonna be a new generation of kids that we have helped survive, but that will develop terrible diseases in the future. [...] So, I think it's sort of why we're sitting here and discussing this because we need to be aware that the general public has an opinion and we carry a very strong responsibility to make sure that we sort of think twice before we just..."

Scientist as person

With the talk of bad research, public mistrust and misinformation, one of the participants was quick to add the following: "I think we should state again that the researchers are, most of the researchers are on the good side, and that they really want to develop treatments, and that they do not want to create Frankensteins or make money out of it and therefore it's not such an ethical issue to give the consent to use the tissue for research purposes, at least in

my view. [...] If it comes to companies that are using the tissues, this is probably...or definitely different, and if it comes to induced pluripotent stem cell lines that are being created from differentiated cells that is also a different issue. But if you do our standard work that we all do now, I think we are still on the good side and we could even show the donors or the people that gave the consent what has been done with the tissue and in which direction the research is going."

In talking about how they reached a moral judgment of a certain act or technology, the participants indicated that different personal factors influence their judgments of right and wrong, and their willingness to work with certain matters or perform certain actions. One of these factors seemed to be personal experience with a disease that was potentially treatable with the technology at hand. This might make a scientist more likely to judge the technology favorably. Other factors mentioned included the way they were raised by their parents, and possible religious influences. In the end, participants seemed to view ethical judgments on the acceptability of a certain conduct or technology as incredibly personal, as one person said: "[F]or me there's no right or wrong, if [other participant X] says her opinion, then her opinion is as good as my opinion."

Discussion

On the basis of the results of two previous rounds of questionnaires, two categories of issues were discussed in two focus group discussions: donation and source of cells. The results of the discussion were divided into three clusters: Tissue, Donor, and Scientist. Where the former two roughly coincide with the two groups of issues that were the result of the previous Delphi rounds, a third, entirely new, subject was discussed by both groups: the role of the scientist in the TE process.

When comparing our results to discussions in the literature on the same topics, several similarities become apparent. For instance, like our participants, articles that discuss informed consent of tissue donors stress the importance of thorough information about future use of their material⁹⁻¹⁹ and protecting the privacy of the donor through anonymity.^{10,12-14,17-21} In our study, we learned of the difficulties that would arise while striving for these ideals in practice, as they were pointed out by our participants.

In surveying the arguments of the focus group participants, one matter is striking. Their way of arguing their case is very personal and subjective: in answering a question, their responses take the form of "if I were in that situation, I would." or "if that were my child, I.." Additionally, participants' answers generally display a consequentialist manner of reasoning: in assessing a situation, the majority of the participants look to the consequences of an act as the criterion for deeming it morally right or wrong. One example is the use of embryonic stem cells and the ensuing discussion of what is considered human life. The ethical literature on the topic generally argues the case in terms of principles (e.g., sanctity of life and human dignity).²²⁻²⁶ However, in these focus groups, the discussion came down to the comparison of different manners of obtaining tissue and their possible negative consequences, with those consequences informing the eventual moral judgment. A similar thing is apparent in the

discussion of paid donation. Where the literature, while also discussing undesirable consequences, argues mostly in terms of violating human dignity,^{18,27-32} the discussion in our focus groups solely focused on the undesirable situations paid donation might result in.

As is known from literature on teaching ethics, certain tendencies are apparent when non-ethicists discuss ethics, most notably skepticism (the belief that ethics has no right or wrong answers) and subjectivism (the belief that ethics is whatever any person feels is right).^{33,34} From time to time, both are also noticeable in our participants' reasoning. As became apparent in the focus group discussions, the participants seem very aware of their personal responsibilities both toward the scientific community and society at large. However, to meet these responsibilities in the complex setting of scientific research in research groups or competitive enterprises, skepticism and subjectivism are insufficient. Working with a group of people toward a common goal, some sort of intersubjective truth or norm is needed, one that transcends mere personal opinion or preference. These ethical norms in research help scientists to coordinate their actions and to establish and maintain the public's trust of the discipline.³⁵

Because the focus groups were part of a larger Delphi study and were preceded by two rounds of questionnaires, the participants were familiar with each other and the study in question. Therefore, during the focus group meetings relatively little time was needed to familiarize the participants with the process, as a cognitive process had already been set in motion.

Our population consisted of a diverse group of TE professionals: participants were involved in different types of fundamental research, and many different countries, nationalities, occupations, and institutions were represented. The views of TE experts outside of the EuroSTEC project, as well as those of ethicists and patients, were lacking from this study. To obtain an even richer overview of the ethical aspects of TE, it is our explicit intention to extend the target population of future empirical research to include these other groups.

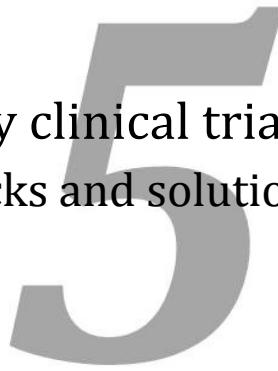
Ethics of TE and regenerative medicine is still a relatively small field. This study is the first to feature qualitative research concerning TE professionals' views on ethical aspects of preclinical research in TE. Although the participants in this study were recruited from one specific project, the relevance of our results need not to be limited to this project. Numerous parallels can be drawn between the project at hand and any other preclinical study in the field of TE. Therefore, we believe that our study will be of relevance to fundamental research in TE in general.

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Regenerative urology clinical trials: An ethical assessment of road blocks and solutions



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Tissue Engineering Part B: Reviews 2013; 19(1): 41-47.

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Abstract

Tissue engineering — part of regenerative medicine — is a promising technology that could potentially offer elegant solutions to urogenital defects, but so far, it has fallen short of its potential. Within experimental studies for bladder and urethra reconstructions, two clinical applications have been described, but extension of these techniques to the broader urological patient population has not happened so far. In this article, we aim to identify the ethical road blocks in the clinical evaluation of tissue-engineered products under the European Medicines Agency and Food and Drug Administration regulations for pediatric urological conditions and, ultimately, to recommend strategies to overcome them. The use of human tissue-engineered products (HTEPs) to treat children with congenital urogenital defects poses challenges in the clinical testing phase, connected to three features of the application of this treatment in this patient group: (1) those associated with the product, namely, the multifaceted complexity of the HTEP; (2) those connected to the procedure, namely, the lack of a randomized controlled trial (RCT)-tested gold standard to compare the new treatment to and difficulties surrounding standardization of the treatment protocol; and (3) the patient's young age and associated problems concerning possible long-term effects and the informed consent process. Due to these problems, a conventional RCT is not the methodology of choice to evaluate this treatment in this patient group. The unpredictability of HTEPs necessitates stringent and long-term surveillance and registry to ensure the safety of patients treated with these products.

Introduction

The goal of regenerative medicine is to induce the regeneration of tissues and organs, either following disease or injury, or when congenital or developmental defects are present. Through tissue engineering (TE), part of regenerative medicine, the body is stimulated to produce new functional and specialized tissue when needed.¹ A human tissue-engineered product (or HTEP) can be developed to replace a dysfunctional tissue with a tissue structure that has the same function, and that preferably remains at the desired location.²

TE is a promising technology that could potentially offer elegant solutions to structural defects. However, so far, the practical applications of the technology have fallen short of its potential. Currently, few clinical conditions are being addressed by TE, and commercial success has been difficult to attain.^{3,4} One of the clinical areas that has seen some promising clinical developments is urology.⁵⁻⁸

The EuroSTEC project (Soft tissue engineering for congenital birth defects in children: from biomatrix–cell interaction–model system to clinical trials), an integrated project funded by the European Commission under the Sixth Framework Program was aimed at the development of treatments for structural disorders present at birth.^{9,10} Two of EuroSTEC's target areas were the bladder and the urethra. In conditions affecting those areas, the success of conventional surgical reconstructions is often diminished by a shortage of native urothelium. Therefore, gastrointestinal tissues are currently used for reconstruction. However, these tissues are associated with complications, such as infection, metabolic disturbances, urolithiasis, perforation, increased mucus production, and malignancy.^{8,11-12}

These complications have stimulated TE research into the creation of implantable bladder and urethral substitutes. There is a fair amount of animal studies examining tissue-engineered constructs for congenital urogenital defects,^{13,14} but as of yet, few clinical studies. The clinical studies that were conducted resulted in either an unsatisfactory outcome as compared to conventional treatment, or were halted because of a significant amount of adverse events.^{7,8,15,16} Therefore, we think that the development of HTEPs for the treatment of urogenital defects can serve as an example. Through surveying the problems that were encountered in the development process of these clinical products, we will highlight the challenges to clinical testing of tissue-engineered products in general.

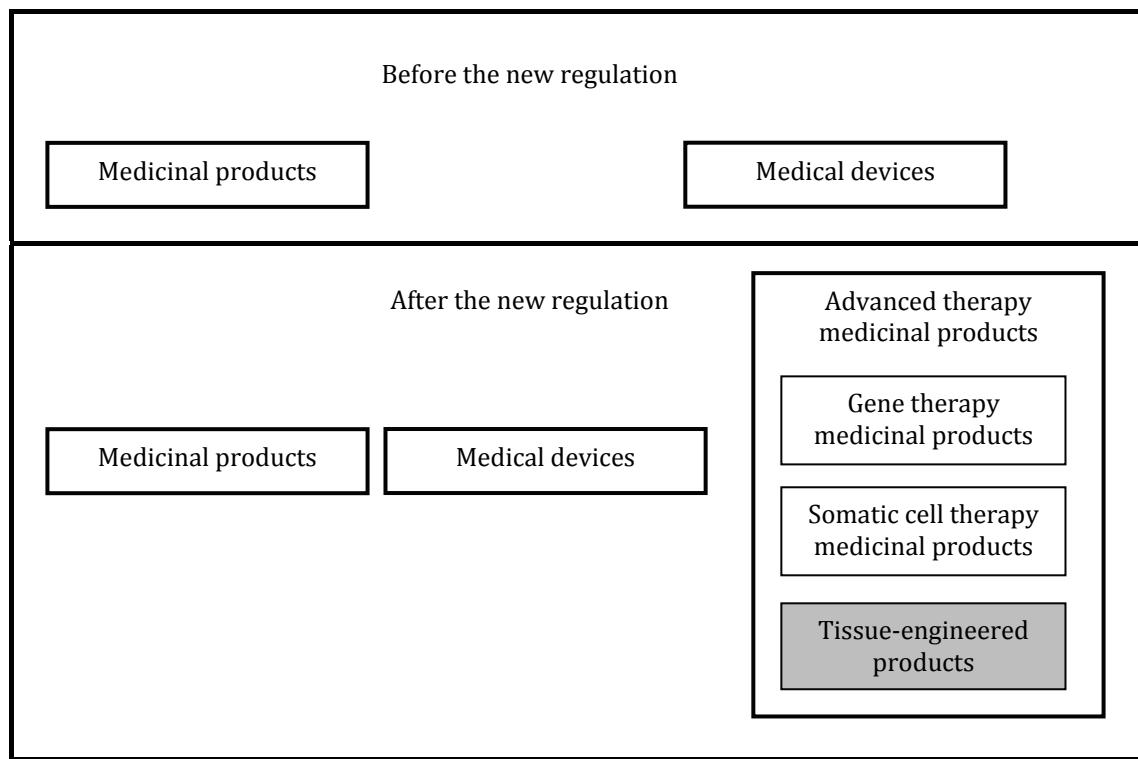
Objective of the current article is to identify the ethical challenges in clinical testing of tissue-engineered products for pediatric urological conditions. To this purpose, we will first survey the regulatory environment created for HTEPs. Subsequently, we will look at the specific challenges associated with clinical testing of HTEPs for this clinical application, and ultimately, recommend strategies to overcome the identified challenges.

The Regulatory Environment of HTEPs

In the past, medical products were regulated as either medicinal products or medical devices. Tissue-engineered products fell between these two categories: in some ways, an HTEP is an active implantable medical device, but there is also a significant role for pharmaceuticals.⁵ Additionally, an HTEP may contain viable cells.¹⁷ In addition to tissue-

engineered products, other cell therapy medicinal products fell between the existing categories as well. This prompted the European Union to create a new class of medical products: Advanced Therapy Medicinal Products or ATMPs (see Figure 1).

Figure 1. Before and after the new regulation



An ATMP is either (1) a gene therapy medicinal product, (2) a somatic cell therapy medicinal product, or (3) a tissue-engineered product (see Table 1).¹⁸ Regulation No 1394/2007 requires those planning to market an ATMP within the European Union to seek authorization from the European Medicines Agency (EMA).

Table 1. Definition of a tissue-engineered product according to Regulation (EC) No. 1394/2007¹⁸

According to the definition used in regulation (EC) No 1394/2007, a tissue-engineered product has the following characteristics:

It contains or consists of engineered cells or tissues;

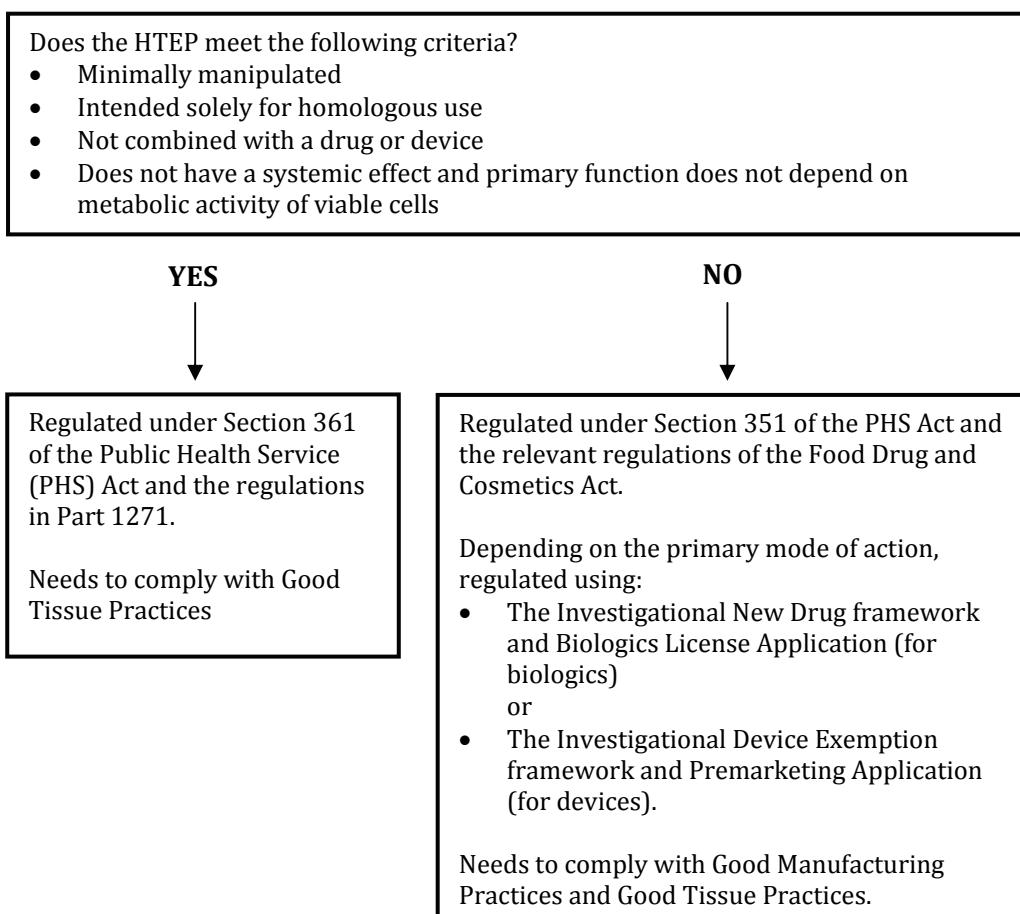
Is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue;

Cells or tissues shall be considered 'engineered' if they fulfill at least one of the following conditions: the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved;

The cells or tissue are not intended to be used for the same essential function or functions in the recipient as in the donor.

In the United States, articles containing or consisting of human cells or tissues intended for transplantation, implantation, infusion, or transfer to a human recipient are regulated by the Food and Drug Administration (FDA) as human cells, tissues, and cellular and tissue-based products (or HCT/Ps).^{19–22} The level of regulation depends on the characteristics of the product (see Figure 2), but good tissue practices (or GTPs) are required regardless of the specific characteristics. GTPs describe the methods, facilities, and controls used in the manufacturing of HTEPs to prevent the infectious disease transmission and cross-contamination.^{19–22}

Figure 2. Criteria to determine level of Food and Drug Administration regulation for human tissue-engineered products.^{22,23}



From preclinical to clinical practice

Before any HTEP can be considered for market authorization, information needs to be collected about its quality, as well as about its behavior in animals and, ultimately, humans. A common step in the process of proceeding to clinical trials are animal studies. In TE, there is some debate on the adequacy of animals as models for the human situation.^{23–25} It appears to be difficult to gather information about regenerative activity and safety of HTEPs in humans from animal trials.²⁶

For clinical research to be justified, three conditions need to be met: (1) minimization of potential risks to the trial participant, (2) enhancement of the potential benefits to individual subjects, and (3) the potential benefits to individual subjects and society are proportionate to or outweigh the risks.^{27,28} Additionally, for a clinical trial of an HTEP to be successful, it should not only confirm therapeutic value, but also provide insight in regenerative activity, safety, and longterm effects of the HTEP.

The risks that are anticipated (see Table 2) need to be weighed against the potential benefits, and against the risk–benefit ratio of existing therapies. Because the process of TE is complex, risk assessment is of vital importance and should be rigorous.

The last step in proceeding from clinical research to clinical practice is market authorization. HTEPs are expected to show greater variability in composition and performance as compared to traditional medicinal products or medical devices, which has consequences for, among other things, labeling and product descriptions. The risk potential varies between different types of HTEPs, which has led both the EMA and the FDA to install the so-called risk-based approach in the market authorization process. This approach is used to determine the amount of data needed in the market authorization application, and is based on the identification of risk factors associated with the quality, safety, and efficacy inherent to the nature of the HTEP in question.^{20,21}

Table 3. Risks for patients associated with human tissue-engineered products²⁹

Risks associated with HTEPs ²⁹ :
Microbiological contamination associated with source materials (e.g. latent viruses)
Disease transmission
Contamination associated with the production process
Risks associated with the delivery of un-wanted cells
Risks of mix-ups in the process (transposing products from one patient to another)
Risks associated with the modification of cells
Risks inherently associated with the scaffold/matrix component
Risks associated with achievement of sterility of the HTEP
Risks associated with the potential toxicity of cryo-preserved, process additives and other residues
Risks associated with the performance of the final product
Unknown risks associated with the interaction between cells and scaffold
Patient specific responses (such as allergies to substances used)

Challenges to clinical testing

A clinical application of an HTEP that was researched in the EuroSTEC project is the use of tissue-engineered constructs in children with congenital urological defects. The use of HTEPs to treat children with these conditions creates an ethically complex situation because of a combination of factors, which have to do with (1) the product (an HTEP), (2) the procedure (a surgical intervention), and (3) the patient (a child). Separately, these three factors complicate the design and conduct of a clinical trial. When combined, they pose numerous challenges to the clinical evaluation of this new treatment.

Conventionally, clinical testing is conducted through several phases. So-called phase I trials, aimed at safety and (in pharmaceuticals) dose-ranging, generally include a small group

of healthy volunteers. Once initial safety has been confirmed, the process moves on to phase II trials. In these studies, efficacy of the intervention is tested in healthy volunteers. Phase III studies are large, randomized controlled multicenter trials in which the intervention is applied in patients and compared to the gold standard treatment. After an intervention is approved for the market, phase IV trials are often started. These studies are aimed at continued safety surveillance.³⁰

Large randomized controlled trials (RCTs) have become a staple of pharmaceutical research, and medical research in general, and as such there is a well-defined, internationally agree-upon set of rules and regulations for clinical research of drugs. Additionally, there has been some history of trials with implantable medical devices, their performance being evaluated in clinical trials and postmarket surveillance procedures.³¹ With clinical testing of HTEPs, however, there is substantially less experience.

Product

One of the most important characteristics of the TE process is its complexity. This complexity has consequences for clinical trial design and evaluation.

First, HTEPs show a certain amount of variability, because they contain metabolically active cells in a dynamic extracellular environment. Second, HTEPs are intended to integrate with the body and eventually achieve regeneration of the tissue. The HTEP itself evolves, the dynamic in the body of the recipient influences the incorporation of the HTEP and, finally, the recipient's body and the HTEP interact with each other. Third, because of this interaction, once the process of regeneration is started, it is impossible to fully reverse it. The HTEP itself can be removed, but cells or biomolecules from the HTEP may have influenced surrounding tissues in a way that cannot be undone. This may lead to problems for the trial participant when the results of a trial with an HTEP turn out to be unfavorable.^{17,27}

Like any clinical study, those focusing on HTEPs will have to confirm their therapeutic value. Additionally, they will have to show whether regeneration takes place, whether the product is safe, and what its long-term effects are.²⁷ A trial of a regenerative medicine treatment is not simply a test of a new medicinal product, but should be considered a trial of a complete process (construction, surgical implantation, and regenerative action of the HTEP in the body of the patient, and the final functional outcome).³²

Procedure

Some challenges in clinical testing of HTEPs for pediatric urological conditions are due to the surgical procedure through which the HTEP is implanted.

In evidence-based medicine, the RCT is the gold standard for assessing the effectiveness of clinical interventions. The RCT is considered the only clinical study design that allows for truly valid inferences considering cause and effect.³³ Therefore, when appropriate, practical, and ethical, a randomized trial design should be used.³⁴ In spite of this, studies featuring RCTs on surgical interventions in children are rarely reported.³³ This means that, as many

new surgical treatments are not tested in classic clinical trials, there may not be a true gold standard to compare the new treatment with the HTEP.

When evaluating a new treatment, a certain uniformity of protocol is necessary to limit the amount of variation in the treatment being studied. However, complete standardization of a surgical intervention is difficult; the way a surgeon conducts an HTEP implantation may be refined over time due to the surgical learning curve and the advance in HTEP construction and the development of instruments. Additionally, different surgeons may refine a technique in different ways. In multicenter studies, the differences in skills and experiences of the operating teams may introduce further variation.³⁵

Patient and parents

The fact that the prospective patient is a child leads to two kinds of challenges: those associated with the patient's life span, and those connected to the informed consent process.

The prospective patients of HTEP-based treatments in question, in this article, are small children with, in the best case scenario, a long lifespan ahead of them. Some of the risks of HTEP-based treatments, if they occur, are expected to happen in the far future. In some TE-based treatments (like cartilage TE for elderly patients), the expected length of time for these adverse events to occur exceeds the average lifespan of the patients in question. In HTEP-based treatments for pediatric urological conditions, therefore, something like tumorigenicity may be a very real concern. As a consequence, follow-up to trials of HTEPs would ideally allow for these long-term negative effects to be taken into account. However, as these adverse events may only occur 20, 30 years into the future, arranging for such a long surveillance period may prove to be a challenge.

Because the prospective trial participant is a legally incompetent child, proxy consent needs to be obtained from the parent(s). In that case, the patient's proxy weighs the risks and benefits of the treatment in question (a decision that may have consequences in the far future, when the patient is no longer a child). The fact that the treatment in question is highly complex, as mentioned before, adds even more difficulty, since the risk of inadequate informed consent is present. The implantation of an HTEP has different goals and risks than a conventional surgical procedure, and is therefore difficult to explain to lay people. This endangers the ideal of a patient's proxy consenting to a treatment based on a clear understanding of the relevant facts.^{27,36}

Discussion

The use of HTEPs to treat children with congenital urogenital defects poses challenges in the clinical testing phase, connected to three features of the application of this treatment in this patient group. First, those associated with the product, namely, the multifaceted complexity of the HTEP. Second, those connected to the procedure, namely, the lack of an RCT-tested gold standard to compare the new treatment to and difficulties surrounding standardization of the treatment protocol. Lastly, the patient's young age and associated problems concerning possible long-term effects and the informed consent process. Due to these

problems, a conventional RCT will be difficult to conduct and is not the methodology of choice to evaluate this treatment in this patient group.

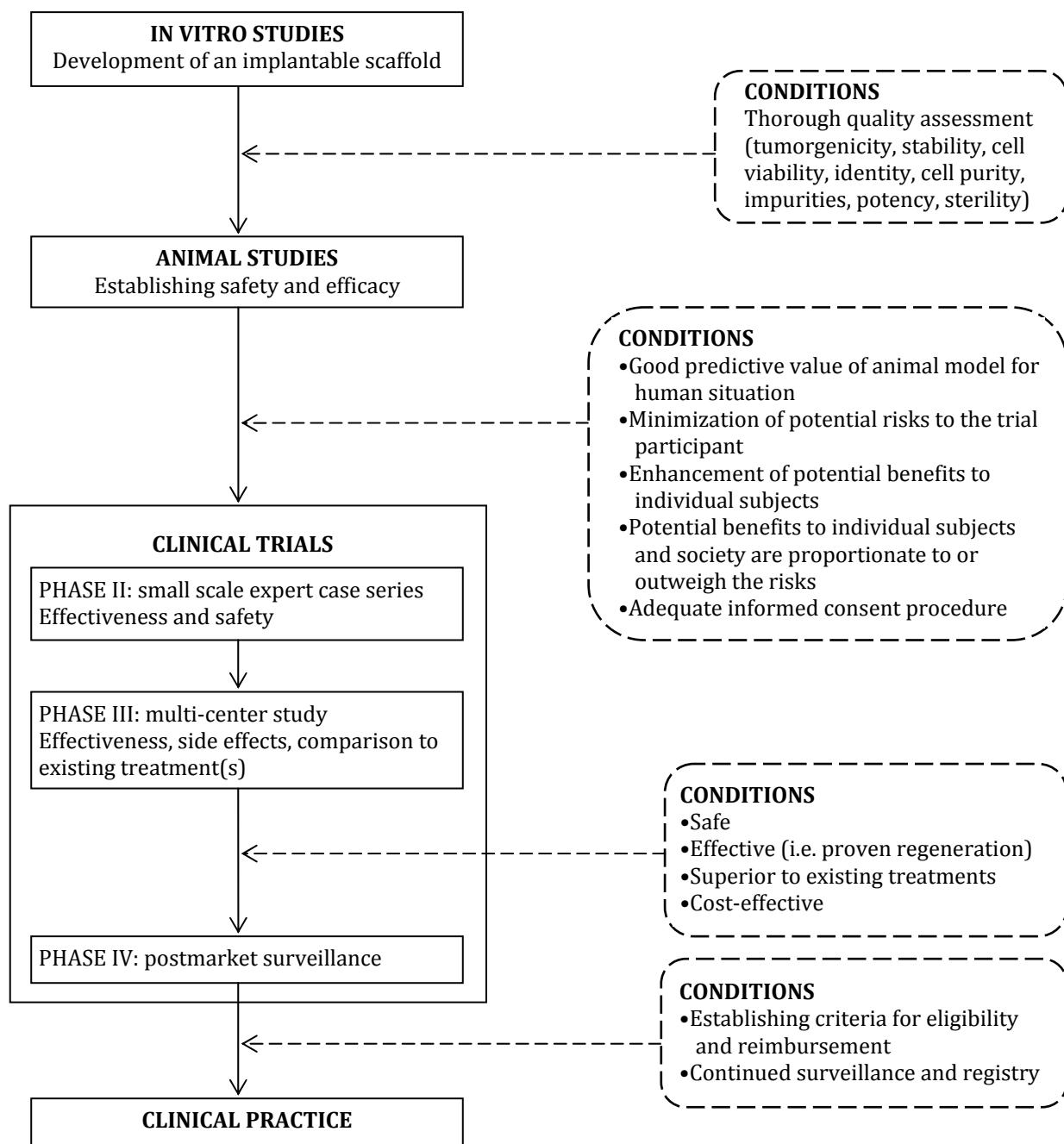
How should clinical evaluation of HTEPs in these patients take place? Implantation of an HTEP is quite a significant intervention. As is the case in, for instance, research on treatments for cancer or HIV infection, this intervention is too great a burden to test in healthy volunteers. Therefore, conventional phase I trials with healthy volunteers are unethical. Therefore, the next step following animal studies will most likely be small-scale expert case series with actual patients. For the transition from animal experiments to use in humans to be justified, three conditions need to be met. First, the animal models used need to be optimal representations of the situation in humans. This may prove to be problematic, as the adequacy of the animal models used in TE has been questioned.²³⁻²⁵ Research on the predictive value of animal experiments in TE-based treatments is therefore of vital importance. Recent developments in the field of systematic reviews of animal models, for the optimization of animal testing, are a step in the right direction.^{37,38} Second, minimization of the potential risks and maximization of the potential benefits to the individual trial subject. The TE process consists of an ex vivo part (manufacturing the HTEP in the laboratory) and an in vivo part (implantation of the construct and regeneration in the body). This necessitates the establishment of Good Manufacturing Practice guidelines pertaining to the ex vivo manufacturing stage, as well as the establishment of Good Clinical Practice guidelines for clinical trials and clinical practice for HTEPs. Third, the informed consent procedure should consist of a comprehensible explanation of the process, the possible benefits and possible risks (both short and long-term).

If the results of the small case series are positive, the next step should be the evaluation of the HTEP-based treatment on a larger scale, where different teams in several expert centers treat patients based on a uniform protocol. Reliable therapies for the conditions in question are currently available — although they do come with complications in certain patients. Ultimately, for introduction of HTEPs in clinical practice to be justified, large clinical trials should prove superiority over conventional treatment. A newly developed treatment should have a more beneficial cost-effectiveness ratio than the previously available treatments. However, there is often no gold standard, RCT-tested conventional treatment with proven cost-effectiveness. Additionally, it seems difficult to demarcate what to include in the calculation of costs of treatment, and therefore cost-effectiveness studies in this field may prove to be very complex.

A treatment in the field of regenerative medicine needs to accomplish an important act: regeneration. HTEPs for pediatric urological conditions are designed not just to patch up a structural defect, but to ultimately, fully function as native urological tissue. Therefore, it is important that clinical studies prove that regeneration takes place. This means that ways to monitor (and possibly control) the behavior and development of the HTEP in the body after implantation need to be devised. Monitoring is also of vital importance to gather data on the behavior of the HTEP and/or the regenerated tissue in the long-term. Recently, the importance of postmarket surveillance and patient registries to track outcomes was stressed

in a public hearing held by the FDA concerning complications of a medical device (a synthetic surgical mesh) for gynecological problems.^{39,40} Since an HTEP contains biologically active molecules and/or cells, its behavior in the body is even less predictable than that of a medical device. Therefore, stringent and long-term surveillance and registry are essential to ensure the safety of patients treated with these products. (see Figure 3).

Figure 3. From bench to bedside



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Towards a richer debate on tissue engineering: A consideration on the basis of NEST-Ethics

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Abstract

In their 2007 paper, Swierstra and Rip identify characteristic tropes and patterns of moral argumentation in the debate about the ethics of new and emerging science and technologies (or “NEST-ethics”). Taking their NEST-ethics structure as a starting point, we considered the debate about tissue engineering (TE), and argue what aspects we think ought to be a part of a rich and high-quality debate of TE. The debate surrounding TE seems to be predominantly a debate among experts. When considering the NEST-ethics arguments that deal directly with technology, we can generally conclude that consequentialist arguments are by far the most prominently featured in discussions of TE. In addition, many papers discuss principles, rights and duties relevant to aspects of TE, both in a positive and in a critical sense. Justice arguments are only sporadically made, some “good life” arguments are used, others less so (such as the explicit articulation of perceived limits, or the technology as a technological fix for a social problem). Missing topics in the discussion, at least from the perspective of NEST-ethics, are second “level” arguments — those referring to techno-moral change connected to TE. Currently, the discussion about TE mostly focuses on its so-called “hard impacts” — quantifiable risks and benefits of the technology. Its “soft impacts” — effects that cannot easily be quantified, such as changes to experience, habits and perceptions, should receive more attention.

Introduction

Much of the moral argumentation and argumentative strategies used in debates on emerging technologies are far from new. Many arguments and patterns of argumentation occur repeatedly in the discourse surrounding any new technology. In their 2007 paper, Swierstra and Rip identify these characteristic tropes and patterns of moral argumentation in the debate about the ethics of new and emerging science and technologies (or “NEST-ethics”).^{1,a}

The idea of user and stakeholder involvement requires that society should be informed about the relevant aspects of an emerging technology while it is still being shaped. It is therefore important that in talking about a technology, its possible impacts are discussed in breadth and depth. Through discussions about the impact of a technology, researchers working on this technology become aware of the concerns of the public, meaning they can respond to these concerns early on in the development process. The public, in turn, is better prepared for the technology, and will be less surprised by the impact it may have on their personal life and on society as a whole. The probability of relevant aspects being brought forward is simply greater in a broad debate than in a debate that is merely focused on risks and benefits. Ultimately, technology as well as society will benefit from a rich debate. In this paper, we will focus on the debate on values and norms relating to one particular emerging technology: tissue engineering (TE).

If, as Swierstra and Rip argue, the debate surrounding a new and emerging technology shows a certain repeating grammar, we should be able to identify these patterns in the discourse of TE. TE is a relatively new and — according to those working in the field — promising technology, which is part of the field of regenerative medicine.² Taking Swierstra and Rip’s NEST-ethics structure as a starting point, we will consider whether all relevant issues are present in the discussion of TE, and argue what aspects we think ought to be a part of a rich and high-quality debate of TE.

In this paper, the following questions will be discussed:

1. Can we distinguish the characteristic recurrent tropes and argumentative patterns of NEST-ethics as described by Swierstra and Rip in the discourse surrounding TE?
2. What aspects of argumentation are missing from the discussion of TE? Why do we think these aspects deserve attention?
3. Based on the analysis of the TE debate, can we point to elements that are not apparent in other debates about NEST?

Methods

We searched the PubMed databases using the terms “tissue engineer*” (or the Mesh term “Tissue Engineering”) or “regenerative medicine” (or the Mesh term “Regenerative Medicine”) in combination with either “ethic*”, the Mesh term “Ethics”, the subheading “/ethics” and/or the publication type “review”. We then used the snowball method to find other relevant papers or books. Additionally, a newspaper search was conducted through the

^a By “trope”, Swierstra and Rip mean a recurring argument or motif that is supposed to have particular force; an argumentative “pattern” consists of two or more ethical arguments that provoke each other into existence.

LexisNexis database. Search terms used were “tissue engineering” or “regenerative medicine”.

To survey the moral discussions on TE apparent in the literature, we used the NEST-ethics structure as presented by Swierstra and Rip in their original paper from 2007 and a paper by Swierstra et al. in which the NEST-ethics grammar is applied to a specific case from 2009.³ The NEST-ethics approach is based on experiences of both authors with debates about new and emerging technologies. Swierstra and Rip analyzed the types of arguments used in these debates, and entered them into their paper. Therefore, the NEST-ethics approach provides an analytical framework with which a new debate can be considered. For every category of arguments mentioned in this grammar, we attempted to find examples in the TE literature.

In our paper, we will first give a brief overview of the development and characteristics of TE, we will then walk through the different categories of arguments used in the discussion of TE and finally, we will highlight the elements that have received little attention in or are absent from the debate, and discuss why they are important.

Tissue engineering

“A salamander can grow back its leg, why can’t a human do the same?”

*Anthony Atala, New York Times.*⁴

The term tissue engineering was first mentioned at a meeting sponsored by the National Science Foundation in California in 1988. This meeting discussed efforts to manipulate existing tissues or combine them with prosthetic materials (Vacanti 2006).⁵ Nowadays, the term is used for the actual generation of tissue, by using artificial support scaffolds on or in which human cells may have been deposited. The interdisciplinary field of TE aims to replace, repair and/or regenerate tissues and organs. As Langer and Vacanti put it in their classical analysis in Science:

“Tissue engineering applies the principles of biology and engineering to the development of functional substitutes for damaged tissue.”⁶

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TE attracted public interest in 1997 when a BBC documentary showed what is now known as the “Vacanti mouse”. Vacanti’s paper showed how the cartilaginous part of a 3-year-old child’s ear was regenerated.⁷ The media upheaval was not so much caused by the experiment, as by the spectacular sight of a nude mouse with a human ear on its back.⁸

TE is generally understood to be one of several different biomedical approaches — together with, for instance, somatic cell therapy and immunomodulation therapy — that are part of the field of regenerative medicine. This emerging medical field is defined as follows:

Regenerative medicine is the process of creating living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage, or congenital defects.⁹

Many TE articles, both in the popular media as well as in the scientific literature, start by mentioning failing and degenerating tissues and organs as a growing challenge to healthcare. The second half of the twentieth century saw developments in the replacement of failing tissues and organs by medical devices or donor organs, or substitutive therapy. Organ transplantation, surgical reconstruction with foreign tissue, artificial prostheses and artificial administration of metabolic products are all interventions attempting to treat organ and tissue damage.¹⁰ Although they are life-saving, cost-effective and safe, these therapies have several drawbacks. Devices or donor organs are not fully incorporated into a patient's body, they require invasive surgery and their lifespan is limited. In addition, there is a chronic shortage of donor organs and many substitutive therapies, such as dialysis, have a significant negative impact on the patient's life. For these reasons, scientists have been looking for alternatives, and TE is presented as a field of medicine dedicated to increasing the therapeutic options available for the treatment of tissue damage and organ failure.

TE treatments promise a more complete recovery with significantly fewer side effects or risks of complications, compared to conventional treatments. A TE application that has proven to be of clinical benefit is skin derived from a TE process, which can be used as a skin replacement or as a temporary wound cover for burns, or as a treatment for diabetic ulcers. TE may also be used for the induction of bone and connective tissue growth, to guide long bone regeneration, and to replace damaged cartilage. In the future, TE grafts could potentially be used in cardiac bypass surgery. And somewhat further away, TE research may yield solid organs for transplantation, treatments for spinal cord injury, and insulin-producing pancreatic islets that could be regenerated by the body to cure diabetes.⁹

Hopeful statements in the early years of TE caused considerable excitement and promised patients quick cures. The field was not able to deliver those promises, however. In spite of significant scientific progress, there are as of now few examples of clinical applications. Some tissue-engineered products are clinically available, but most TE applications are still in the pre-clinical phase, making TE still very much an emerging technology.¹¹

Although the focus in the scientific literature is on clinical applications, TE may be used for other purposes as well. For example, TE constructs can serve as simulations of biological systems, or as disease models in research.¹²⁻²⁰ They can be used as alternatives for animal testing, such as a TE skin substitute to test the toxicity of certain chemicals.^{21,22} TE products can also be used as biological and chemical sensors.^{23,24} Some laboratories are working on the creation of consumable meat products ("in vitro meat") made from TE animal muscle cell constructs.^{25,26} And finally, what to think of so-called bio-jewelry, such as a wedding ring made from TE bone of your partner.^b

^b See Biojewellery: Designing Rings with Bioengineered Bone Tissue at www.biojewellery.com (last accessed June 3rd, 2012).

NEST-ethics of tissue engineering

According to Swierstra and Rip, the discussion about NEST takes place at two levels:^{1,3}

1. Discussion of issues related to the dominant moral standard referred to implicitly or explicitly. These include:
 - Consequentialist arguments (utilitarianism/consequentialism)
 - Fundamental principles, rights and duties
 - Arguments from justice
 - “Good life” arguments.
2. Discussion of the relationship between technological and moral change, in which the authors distinguish (1) arguments of technological determinists and voluntarists,^c (2) arguments of optimists and pessimists, and (3) the discussion of moral change induced by the technology.

Consequentialist arguments

Benefits

In the discussion of NEST, proponents of the technology in question refer to its desired consequences. They talk about the benefits the technology will bring about and express ideas about how it will increase our well-being. This certainly happened for TE as becomes clear from newspaper articles on the topic. Scientists tend to overstate the potential benefit to patients or give unrealistic timelines for a product to reach the clinic in order to interest investors.¹¹

Charles Vacanti, one of those at forefront of the development of TE, spoke of the promise of the technology as follows:

“It could ultimately be the end of all organ donor transplants”⁴

Promises of a medical revolution evoke the concerned reaction of those that worry about the ignorance concerning the effects of TE. Remarkably however, there was relatively little public commotion about the principle of TE itself. Rather than being outright opponents, those critical of TE appear to be more skeptical. These skeptics do not dismiss TE-based therapies as such, but question the projected timeframe and feasibility of the projected benefits. Something like a muscle or a skin flap of 5 square inches is a completely different story than a solid organ that serves many complex functions, such as a kidney or a liver. The plausibility of the claims made about the creation of these complex solid organs in the semi-recent future is questioned by skeptics and even considered “a pie in the sky”.²⁷

Risks

^c Swierstra and Rip understand “technological voluntarists” to mean those that counter arguments of technological determinists (morals cannot influence the course of technological progress) by arguing that technology is influenced constantly by societal forces, and can thus be steered in morally desirable directions.³

Many authors warn against different risks associated with TE research and clinical applications. For instance, there is some risk involved in the use of xenogeneic or allogeneic cells. Xenogeneic cells might introduce pathogenic agents into humans or lead to serious immunological problems if not genetically altered or physically isolated.²⁸⁻⁴⁰ Risks of using allogeneic cells are considered less great, but these cells may still cause immunological problems or disease transmission.^{29,36,37,41}

Other risks are associated with paying women for the donation of their oocytes, that will then be used in therapeutic cloning to create source material for TE research. These risks include hyperstimulation of the ovaries and complications of the recovery (either through surgery or transvaginally) of oocytes.⁴²⁻⁴⁸ Any discussion of paid donation of source material of TE leads to discussion of risks of the exploitation of poor people.^{41,49-51} Cord blood banking is sometimes mentioned as something that parents feel they should do for their child, to enable or facilitate the TE process if needed. Critics point to the risk of creating false hope by doing this.⁵²⁻⁵⁶

The clinical trial phase is often mentioned as one of the more problematic research phases, where there is still a lot of work to be done. Authors point to the uncertainty of projected benefits and risks, both in the short term (introduction of pathogens) and the long term (tumorigenicity). This complicates the risk–benefit analysis of clinical trials.^{37,57,58}

Yet-to-be developed TE-based treatments are relatively expensive. Tissue-engineered products are not (yet) so-called off the shelf products; there is no one size, thickness and (most importantly) metabolic, biological and chemical composition of a tissue engineered construct that fits all. At this point, for instance in the case of soft TE of muscle flaps, a scaffold is still prepared for one specific application. This makes these treatments more expensive than the available ones.⁵⁹⁻⁶⁴

Fundamental principles, rights, and duties

Fundamental principles, rights, and duties are often appealed to when the interests of the individual have to be protected from being sacrificed for the greater good. In this context the principles of beneficence, non-maleficence and autonomy are often invoked. In the TE context, these rights and duties are discussed in reference to for instance prospective patients and their parents, physicians, tissue engineers, tissue donors, human embryos, trial participants, and laboratory animals. In the debate on TE the principles of autonomy, the right to pursue health, respect for human dignity, the question of informed consent of donors and trial participants, the privacy of donors and trial participants and the debate on human stem cell technology are relevant. Most of the ethical issues mentioned in a qualitative study among the experts involved in the EuroSTEC project referred to these principles.⁶⁵

The debate on stem cell technology — the use of embryonic stem cells and the creation of human embryos for research purposes — is very prevalent in the literature on TE, often somewhat hijacking the debate.⁶⁶ Opponents of the use of human embryonic stem cells call upon the principle of the protection of human life when discussing the destruction of human embryos in order to obtain the human embryonic stem cells.^{42,67-71} Additionally, the principle

of human dignity is mentioned in relation to the patenting of tissue-engineered products and the commercial use of bodily material such as ova. Some authors warn that it may lead to the commercial exploitation of (female) donors.^{49,72,73}

TE research and allogeneic TE applications often use cells from donors. The ideal of informed consent is often stressed, framed in terms of duties to and rights of the tissue donor; the right of information, the duty to inform the donor, the right to withdraw from research, and the duty to protect the privacy of the donor.^{50,52,58,67,74-80} In these cases, the protection of the donor's privacy often conflicts with the ideal of informed consent (and the right to withdraw from research); since it is often impossible to be sure of the exact purpose of the donated cells in advance, some identifiable data will have to remain attached to the tissue sample to be able to inform the donor of future use.^{62,65,81}

In the phase of clinical trials and ultimately clinical practice, the duty to protect individual patient-participants is important. The design of a safe, valid and valuable randomized clinical trial of TE is difficult.⁸² Furthermore, the ideal of informed consent is virtually impossible to achieve, since the consequences of implanting a TE product are virtually impossible to oversee.⁸³ Since TE is relatively new, the long term effects of implants with regenerative potency are still unknown.^{59,73} The lack of systematic knowledge about unproven stem cell therapies is a fundamental problem for patients considering their treatment options, as well as physicians advising their patients.⁸⁴ Trommelmans et al. therefore conclude that there is a need for a comprehensive, specific ethical guidance of TE research.⁸⁵

Arguments from justice

A third cluster is the just distribution of benefits and risks of TE. In an empirical study of ethical issues in TE, the tissue engineers involved in the EuroSTEC project labeled distributive justice as one of the issues of minor importance.⁶⁵ Distributive justice does not seem to be discussed much, possibly since most TE based treatments are far from clinical implementation.

A topic in this context is the distribution of benefits between developed and developing countries. Developmental costs of bio-engineered products are usually high because of the biological nature of the therapies involved; a reason some clinical trials were put on hold.⁸⁶ A just distribution of the benefits of TE treatments between richer and poorer nations does therefore receive some attention in the literature.^{28,57,66,87} Since TE is a highly interdisciplinary technology that requires expensive equipment, it is unlikely that developing countries will be able to apply the technique soon, even though certain problems that could potentially be treated with TE (such as burn wounds or injuries sustained during delivery that lead to problems in the female urogenital tract) are arguably much more prominent in developing countries. Additionally, money spent on TE is not being spent on further sophisticating already existing solutions.⁸⁸ There are some concerns that paying women for the donation of their oocytes or making a profit on donated source material used in TE might persuade poor people to donate bodily material while the richer profit from the therapies.⁷²

Justice arguments are also used when considering who should predominantly benefit from TE based treatment. Degenerative diseases are excellent candidates for treatment with TE — of course, older people suffer most often from these afflictions. Another target for TE are children suffering from congenital birth defects, for which TE might provide a long-term solution far superior to any existing treatment. The question is who would benefit most from the quality of life increase provided by a treatment using TE.⁶⁶ One example of this is the EuroSTEC project, which was funded to find new treatment options for congenital birth defects, such as TE constructs as bladder or urethra substitutes. At this point, however, one of the most viable therapeutic options to come out of research on TE for the urogenital tract is the urostoma, an engineered urethra that is primarily suitable for adults with urinary tract problems. The market for pediatric (prenatal as well as postnatal) surgery products for these types of conditions is simply too small to be commercially viable (personal communication).^d

“Good life” arguments

What do we consider a good life, influenced by the new and emerging technology? Proponents' arguments in this category, according to the NEST-ethics grammar, stress that we as human beings should always strive forward and upward. There are no limits, merely “frontiers that should be transgressed”.³ The good life, as envisioned by some TE proponents, is a life in which organs and tissues are not only repaired, or at most restored to their original function, but in which they will even be regenerated. A TE implant will be indistinguishable from the original tissue. Transplantable hearts will be available off the shelf⁸⁹, amputated legs will grow back⁹⁰ and thousands of premature births will be prevented.⁹¹

In this vision of the “good life”, the technology may be used for purposes beyond treatment, or may blur the line between treatment and enhancement. Will application of TE in treating conditions related to advanced age lead to a medicalization of ageing; i.e. would we start to consider ageing a medical problem that needs to be treated rather than a normal part of life⁶⁶? Although few authors discuss uses beyond treatment, some possible applications are mentioned, such as extending the range of our senses, improving cognitive function through cell-based interventions and using TE products for cosmetic purposes such as more natural breast implants.^{87,92-94}

There is little ethical discourse on TE's impacts on the good life. An exception is Mechteld-Hanna Derkzen, who in her dissertation as well as in other publications develops a phenomenological framework for analyzing TE.^{73,95} Building on the work of Ihde, Svenaeus and Weiss, she uses the concepts of transparency and lived integrity to describe how tissue engineers view the ideal body (i.e. the body to live the “good life”).⁹⁶⁻¹⁰⁰

^d This is an example of the well known fact that researchers often do not ultimately determine the use of the technological artifact they create. A technology may be used for other purposes than it was intended for, thus making it important to engage in an imagination about possible applications of a technology that go beyond the purposes for which it was created. These other applications may raise different questions.

Derksen describes how tissue engineers discuss TE heart valves as ideal valves, exactly because they mimic the normal healthy situation as much as possible and therefore involve a greater degree of transparency than mechanical or biological substitutes. When engineers speak of TE in terms of natural tissue or self-healing, this emphasizes stability rather than the change of bodies. Derksen argues that this kind of striving for transparency as a means to achieve the good life is too limiting. Conceptions of good embodied life should go beyond mere transparency, and should do justice to experiences of a changing body that may not always be exclusively negative, such as during pregnancy but even when experiencing an illness.

Relation between technological and moral change

In their original description of the “grammar” of NEST-ethics, Swierstra and Rip refer to a category of arguments as “meta-ethical issues”. They use the term to address the relation between technology and morality, with a particular focus on the “new and emerging”.¹ Considerations at the meta level also deal with how actors involved in the new technology relate to the control of its development and the relation between technology and morality. In a 2009 publication the term “meta-ethical” is no longer used and the “issues” are framed somewhat differently.³ Here, they refer to a cluster of NEST arguments that deal in more general terms with the relation between technological and moral development. Although formulation and framing are somewhat different, the content of the NEST-ethics approach does not differ substantially between the two articulated versions.

The first issue is the question of determinism; is the course of development of TE preordained, either by internal logic or external influences (international competition), or can technology be steered in morally desirable directions? These questions of determinism/voluntarism and agency could not be identified in the TE debate.

Secondly, Swierstra and Rip name the issue of technology optimists confronting technology pessimists. As mentioned before, TE certainly has its proponents that promise a very positive impact on our health and well-being. In the NEST-ethics “grammar”, pessimists tend to claim in response that the technology in question is the cause of our problems. This does not seem to happen in the TE debate, possibly since those critical of TE tend to be more “skeptical” about its realization than completely opposed to the technology as such.

Thirdly, moral change induced by NEST is differently appreciated and perceived by pro- and opponents. Talking up the revolutionary aspect of a technology may be tempting for scientists, especially in an environment where competition for funding and media attention is fierce.² Moreover, to be published in a newspaper, the message has to be new and eye-catching. Since the debate over genetically manipulated food created a huge public backlash against the “Franken foods”¹⁰¹, scientists seem to be more careful in promoting their technology. This may be why TE researchers usually claim that their technology is nothing new. Authors often use historical stories or list previous treatment strategies to show that TE is just the next step in a long medical tradition.

"The concept of tissue regeneration is by no means new- [...] as illustrated by the famous legend of Prometheus [...] tissue regeneration is also a primitive event, occurring in many organisms [...] in humans, [...] solid organ transplantation and cell therapy have been practiced for many years..."¹⁰²

In describing the programs they finance, the European Union, one of the larger funding bodies, describes TE research as "leading to new treatment strategies for children with severe congenital defects" and emphasizes that the cooperation of different research groups is the novelty (rather than the technique).¹⁰³ TE is seemingly similar to established interventions such as the use of medical devices and transplants², therefore it is easy to regard it as just another strategy. However, Trommelmans et al. state that TE is new in its aim (regeneration instead of restoration or repair) and its methods (TE products will always show variability and interact with the recipient's body, the intervention is irreversible).⁸²

The NEST-ethics structure describes that this type of argument (the technology is new, but it is actually business as usual) is often followed by a de-legitimization of the current practice; in other words, opponents then argue that the current practice is also not desirable. In the TE debate, this is true for parts of the technology: the use of stem cells is widely debated, as are animal experiments, and the creation of chimaeras^{66,72}, but apparently the objective of restoring organ function is commonly accepted, and even applauded. TE is legitimized by the promised future solution for the problem of the donor organ shortage.

Discussion

The debate surrounding TE seems to be predominantly a debate among experts. Whereas the implications of technologies like genetically modified crops or mobile telephones were much more publicly discussed¹⁰⁴⁻¹¹⁰, the talk about TE has mostly taken place in laboratories, at conferences, in hospitals and in scientific papers, maybe with the exception of the well-known "Vacanti-mouse", which was picked up in the popular media.^{8,11} From the idea of early involvement of users and stakeholders, this is problematic. After all, for a debate to be truly "rich", it should not only be broadly encompassing in terms of the topics it addresses, but also in terms of its participants — both experts as well as the public at large. The public needs to be informed and take part in the discussion to be truly involved.

In contrast to other technologies, it seems there are hardly any clear opponents who dismiss TE outright. While there are certainly numerous strong and vocal advocates of TE-based treatments, those that are not as enthusiastic about TE should probably be classified as "skeptics" rather than "opponents". They do not so much dismiss the technology, but question the timeframe and wide range of treatment options promised by TE advocates, and warn against the uncertainty surrounding predictions of risks.

NEST-ethics of tissue engineering

We started this paper by asking three questions. To answer the first: part of the tropes and arguments in NEST-ethics can also be found in the TE debate. When considering the NEST-

ethics arguments that deal directly with technology, we can generally conclude that consequentialist arguments are by far the most prominently featured in discussions of TE, which was apparent in both the scientific literature as well as in personal communication with and empirical research among tissue engineers.^{65,81} Proponents project the benefits of TE-based treatments, and skeptics contest these benefits through questioning the plausibility, side effects and cost/benefit ratio. In addition, many articles discuss principles, rights and duties relevant to aspects of TE, both in a positive and in a critical sense. Justice arguments are only sporadically made, possibly because of the immaturity of the field (in terms of clinical applications). Some “good life” arguments are used, others less so (such as the explicit articulation of perceived limits, or the technology as a technological fix for a social problem).

Missing from the debate

As to the second question — what aspects do we feel are missing from the discussion of TE? From the perspective of NEST-ethics, the second “level” of arguments — those referring to techno-moral change connected to TE — receive much less attention. The technology may for instance change the role of actors and their responsibilities. A technology may change the way we think and lead us to question the existing moral frameworks. These matters are generally not (explicitly) mentioned in the discussion of TE.

In this context, Swierstra’s distinction between hard and soft impacts is relevant. Hard impacts are defined as quantifiable consequences of a technology on the wellbeing of living beings. Soft impacts, on the other hand, cover the category of effects that cannot as easily be quantified, such as changes to experience, habits and perceptions.¹¹¹⁻¹¹³ These soft impacts include, but are not limited to, the so-called second “level” of NEST-arguments. Swierstra and Te Molder argue that taking soft impacts into account is important for two reasons: firstly, many laypersons are concerned about soft impacts, and therefore democracy requires that they should at least be assessed and discussed openly. Secondly, the aim of technology assessment is ultimately a better technology. Therefore, all impacts should be taken into account, not merely the quantifiable risks of a technology. According to Van der Burg, public institutions for research funding tend to steer the attention of researchers away from the soft impacts, due to the methods that they choose to evaluate research. Therefore, there is a genuine risk that ethical debates only focus on the hard impacts of a technology, and ignore its soft impacts.¹¹² As becomes clear when viewing the debate on TE, there is a strong focus on the hard impacts, the quantifiable risks and benefits, of the technology, while the more intangible consequences of TE receive little or no attention.

What soft impacts come to mind when considering the impact of TE? The availability of tissue engineered organs might change ideas about the body. For the longest time, the body was a clearly demarcated entity; “everything inside the skin encasing an organism”. But with “replacement” tissues and organs available off the shelf, this conception of the body might be stretched. In addition, it may impact ideas about ownership; does a kidney made from my cells and stored in a laboratory belong to me, to my body? And will TE change our idea of

responsibility towards our own body, i.e. will we give our body the same care and attention when a diseased organ can easily be substituted by a brand new one?

As previously mentioned, through a public that is aware of the full impact of a technology on their life, researchers learn about the eventual public acceptance (or rejection) of their technology. Will the public be happy with TE? Will they accept it? What are people resistant to, and can this be changed during the development process, either by refining (aspects of) TE or informing people differently? Additionally, an uninformed public is less well prepared for TE products. It may be surprised by questions and problems connected to the technology, and might find it difficult to deal with. A timely and rich debate, both in terms of its content as well as its participants, may prevent these problems from occurring.

Specific to tissue engineering

There are several well-developed normative debates that touch on or overlap with certain characteristics of TE, such as the debates on human embryonic stem cells, commodification of human body materials, perceptions of the human body, and the treatment/enhancement distinction.^{10,32,36,73,114} As became evident in the literature review of De Vries et al., the ethical discourse on TE has been somewhat hijacked by political discussions about therapeutic cloning and the use of human embryonic stem cells.⁶⁶ These debates are relevant to TE because they discuss certain aspects of TE. However, they are not unique to TE — they play a role in the discussion of many different NEST. TE does have some features that set it apart from other NEST and may influence what is talked about when people talk about TE.

It is fairly striking that the ethical debate surrounding TE is less well-developed than, for instance, the debate on nanotechnology; there is a journal dedicated to nano-ethics, Swierstra and Rip used the technology as an example to show the many different recurring rhetorical tropes and arguments in a NEST debate, and numerous public engagement activities have been undertaken to foster the public discussion.¹¹⁵⁻¹¹⁸ This may be due to the nature of the technology; there is not one clearly defined “nanoproduct”, the possibilities are seemingly endless, inviting wild speculation about potential benefits and risks. This is a clear difference with TE: tissue engineers envision TE as the development of a very specific product, created to restore a particular biological function. To a certain extent, a TE product is a known entity; it is a substitute for something we are already familiar with (normal organs or tissues). In addition, in the beginning there is an artifact, but if the tissue engineer is successful, over time this artifact will virtually disappear. For example, in talking about an animal experiment in which a TE patch was implanted in a bladder defect created in a fetal lamb, a tissue engineer described the desired outcome in 6 months time as “we’d open up the lamb and wouldn’t be able to distinguish between the healthy bladder tissue and the patch we implanted 6 months earlier” (personal communication).

The aim and resulting product of TE are presented as more clearly demarcated than, say, that of nanotechnology or genetic engineering. Tissue engineers describe the process as attempting to exactly mimic the normal healthy situation, by using living material (and in autologous TE, even made up of the body’s own cells). They often stress the “naturalness” of

TE, describing it as “persuading the body to heal itself”, “mimicking nature” or “moving a natural process outside the body”.⁷³ As Derksen has argued, emphasizing this perceived naturalness rather than framing TE as “designing living human body parts” might seem beneficial to tissue engineers. Referring to nature makes TE seem natural and good (as opposed to unnatural and dangerous). Biomedical engineering is often perceived as unnatural, as alien, dangerous and evil, and by stressing the naturalness of the process of TE, certain questions or fears might be avoided.⁷³

The TE process usually includes an ex vivo and an in vivo part: tissue engineers create a construct in the lab, which is then implanted in the patient. The TE process does not end with the implantation; one could say the brunt of the work is only then starting. After all, TE implies regeneration, and this regeneration only takes place inside the body, as the tissue will remodel by adapting its structures to withstand the pressures in the body. (At least, that is the assumption.) During the ex vivo part of the process, the engineer is the one in charge; he or she shapes and manipulates the construct to his or her desires. During the in vivo part, the body takes over, leaving the engineer at the mercy of the processes that take place inside.

The previously mentioned features — a clearly defined product and aim that we are familiar with, a disappearing artifact and the idea that tissue engineers are mimicking nature — all help to downplay, whether consciously or unconsciously, the perceived danger or “alien-ness” of TE. It is important to be aware of this, so as to pay due attention to the consequences and influence of this technology.

Conclusion

Based on our analysis of the TE debate, we reach a threefold conclusion. Firstly, pertaining to the “naturalness” of TE. One of the specific patterns of moral argumentation that the NEST-ethics grammar puts forth is the sequence of actions and interactions between proponents and opponents of the NEST. Swierstra and Rip argue that technology proponents often play down the novelty of the NEST in answer to opponents pleading for prudence, stressing this novelty and therefore the ignorance about its effects. What proponents first present as “revolutionary” is now “business as usual”; there are all kinds of precedents for the emerging technology. In a way, the fact that tissue engineers often stress the “naturalness” of TE could be viewed as a similar strategy to the “business as usual” argument. However, we should not forgot that TE is a technology, which ultimately brings a foreign artifact into the human body: it introduces a dynamic product into a dynamic structure (the human body), which brings about a dynamic interaction between the two. The exact behavior of this artifact is unknown, and once introduced, the process that has started cannot be completely reversed. Presenting TE products as natural may lead us to disregard these features of TE.

Secondly, missing topics in the discussion, at least from the perspective of NEST-ethics, are the soft impacts of the technology. In what way TE will impact our experiences, habits and perceptions — for instance through changes in concepts of the body, changing responsibilities to our body, and different views on aging as a normal part of life? In addition, we feel that the discussion of justice is lacking; we should discuss the just distribution of

benefits of TE between different groups in society (such as children with congenital defects and elderly people) and between developing and developed nations, especially since many problems that could potentially be treated with TE are arguably much more prominent in developing countries.

Finally, taking into account the values and concerns of envisioned users aids developers in imagining the full range of effects TE may have; both its hard and especially its soft impacts. Ultimately, a richer discussion of the different possible impacts of TE and the inclusion of different viewpoints and interests during the development process, both from experts as well as the public at large, will benefit the development of this technology.

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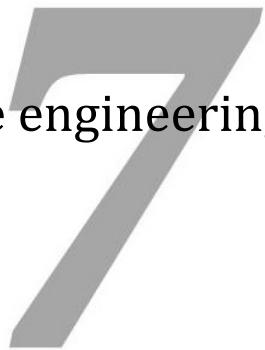
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Hype and expectations in tissue engineering



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7

Abstract

Scientific progress and the development of new technologies often incite enthusiasm, both in scientists as well as the public at large. Enthusiastic ideas about the future are especially apparent in discussions of emerging medical technologies, such as tissue engineering (TE). Future-oriented narratives are also typical of a field associated with significant hype and expectations about potential applications, which are not met later on.

In this study, we analyze the discourse on TE, its history and the promises present in the discourse surrounding it. Subsequently, we regard discussions of the implantable bioartificial kidney, and consider the concepts of hype and expectations in TE in general. Finally, we discuss what ethically responsible choices should be made in discussing TE to adequately deal with the scientific reality and public expectations surrounding this technology.

Introduction

Scientific progress and the development of new technologies often incite enthusiasm, both in scientists as well as the public at large. It seems natural to be excited about the potential of a technology, as talk about technology is usually rife with promises for the future. These so-called “promissory narratives” are especially apparent in the discussion of emerging medical technologies. It is virtually impossible to work on the development of a technology without engaging with some type of future-oriented abstractions about the technology.¹ However, those future-oriented narratives are also typical of a field associated with significant hype and expectations about potential applications, which are not met later on. Through talking about these expectations (usually in the form of shared technological visions), proponents of the technology attempt to recruit actors and mobilize resources.¹⁻³

Tension is apparent when considering how to discuss the future of an emerging technology. On the one hand, it can be helpful to boost expectations in order to support the materialization of the promises made (in competition with many other claims on scarce resources), while hoping that disappointment will not run too high — as Swierstra and Rip put it: “one has to claim more than is reasonable, in order to be able to realize what is actually a reasonable claim”.⁴ On the other hand, one can try to avoid a backlash by being modest in claims about the future (and thereby risk not mobilizing enough funding).

In this study, we will analyze the discourse surrounding one particular emerging technology, tissue engineering (TE), a relatively new and — according to those working in it — promising field.

The following questions are leading in the analysis:

1. What promissory narratives are present in the discourse on TE?
2. In what way do the concepts of hype and expectations play a role in the TE discourse?
3. How should we proceed in talking about the future of TE?

We will first regard the history of TE and the promises present in the discourse surrounding it. Subsequently, we will address a practical example of the use of future visions and promises in the discussions of the implantable bioartificial kidney. Then, we will consider different ideas about the concepts of hype and expectations, and the role it has in TE. Finally, we will discuss what ethically responsible choices should be made in discussing TE to adequately deal with the scientific reality and public expectations surrounding this technology.

Tissue engineering: initial promises

The term tissue engineering was first mentioned as such at a meeting sponsored by the National Science Foundation in California in 1988. This meeting discussed efforts to manipulate existing tissues or combine them with prosthetic materials. Nowadays the term is used for the actual generation of new tissue, using engineered scaffolds, possibly with

living cells.⁵ The discussion of failing and degenerating tissues and organs as an increasing challenge to health care is a staple of articles on TE. The technology is hailed as the solution to increase therapeutic options currently used, by replacing or refining available treatments (such as conventional organ transplantation, surgical reconstruction with foreign tissue, or the use of artificial prostheses).⁶ Langer and Vacanti's classic 1993 paper⁷, one of the first to discuss the technology in depth, describes the economic costs and problems associated with organ shortages and imperfect reconstructive surgeries. They end their paper with:

"Current methods of transplantation and reconstruction are among the most costly therapies available today. Tissue engineering offers the possibility of substantial future savings by providing substitutes that are less expensive than donor organs and by providing a means of intervention before patients are critically ill. [...] Few areas of technology will require more interdisciplinary research than tissue engineering or have the potential to affect more positively the quality and length of life."⁷

In the 1990s TE was rapidly expanding, many universities and several privately funded ventures in TE around the world began to arise. In 1995 the Tissue Engineering Society was founded and the journal *Tissue Engineering* was launched in 1996. TE first attracted widespread public interest in 1997 when a BBC documentary showed what is now known as "the Vacanti mouse". Vacanti's paper showed how the cartilaginous part of a 3-year-old child's ear was regenerated.⁸ The media upheaval was not so much caused by the actual experiment, but even more by the spectacular sight of a nude mouse that had grown a human ear on its back.⁹

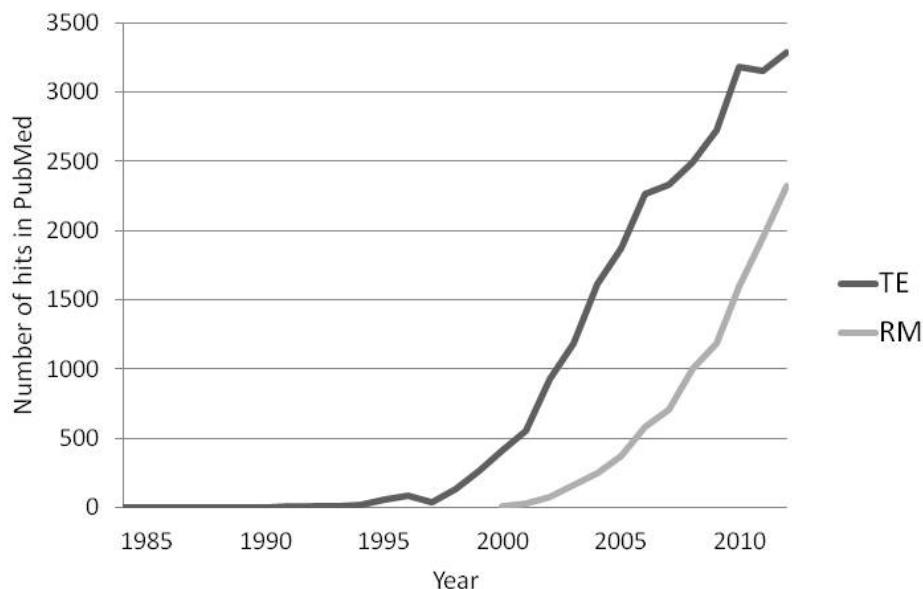
In the late 1990s, discussions of TE often involved reference to a new field of medicine: regenerative medicine (RM). The terms tissue engineering and regenerative medicine are often used interchangeably — broadly speaking, they are both concerned with the replacement, repair and/or regeneration of tissues and organs.^{10,11} (For a visual representation of the use of the terms "tissue engineering" and "regenerative medicine" in scientific literature throughout the years, see Figure 1.) RM is a multidisciplinary field that involves the application of principles and methods of medicine, life sciences and engineering toward the development of biological substitutes to restore, maintain and improve body functions.^{5,12,13} As such, the technology TE can be said to be a part of the field of RM.

In an early paper on TE, Nerem says of its promise:

"[...] tissue engineering is evolving rapidly, and there is reason to believe that as we enter the twenty-first century, the tissue engineering industry will have begun to approach the size of today's recombinant DNA industry. It will involve products ranging from artificial skin or skin equivalents, to engineered cardiovascular substitutes, to such metabolic organs as the artificial pancreas and liver. There also

are nervous system needs including applications to both nerve regeneration and pain killers.”¹⁴

Figure 1. The number of hits for “tissues engineering” and “regenerative medicine” in PubMed



Hopeful statements raised considerable excitement in the media and promised patients quick cures. Respected business journals were enthusiastic about the future which generated funds for more research. By 2000 the total private sector activity had increased to \$610 million.¹⁵ There were great expectations, and the future appeared to be unlimited. This period in the development of TE is sometimes referred to as the “hype” in TE.^{11, 16-18} The field was not able to deliver on its earlier promises. In spite of significant scientific progress, there were few examples of clinical applications. Lysaght et al describe the decline in TE's development in a 2008 paper as follows: “*Between 2001 and 2003 things went very wrong, very quickly.*”¹⁹

The disappointing results had multiple causes. Companies in TE had a variety of problems; they may have overestimated the patient need and the market size, and there were problems with regulatory approval (since the product is neither solely a technique, nor just a drug, it failed to meet one category) and there were delays in reimbursement. The bottom line was that the time from bench to product had taken too long and several companies declared bankruptcy.¹⁵ Bringing a relatively simple device to a clinical reality takes a minimum of 10 years and since the technology for TE was less mature, the progress would take decades rather than years.⁹ Furthermore, TE is a multidisciplinary field where acquired knowledge from individual classical disciplines no longer sufficed to make substantial leaps. Moreover, there were all kinds of technical issues: it proved difficult to produce a tissue-engineered product or strategy that could be available off-the-shelf;

bioactive products are difficult to produce in large batches; tissue-engineered products will be immunogenic and larger implanted tissues have to be innervated and vascularized. In addition to these technical problems, research on human stem cells raised considerable ethical debate. Due to the emerging of stem cell research in the private sector, the regenerative medicine field made some progress nonetheless.^{1,11,19}

Though the major expectations faded, TE research is currently still being conducted for nearly all tissue and organ types, such as bones, liver, pancreas, intestine, heart valves, heart, blood vessels, oesophagus, trachea, cornea, retina, breasts, and bladder.²⁰⁻²² Some industrial tissue engineered products are being applied in clinical practice. These are largely skin substitutes such as TransCyte, Appligraf and Dermagraft, and Carticel (an autologous cell procedure for treating cartilage defects).¹¹ Pediatric surgeons also successfully implanted engineered skin in patients with burn wounds.²³ A clinical trial for implanting engineered bladder tissue in patients with end-stage bladder disease was successful in the beginning, but was terminated in phase II after adverse events occurred.^{24,25}

The case of the tissue-engineered kidney

In the previous section, we surveyed the history of TE, and looked at expectations connected to this technology. To consider the way in which these technological promises can be utilized in practice, let us look at an example: the case of the tissue-engineered kidney.

There is a worldwide shortage of donor kidneys for people in need of a kidney transplant. Using TE solutions to improve renal function or, ultimately, create an entirely new kidney, could potentially help a great number of people. Worldwide, different research groups are working on growing kidney cells *ex vivo*, and one of the countries that is part of this research is The Netherlands.

The Dutch Kidney Foundation is a large foundation, raising funds to finance research programs aimed at prevention and treatment of kidney disease. Every year, there is a large fundraising campaign, with commercials on television and advertisements in other media, to coincide with door-to-door collections. In 2005, topic of the campaign was the so-called implantable bioartificial kidney. We spoke with two employees of the Dutch Kidney Foundation: "P.", a program manager with a scientific background in TE, and "C.", manager of communications and marketing of the foundation.

The idea for the campaign arose in the early 00s, when a group of physicians and scientists visited a conference of the Society of Artificial Internal Organs in the United States, where research on the culture of organs was presented. These physicians and scientists were part of the W.J. Kolff Foundation, affiliated with the Kidney Foundation and named for Dutch nephrologist Willem Kolff, the inventor of the first artificial kidney. They returned to the Kidney Foundation with great enthusiasm for the topic. Back then, few projects were aimed at completely curing kidney disease. Wouldn't it be great if the Netherlands, with its history of the invention of hemodialysis, would now be at the forefront of research into the TE of kidneys? And after all, the prerequisites for this to be successful were present: the

Netherlands had extensive knowledge of nephrology research, good technical universities and a government willing to invest in innovation.

Initially, the foundation's scientific board, consisting of both physicians as well as scientific researchers, is divided on the idea. The physicians argued that the foundation's funds, raised through donation, should be invested in projects that would improve the life of patients in the short term. The scientist members, however, were more used to long term thinking and saw something in the idea of an implantable tissue-engineered kidney. Eventually, one of the members of the board, a clinician who was also involved in scientific research made a statement that stuck with P.:

"He said it beautifully at a certain point: 'with this project, the Kidney Foundation plants a flag on a hill, and hopes that in the future, researchers will use this as a goal to work towards, as a challenge to meet.' I liked this metaphor very much, because I think it actually ended up working like that, and still does, because you formulate a vision and phrase it very explicitly in the shape of the implantable bioartificial kidney. In it is in fact everything we want to achieve — something that may in the long run, we don't say this too explicitly, but may in the long run make transplantation obsolete. You just notice that that is a very concrete goal that makes everyone enthusiastic. The scientists know that we are a long ways away, but for both co-investors as well as for patients or the larger public, your ultimately goal and long term ambition become immediately clear."

As C. mentioned:

"At a certain point it's a topic of discussion, it is talked about, and you're like — this is something we are going to do as the Kidney Foundation and there is support, it is not just a dream, no, there is support among scientists and researchers and they want to commit to this. So then it becomes something we want to work on as the Kidney Foundation, something we are going to invest in, because once you start believing in something, you are going to invest in it."

C. drew explicit parallels between the history of Willem Kolff, who in his time was seen as somewhat of an oddball, working relentlessly but unable to get his research financed, seeing people dying in his hospital, very determined to make his dream a reality. The invocation of important historical figures, of a "founding father", is part of a pattern in the discussion of emerging technology. Oftentimes, the deployment of scientific "origin stories" is apparent; stories that describe the historic founding and pedigree of a certain discipline or field.⁴ The Kidney Foundation, said C., can be considered an extension of Kolff's work — one should be ambitious, because if you let yourself be retained by the establishment, you will never amount to anything. You need to have guts, and be daring.

In 2005, a national campaign focused on the implantable bioartificial kidney. In it, two explicit statements were made: an implantable bioartificial kidney could be ready in 10 to 15 years, and the Kidney Foundation needed to raise 40 million euros to achieve this goal. The timeframe mentioned in the communications was entirely unrealistic. Asked how these explicit statements on time and funds needed came about, both interviewees were unclear on the exact source. P. said:

"Maybe those fifteen years, I'm not sure but maybe those fifteen years came about because that is the average horizon for a scientist when working on things that are farther in the future. I just think it's like, fifteen years is far enough away to know it's not tomorrow. And it is close enough to know that, you know, we'll be there to witness it. I just feel like that might be what prompted the fifteen years."

Asked whether they received any negative feedback on the campaign and its explicit statements, they mentioned they did hear from physicians who had patients come into their office saying "don't put me on the transplant list, I'll wait for that implantable kidney". Multiple nephrologists mentioned this as problematic — not the fact that the foundation funds "dream projects", but that it fostered expectations in patients that were not realistic at that time. (The foundation did not receive any negative reactions from patients themselves.)

In the years that followed, the Kidney Foundation co-funded several large research projects into (aspects of) nephrological TE, all part of the BioMedical Materials Program (BMM). A 2009 report by the Dutch National Institute for Public Health and the Environment²⁶, looking at the state of the art in Dutch TE, states:

"In the Netherlands a similar approach [to US-based clinical trials; AO] is aimed to be developed as part of the BioMedical Materials Program (BMM). Although the ultimate goal is to develop an implantable bioartificial kidney, the first big milestone will be the creation of such an extracorporeal artificial bioreactor. Nevertheless, this program has just started and clinical studies in the Netherlands with cell-based artificial kidneys to repair, replace and reconstruct renal function are not expected in the coming 5-10 years."²⁶

Communication from the Kidney Foundation about the implantable bioartificial kidney seemed to take on a different character: where it used to be presented as a short term goal, it is now used as a long term ideal vision. A press release from the Kidney Foundation about a new research project on the bioartificial kidney in 2009²⁷ reads:

"It is a first step on the way to the ultimate goal, namely to achieve the implantable artificial kidney via the biological artificial kidney. There is, however, a long way to go."²⁷

In 2010, the bioartificial kidney returned as the focus of the Kidney Foundation's national campaign. However, this time they only mentioned the implantable bioartificial kidney as their "ultimate dream", and focused on the portable artificial kidney as a stepping stone towards reaching that goal. The portable kidney, focus of the current communication, sits better with nephrologists, possibly because it is easier to explain to patients (as a mini-dialysis machine you can carry with you).

Both P. and C. still considered the initial reporting on the implantable bioartificial kidney as a positive effort. Saying that if they would have been more conservative in their statements, they would never have entered the network they are now part of, and would not have profited from the available knowledge and financing possibilities.

P.: "If you ask me — would you do this again? I think the consensus is that we do want to communicate about the dream of the implantable bioartificial kidney, but looking back, we maybe would have constructed it differently, the process, more through patients, informing professionals before it's in the newspapers like 'the Kidney Foundation wants forty million for the implantable bioartificial kidney'."

However, he also said:

"I think that, if during that time the Kidney Foundation had not explicitly stated what the plans were and we would have stuck to projects that we now know are achievable and much more realistic, a portable artificial kidney for instance, I doubt whether we would have been where we are today."

C. agreed, and in the end does not regret the way things went:

"I still have the feeling, even though you don't really imagine it like this in advance, that it did more good than harm. Even though you would make different choices knowing what you know now, because you now know what to tackle, or how you should have communicated about things. But I do think it had a huge driving effect."

Hype and expectations in TE

We have previously considered the history of TE and looked at an example of the instrumentalization of future visions of a TE application. Now let us consider technological expectations and the concept of hype somewhat more in depth.

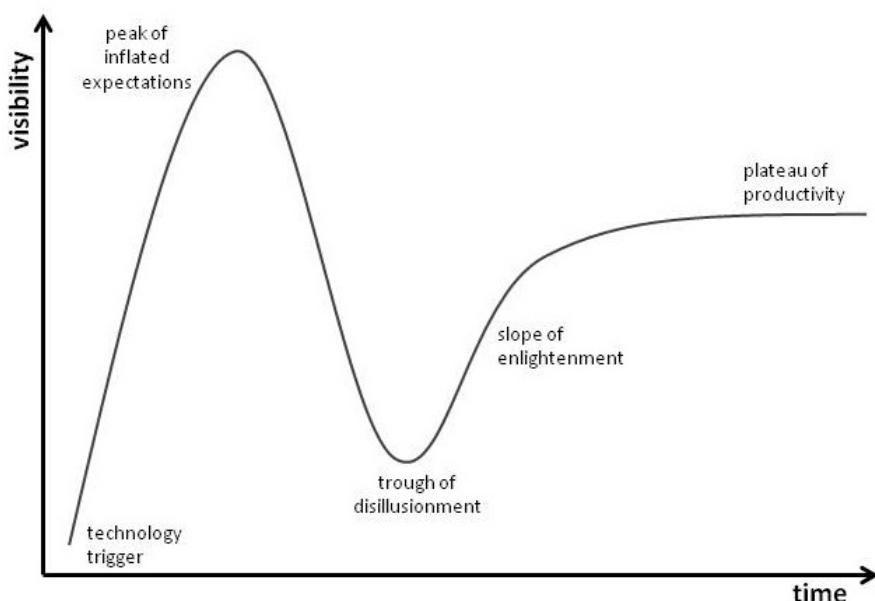
After the downturn in TE's development in the early 00s, following TE's "hype" phase, there was (and is) a clear "lessons learned" rhetoric. Where the period from 1985 to 2002 (called "Regenerative Medicine 1.0" by Mason²⁸) was deemed "the go-go years"¹⁵ and "the best of times"¹⁹), this era has now ended, in comparative failure. However, we have learned from the

past, from unrealistic expectations, and are ready to move up again, seems to be the consensus.¹ Consider the following paragraph from a Dutch newspaper article entitled "The long road from hype to hope"¹⁸, for instance, in which cardiac tissue engineer Carlijn Bouteren is quoted:

"Bouten has learned from the past. 'Because it isn't completely new,' she admits. 'Ten years ago, when tissue engineering was still in its infancy, a true hype emerged.' The media spoke of meat factories and made references to Frankenstein. 'The problem was that we didn't yet know how everything would work. How does a sick body react when stem cells are injected or cultured tissues are implanted? And how does engineered tissue behave when there are changes in the body, such as in pregnancy or with high blood pressure.' The expectations, says Bouten, were unrealistically great and the scientific challenges were underestimated. 'We learned the hard way. Meanwhile, the hype has passed and we are in the phase of hope.'"¹⁸

Hype in biotechnology is commonly understood to mean the positive portrayal of a biotechnology including "the developments of clinical products and services, economic prosperity, commercial benefits, and solving major health issues."²⁹ A well-known graphic representation of the dynamics of a hype is Gartner's hype cycle³⁰ (see figure 2), in which the visibility of a technology is shown over time. The aforementioned case clearly showed the very positive representation of a possible future application of TE. The fully functional, implantable kidney that would make conventional therapies obsolete was described as a "perfect" solution that would soon become available.

Figure 2. Gartner's Hype Cycle, a simplified graphic representation of the maturity, adoption and business application of specific technologies (adapted from³⁰)



Hyping science can lead to several problems. Firstly, hype may negatively influence the public's views of science. It may lead to an increase of concerns and anxiety about the risks of a technology, says Brown: "risk and opportunity are the flip sides of hyperbolic expectations, inflating one another in equal measure."³¹ Additionally, inflated expectations may lead to disillusionment when these promises are not met. This disappointment leads to damage to reputations and to the public's trust, which can happen very abruptly.³² Secondly, hyping a certain science or technology may cause scientists or politicians to invest their attention and resources in the hype, diverting it from other, possibly more worthy, causes.³³ Thirdly, it may lead to a possible translation of research to application in practice, before enough evidence of its usefulness and/or safety has been gathered. And finally, unduly hyping a science or technology goes against the ethical and professional integrity (to behave honestly, to be truthful etc.) of scientists and other professionals. Of course, it is not always clear in advance whether promotion of a certain science or technology is excessive, and therefore constitutes a hype.²⁹

Expectations about the future of a technology have what is called a "performative" and "generative" influence in the present, i.e. hype, expectations, and projected benefits all promote the current development of a technology towards a future reality.³¹ That foreseen reality guides activities, provides structure and legitimization, attracts interest of different actors (innovators, investors, regulators, users etc.) and fosters investment. Expectations are "real-time representations of future technological situations and capabilities."² Expectations define roles and duties of those involved, and help build relationships between actors and agendas. This becomes very apparent when considering the aforementioned case study — a hype, a future vision (of an implantable tissue-engineered kidney to solve the organ donor shortage) is used to 1) garner funds from the general public (the "generative" function); and 2) set an agenda for researchers in the field to work towards, thereby building networks between different interested parties (the "performative" function). Harro van Lente describes these mutually shared expectations and vision as the "dynamics of promise and requirement" — the fact that someone commits themselves to something, requires that this person takes action to achieve the goal.³⁴ We see this in the case study as well; ultimately, the decision of the board to commit to a campaign on the tissue-engineered kidney, lead or at least contributed to the start of several research project in the field of kidney TE.

Additionally, future expectations give some idea of how to prepare for opportunities and for risks. Since hype in itself is not restricted to a positive portrayal of the technology in question, exaggeration of the negative effects (or risks) of a technology could equally be considered a hype.²⁸ Both positive as well as negative expectations (fears of risks) have a substantial impact on the discussion of technological change.²

Ethically responsible choices

From “hyped” future to stepwise approach

Hyping technology can lead to problems. How, then, should we proceed in talking about the future of TE? Let us turn again to the case of the implantable kidney. The evolution of the foundation’s communication strategy about the implantable kidney is notable. They moved from communicating very explicitly about an implantable kidney being available in ten to fifteen years, to discussing this implantable kidney as an ultimate dream, with several concrete steps (materialized in actual research projects) that have to be undertaken to reach this goal. This type of approach, while still incorporating a “great expectation” that appeals to the imagination, is more modest in its claims, and lays out a concrete plan of action. It is still both performative as well as generative: it plants a proverbial flag on a hill for people to work towards and be inspired by, and it is concrete enough in its claims to garner funds from investors and be able to live up to them. This type of approach addresses the problem of the so-called “translational gap” — the gap that exists between knowledge produced at the lab bench and its practical use at a patient’s bedside.^{22,35} With their approach, the foundation seems to have struck the happy medium between appealing to the imagination with an attractive vision for the future, while still being sensitive to the risks of creating false hope in patients or prospective users. In a way, they attempt to close the translational gap by providing stepping stones between bench and bedside, in the form of concrete research projects. An approach that could serve as an example for others working on TE, and relating their expectations for this technology.

Different roles, different skills

Having expectations is a human characteristic. As a scientist, however, boosting those expectations can be detrimental; both to the development of the technology as well as to people you give false hope. Let us look at two possible dual roles of TE scientists that involve dealing with expectations in different ways: the scientist as an entrepreneur and the scientist as a physician.

Boosting expectations without a factual ground is counter to the integrity scientists should exhibit. However, although the virtue of honesty may make someone a good scientist (in the moral sense), it may make him or her a bad entrepreneur. Different roles ask for different skills in a person. Modern scientists are increasingly being asked to exhibit skills from the entrepreneurial skill set: talking up the promise of their work to garner attention, and hype their promises in research proposals to yield funding. It is easy to see that these two roles could come into conflict: where the entrepreneur stands to benefit from strong promissory claims in the short run, the problems this over-hyping may cause fall on the shoulders of others (investors, patients, policy makers).³³

TE is a technology with predominantly medical applications, meaning that some involved in TE research have yet another role: that of physician. The clinical context makes medical

technology a specific subcategory of technology — envisioned users are (often) patients suffering from some type of disease or disorder. This may make them more vulnerable to and/or more eager to believe in promises made by technology developers or the media. As we saw in the case of the tissue-engineered kidney, glowing talk about a (distant) future, even mentioning a (completely unrealistic) timeframe, gave at least some patients false hope for a quick cure. Another example, this time from a pediatric urologist. In 2006, Anthony Atala's tissue-engineered neo-bladder was big news. It was featured in numerous publications, both scientific as well as popular, and was shown on television. The Dutch *Jeugdjournaal*, a news program specifically aimed at children, showed an item about Atala's bladder. Sometime in the next few days, a Dutch urologist was asked by one of his patient's parents whether they needed to go to the United States for this bladder, or if the surgery could take place in Holland, clearly expecting it to be available to their child at present (personal communication).

As these examples show, in their excitement scientists have contributed to TE's hype by overstating the potential benefits to patients or giving unrealistic timelines for a treatment to reach the patient's bedside.¹¹ The fact that one is dealing with patients, often highly motivated to find a cure and eager to hear about it, brings with it a special kind of responsibility for those developing and those discussing medical technology. A physician-researcher who comes into regular contact with the ultimate user of his/her work (a patient) may therefore be more sensitive to the risk of overhyping or exaggerating expectations to garner funds, because he or she is intimately aware of the impact this may have for the patients involved. In this context, let us turn to a "best practice" example, a European research project that several of the authors were involved in (AO, WD): the EuroSTEC project.³⁶⁻³⁸ This FP6 project united researchers from companies, universities and hospitals, working towards a common goal — the development of new treatment modalities for children with congenital birth defects. It encompassed all phases of research: fundamental (in vitro) research, animal experiments, and (preparation of) clinical trials. In biannual meetings (at which AO and WD were present), all involved presented their work to each other. This made fundamental researchers aware of the needs of physicians involved in the project, and of the needs of patients their research was ultimately aimed for. In turn, it showed physician-researchers the possibilities and limitations of preclinical research.

These dual roles — scientist/entrepreneur and scientist/physician — show that while the increased demand on scientists' entrepreneurial skills may tempt them to hype their work, confrontation with patient stories may serve as a counterweight to this temptation. Bringing (non-physician) scientists in contact with patient stories may give them some restraint when talking about their expectations of TE and may decrease the extent to which they "hype" their work.

Conclusion

We started this paper by asking three questions:

1. What promissory narratives are present in the discourse on TE?
2. In what way do the concepts of hype and expectations play a role in the TE discourse?
3. How should we proceed in talking about the future of TE?

As to the first, the idea that TE may in the future make organ donation and transplantation obsolete, is often present in the discussion of, and even in definitions of, TE. Some even explicitly mention a timeframe, as we saw in the case study of the implantable bioartificial kidney.

As to the second question: although public discussion about TE has so far been fairly modest³⁹, scientific papers and the popular press do refer to the promises of TE. As we now know, those early promises were not fulfilled. Looking back, the projected timeframe was clearly unrealistic. Tissue engineers themselves sometimes refer to this phase as the “hype” in TE, mostly to indicate that we have now learned from the past and know how to proceed to make promises a reality.

As to the third, while communicating about an ultimate goal, scientists should refrain from indicating a timeframe that they themselves know is unrealistic. Instead, they should be more modest in their claims, and lay out concrete steps on the way to reaching an ultimate goal.

Integrity and honesty are important characteristics of a scientist. Scientists nowadays are often expected to be entrepreneurs too, and those characteristics can come into conflict with the requirements of a successful entrepreneur. Confronting scientists with patient stories may decrease the extent to which they hype their work.

Future perspective

The majority of TE research is currently still in the preclinical phase. Those involved in the field expect TE to continue to develop towards clinical trials and application in clinical practice in the coming decade. Our recommendations concerning ethically sound ways of dealing with hype, then, will only become more relevant. A responsible way of dealing with the communication of research results and associated expectations is needed to ensure the public’s understanding and acceptance of TE’s products, and to prevent the creation of false hope and a possible backlash against TE.

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General Discussion

8

8

Tissue engineering: from lab to clinic

"First Bladders Grown In Lab Transplanted"², "Woman receives windpipe built from her stem cells"³, "World's First Tissue-Engineered Urethras Deemed A Success"⁴, "Swedes implant tissue-engineered vein in 10-year-old girl"⁵ — a grasp from tissue engineering-related headlines from recent years. Pioneering efforts in treating patients with this technology received ample attention in the popular press. Tissue engineering (TE) treatments promise a more complete recovery with significantly fewer side effects or risk of complications, compared to conventional treatments.

Currently, if a tissue or organ shows dysfunction, either because of a congenital anomaly or through injury or disease, several treatment options are available. For instance, the affected tissue can be replaced by an implantable device that can substitute the mechanical or physical function, as is the case with mechanical heart valves, silicone breast implants and titanium knee joint prostheses. Although these materials can fulfill a physical or mechanical function, they lack an active biological function, which may be a problem for some applications. In addition, the inert material may be damaged through regular wear and tear, and become in need of replacement.^{6,7}

A second option in case of tissue or organ damage is the use of extracorporeal devices to substitute the function of the affected tissue, such as in haemodialysis to sustain patients with renal insufficiency. Here, too, normal function is not completely substituted but only partially replicated, leaving patients with subnormal function and an impaired quality of life.^{6,7}

Another available treatment for some afflictions is the use of tissue from elsewhere in the body to reconstruct a tissue or organ. Think, for instance, of patients in need of bladder augmentation, such as children with spina bifida or bladder exstrophy. A current possible treatment consists of the use of the patient's own intestinal tissue to augment the size of the bladder. This comes with problems, however, since this tissue does not have the metabolic properties of native bladder tissue. Additionally, in the long-term these patients run the risk of developing cancer in their augmented bladder.^{8,9}

Finally, transplantation of tissues or organs, harvested from either living or deceased donors, is used to treat organ failure. There is a worldwide shortage of donor organs, meaning that many patients spend years waiting for an organ (sometimes in vain). Once a patient receives a donor organ, transplantation itself is associated with problems, including rejection which requires the patient to take life-long immunosuppressive medication.^{6,7}

TE organs or tissues, especially those created from the patient's own cells, would theoretically solve almost all problems associated with the aforementioned conventional treatments. TE research is currently still being conducted for nearly all tissue and organ types, such as bones, liver, pancreas, intestine, heart valves, heart, blood vessels, oesophagus, trachea, cornea, retina, breasts, and bladder.^{6,7,10-12} However, besides applications in the field of skin and cartilage TE, there are as of yet few clinical applications available on the market, which is why incidents of successful treatment of a patient with a TE bladder, TE trachea, or TE urethra still lead to small media hypes in worldwide news. The solutions TE can provide

to many problems have been promised for years, but as of yet with little evidence of clinical success. For most examples of TE, there remains a substantial gap between the laboratory bench and the patient's bedside, and for almost all there still is a large ravine looming between early clinical experiments and widespread market success. Let us look at an example of a large-scale project that attempted to bridge this gap: the EuroSTEC project.

The research in this thesis took place within the context of the EuroSTEC project (Soft tissue engineering for congenital birth defects in children: from biomatrix — cell interaction — model system to clinical trials). EuroSTEC united fifteen partner organizations (ten research institutes and five companies) from nine European countries, ultimately aiming to develop treatments for structural disorders such as spina bifida, bladder exstrophy, diaphragmatic hernia and esophageal atresia. The project was designed to expressly pay attention to all phases of development: it consisted of five research areas that together show the entire translational landscape of fundamental research to clinical applications. From fundamental in vitro research in research areas 1 and 2 (the development of biomatrices (collagen/polymers) for TE, and research on cell culture systems and cell and biomatrix interactions), to animal studies in research area 3 (the development of model systems for congenital anomalies and fetal interventions) to the phase of clinical testing in research area 4 (clinical pilot studies and instrument development). These research projects took place simultaneously, and in dialogue with each other. To facilitate the cooperation between different research groups working in the same development phase, and cooperation between the different phases, biannual meetings were held, at which research was presented and work discussions could take place. In the beginning of the project, there was some awkwardness at these meetings, with some research groups (especially those connected to companies) struggling with how to strike a balance between competition and cooperation. However, as the project and its cooperations matured, clear attempts to bridge the translational gap, so to speak, were apparent. Those working on creating collagen biomatrices, for instance, presented their recent work and talked about the thickness and rigidity of their constructs. When it came time for questions, one of the physician-researchers (involved in a different research area and research group) asked whether the construct would be able to hold the stitches needed to fix the construct to cover a defect *in vivo*, and what the largest surface area that could be created was. These types of dialogues—the exchange of wishes (requirements) and possibilities (limits)—happened throughout the course of the project. Although the long-term success of the results of the EuroSTEC project is still unclear, the cooperation between the actors involved in the different phases of TE and their mutual understanding of the requirements and limits of the separate contributions to the TE process, appear to provide stepping stones to close the translational gap that has so often faced TE research in the past.

Like the EuroSTEC project, other endeavors have shown that TE has taken some steps in bridging the translational gap, and more and more authors expect it to move toward broader

application in clinical practice in the coming years.^{10,11} 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.

Towards a richer debate

For researchers in the field of TE, it is important to take the ethical issues raised by their field into account. Not only because this is part of their responsibility towards society, but also because it is in the interest of the field itself. Recognising these issues and aptly responding to them enables the field to flourish by preventing it from investing time and money in directions that are likely to lack societal support.

There are clear indications that tissue engineers are aware of important ethical questions raised by their field.¹³⁻¹⁵ As became apparent in our empirical research, the participants seem very aware of their personal responsibilities both toward the scientific community and society at large. However, meeting these responsibilities can be very difficult in the complex setting of scientific research in research groups and competitive enterprises. After all, there is a difference between being aware of an ethical issue and being able to understand, articulate and substantiate one's own view on the issue (for instance, in an application to an ethical committee), take action towards trying to the problem, or engage in a dialogue about it with "outsiders" (journalists, laymen, opponents).

This engagement of science and society, of scientists and the general public, is a necessary step in early user and stakeholder involvement.¹⁶⁻¹⁹ As we saw in our research, the talk about TE has mostly taken place in laboratories, at conferences, in hospitals and in scientific papers.²⁰ When considering the current TE debate, it is striking that the debate is very much an expert debate. If tissue engineers were to engage with the public about this new technology, then the public needs to be well-informed about TE and its impacts.

Let us turn to the discussion of TE's impact on society. The almost singular focus of the debate on short-term risks and benefits of the technology is remarkable. As we saw in both our literature research and our empirical work, some of these issues still need to be worked out further, such as donor/trial participant informed consent, adequacy (and justifiability) of animal models, development of Good Clinical Practice and Good Manufacturing Practice, monitoring of regeneration and adverse effects, cost-effectiveness, and reimbursement/distributive justice issues.^{13,15,21}

However, TE is not only expected to have fairly straight-forward, quantifiable consequences, but we think TE will have a long-term, less quantifiable impact on our routines, culture, morals and politics. The technology may for instance change the role of actors and their responsibilities. It may impact the way we think and lead us to question the existing moral frameworks.²² These matters are generally not (explicitly) mentioned in the discussion of TE. Taking these so-called soft impacts into account is important for two

reasons: firstly, many laypersons are concerned about soft impacts, making it important that they are at least being assessed and discussed openly. Secondly, the aim of technology assessment is ultimately better technology. To achieve this, all impacts should be taken into account, not merely the quantifiable risks of a technology.²²

What soft impacts come to mind when considering the impact of TE? Some questions that were brought up and discussed in the discourse on post-mortem and living-donor tissue and organ donation and transplantation are relevant to TE as well. After all, as we have seen before, TE and organ transplantation share some characteristics. Both lead us to questions of ownership, changing views of the body, and commodification of human material. If my brother donates one of his kidneys and it is implanted in my body; is it mine, is it still his, or does it belong to the both of us? If damaged lungs and diseased livers can be replaced by healthy ones, does that have an impact on people's motivation to live a healthy life? And should people be able to sell their organs? It is ethically justifiable that tissues and organs could potentially become a marketable good?

There is an important difference between conventional organ donation and TE, however. The potential of TE to change certain basic concepts is far greater than in conventional organ donation: TE technology enables application on a much wider scale, with less immediate drawbacks (limited availability, burden of the procedure on living donors, rejection) than organ donation and transplantation. The use of 3D printers to create the scaffolding for TE constructs, for instance, could potentially enable large-scale TE construct production, bringing the availability of "off the shelf" replacement tissues and organs closer to reality. The potential impact of TE applications makes early ethical analysis essential. The extent of this impact is due to an important feature of TE: its existence seemingly inbetween technology and nature.

Between technology and nature

TE as a technology falls inbetween different categories. TE constructs are not (only) pharmaceutical, not (only) metabolic, and not (only) a device. It is not just the surgical implantation of inert material, or a fully mature donor organ — TE involves the implantation of a construct with regenerative potential, that will instigate a dynamic interaction with the human body it is implanted into. The confusion that is associated with this "inbetween" status is, for instance, clearly apparent in the long process of designing a way to deal with TE products in laws and regulations.²³⁻²⁶ On a more fundamental level, TE is an "inbetween" entity: it seems to fall between nature and biotechnology. A TE construct is not really a technological artifact that we "use" like we would use a tool. Tissue engineers envision TE as the development of a natural product, created to restore a particular biological function. To a certain extent, a TE product is a known entity; it is a substitute for something we are already familiar with (normal organs or tissues). While in the beginning there is an artifact, if the tissue engineer is successful, over time this artifact will virtually disappear. Tissue engineers describe the process as attempting to exactly mimic the normal healthy situation, by using living material (and in autologous TE, even made up of the body's own cells). They often

stress the “naturalness” of TE, describing it as “persuading the body to heal itself”, “mimicking nature” or “moving a natural process outside the body”.²⁷ As Derksen has argued, emphasizing this perceived naturalness rather than framing TE as “designing living human body parts” might seem beneficial to tissue engineers. Referring to nature makes TE seem natural and good as opposed to unnatural and dangerous. In recent years, there have been several “scandals” in the media surrounding implants made from synthetic material. Among others, silicone gel PIP implants and gynecological surgical meshes were found to have adverse effects in some people they were implanted into, causing quite a stir about biomedical implants in general.²⁸⁻³⁰ Biomedical engineering is often perceived as unnatural, as alien, dangerous and evil, and by stressing the naturalness of the process of TE, certain questions or fears that are or have become associated with biomedical implants might be avoided.²⁷ The aforementioned scandals may even add to the perceived dangerousness of synthetic implants, and may increase the attractiveness of more natural implants such as TE constructs.

So far, the occasional media reports of pioneering efforts of scientists and doctors such as those who treated Claudia Castillo, who received a TE trachea, have been met with enthusiastic reactions from the public.^{3,31} However, one need only look at the history of gene therapy and the case of Jesse Gelsinger, who passed away during a gene transfer clinical trial, to find evidence of the backlash a technology can suffer.^{32,33} Public trust in science can be fragile, and damaged virtually irreparably due to adverse events like these. In making the transition from pre-clinical to clinical trials, however great the amount of pre-clinical research that was done, there is always a degree of unpredictability in how the object of study will behave in human subjects.

It is not difficult to see this unpredictability surrounds TE constructs, too. A TE organ is not just a copy of a natural “thing”, doing exactly what natural organs would do. The TE process does not end with the implantation; one could say the brunt of the work is only then starting. Once a TE product is introduced into the body, a dynamic process is started, closely and irreversibly linking TE construct and body. After all, TE implies regeneration, and this regeneration only takes place in the body, as the tissue will remodel by adapting its structures to withstand the pressures in the body. (At least, that is the assumption.) During the *ex vivo* part of the process, the engineer is the one in charge; he or she shapes and manipulates the construct to his or her desires. In the *in vivo* part, the body takes over, leaving the engineer at the mercy of the processes that take place inside.

We are used to thinking of the human body as natural, and of technology as “other”, artificial, alien or foreign. Some philosophers have attempted to find a way of dealing with new types of “inbetween” technologies such as TE, in which nature and technology are intimately entwined. Building on Don Ihde’s work, Peter-Paul Verbeek describes a variant of human-technology relations, in which technologies merge with the human body instead of just being embodied, creating a new, hybrid entity referred to as a “cyborg”.³⁴⁻³⁸ Verbeek calls these “cyborg relations” or “fusion relations”, in which there is such an intimate association between human and technological artifact that the technology does not merely

change the interplay between human being and world, but physically changes the human entity. There is no “I” and “technology” anymore, there is a new “I” – an amalgam of body and technology.^{34,39}

TE is not the only technology to fall into this category. Recent years have seen developments in the convergence of nanotechnology, biotechnology, and information technology that have made it possible to intervene directly in human nature. This has lead to technologies such as deep brain stimulation to mitigate the symptoms of Parkinson’s disease and depression, neural implants to make deaf people hear, psychopharmacological drugs to improve mood, and treatments in the field of genomics to intervene in human genetic material.³⁴

The intimate linking of humans with technology in TE, the fact that body and technology literally fuse, blurring (or maybe even eliminating) the line between human and technology, means that the impact of technology becomes less reversible. This makes ethical reflection about the impact of technologies such as TE even more important. Reflecting on this impact needs to be done by those involved in the development of the technology in dialogue with its eventual users. Through a public that is aware of the full impact of a technology on their life — both its hard and its soft impacts — researchers in question learn about the eventual public acceptance (or rejection) of their technology. What are people resistant to, and can this be changed during the development process, either by refining (aspects of) TE or informing people differently? An uninformed public is less well prepared for TE products. It may be surprised by questions and problems connected to the technology, and might find it difficult to deal with. A timely and rich reflective analysis, both in terms of its content as well as its participants, may prevent these problems from occurring.

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Summary

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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.

The research in this thesis took place within the context of the EuroSTEC project, which aimed to develop TE-based treatments for congenital closure defects. Part of the EuroSTEC design was an extensive ethical analysis, which focused on all three phases of the project — fundamental or *in vitro* research, animal experiments and clinical trials — and would also look ahead to the application of soft TE in clinical practice. The chapters of this thesis are the result of the ethical analysis of the development and application of neonatal interventions using TE products.

In *chapter 2*, we mapped which ethical issues related to TE have already been documented in the scientific literature. The issues that turned out to dominate the debate were the use of human embryonic stem cells and therapeutic cloning. Nevertheless, a variety of other ethical aspects were mentioned, which relate to different phases in the development of the field. In addition, we discussed a number of ethical issues that have not yet been sufficiently raised in the literature, including informed consent of donors, the need for adequate animal models, the difficulties involved in TE clinical trials, just allocation of TE applications, and the desirability of non-medical applications.

To be able to respond adequately and timely to current and possible future ethical issues in the EuroSTEC project, and in TE at large, a prospective and anticipatory ethical analysis is essential. In *chapter 3*, we aimed to identify what ethical issues the experts involved in research on soft TE for closure defects expected to occur during the different phases of the EuroSTEC project. For this purpose, we used the Delphi method. The professionals directly involved in the EuroSTEC project were questioned about their views on possible ethical issues. The first round yielded 27 ethical issues, which the respondents were asked to prioritize in the second round. For the fundamental research phase, issues deemed most important were privacy and informed consent of the tissue donor. For the animal experimentation phase, three issues were mentioned (in order of decreasing priority): the suffering of animals, the use of animals as means to an end, and the limited adequacy of the animal models. Issues that were deemed most important during the clinical (trial) phase pertained to the problem of weighing risks and benefits for the fetus/child and the pregnant woman.

On the basis of the results of the two previous rounds in the Delphi study among EuroSTEC project members, two topics were selected for discussion in focus groups: ethical issues associated with (1) source of cells and (2) donation. In *chapter 4*, we reported on the results of these focus groups, which could be divided into three clusters: Tissue, Donor, and Scientist. Regarding the topic of “tissue”, participants discussed the source of the material

used in TE, and the concept of “life” in relation to embryonic stem cells. With regard to the topic of “donor”, participants discussed the idea of helping, and issues surrounding control over the use of donated material, among other topics. Where the former two clusters, tissue and donor, roughly coincide with the results of the previous rounds, the third subject was entirely new but discussed by both groups: the role of the scientist in the TE process. Regarding this topic, participants discussed the future of science, the relationship between scientist and society, and reflected on the scientist as a person.

TE could potentially offer elegant solutions to urogenital defects, but so far, it has fallen short of its potential. Within experimental studies for bladder and urethra reconstructions, two clinical applications have been described, but extension of these techniques to the broader urological patient population has not happened so far. In *chapter 5* we aimed to identify the ethical road blocks in the clinical evaluation of human tissue-engineered products (HTEPs) under the European Medicines Agency and Food and Drug Administration regulations for pediatric urological conditions and, ultimately, to recommend strategies to overcome them. The use of HTEPs to treat children with congenital urogenital defects poses challenges in the clinical testing phase, connected to three features of the application of this treatment in this patient group: (1) those associated with the product, namely, the multifaceted complexity of the HTEP; (2) those connected to the procedure, namely, the lack of a randomized controlled trial (RCT)-tested gold standard to compare the new treatment to and difficulties surrounding standardization of the treatment protocol; and (3) the patient’s young age and associated problems concerning possible long-term effects and the informed consent process. Due to these problems, a conventional RCT is not the methodology of choice to evaluate this treatment in this patient group. The unpredictability of HTEPs necessitates stringent and long-term surveillance and registry to ensure the safety of patients treated with these products.

In their 2007 paper, Swierstra and Rip identify characteristic tropes and patterns of moral argumentation in the debate about ethics of new and emerging science and technology (or “NEST-ethics”). In *chapter 6*, taking their NEST-ethics structure as a starting point, we considered the debate about TE, and argued what aspects we think ought to be a part of a rich and high-quality debate of TE.

The debate surrounding TE seemed to be predominantly a debate among experts. When considering the NEST-ethics arguments that deal directly with technology, we could generally conclude that consequentialist arguments are by far the most prominently featured in discussions of TE. In addition, many papers discussed principles, rights and duties relevant to aspects of TE, both in a positive and in a critical sense. Justice arguments and “good life” arguments were only sporadically used.

Missing topics in the discussion, at least from the perspective of NEST-ethics, were “second level” arguments — those referring to techno-moral change connected to TE. Currently, the discussion about TE mostly focuses on its so-called “hard impacts” —

quantifiable risks and benefits of the technology. Its “soft impacts” — effects that cannot easily be quantified, such as changes to experience, habits and perceptions — should receive more attention.

In *chapter 7* we considered the concept of hype and its role in the TE discourse, and looked at a practical example of the instrumental use of hype and its possible pitfalls – the discourse surrounding the implantable bioartificial kidney.

Expectations about the future of a technology have what is called a “performative” and “generative” influence in the present. Hyped a technology, such as TE, can lead to several problems. Therefore, scientists should refrain from indicating a timeframe that they themselves know is unrealistic. Instead, they should be more modest in their claims, and lay out concrete steps on the way to reaching an ultimate goal.

The dual roles of some TE scientists — scientist/entrepreneur and scientist/physician — show that while the increased demand on scientists’ entrepreneurial skills may tempt them to hype their work, confrontation with patient stories may serve as a counterweight to this temptation.

Chapter 8 discussed the main implications of the work in this thesis. For most examples of TE, there remains a substantial gap between the laboratory bench and the patient’s bedside, and between early clinical experiments and widespread market success. Although the long-term success of the results of the EuroSTEC project is still unclear, the cooperation between the actors involved in the different phases of TE and their mutual understanding of the requirements and limits of the separate contributions to the TE process, appear to provide stepping stones to close the translational gap that has so often faced TE research in the past.

Public trust in science can be fragile, and damaged virtually irreparably due to adverse events associated with a technology. The intimate and irreversible linking of humans with technology in TE makes ethical reflection about the impact of technologies such as TE even more important. Reflecting on this impact needs to be done by those involved in the development of the technology in dialogue with its eventual users. A timely and rich reflective analysis, both in terms of its content as well as its participants, may prevent problems from occurring.

Samenvatting

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Tissue engineering (TE) is een veelbelovende nieuwe technologie. Zoals andere nieuwe technologieën is TE echter niet vrij van ethische problemen. Het vroegtijdig identificeren van deze ethische vragen is niet alleen onderdeel van de verantwoordelijkheid van wetenschap voor maatschappij, maar ook in het belang van het veld zelf.

Het onderzoek in dit proefschrift vond plaats in de context van het EuroSTEC-project, wat als doel had om TE-gebaseerde behandelingen te ontwikkelen voor aangeboren sluitingsdefecten. Deel van het EuroSTEC-project was een uitgebreide ethische analyse die zich richtte op de drie fasen van het project — fundamenteel of in vitro-onderzoek, dierexperimenten en klinische studies — en ook vooruitkeek naar de toepassing van soft-TE in de klinische praktijk. De hoofdstukken van dit proefschrift zijn het resultaat van de ethische analyse van de ontwikkeling en toepassing van neonatale interventies die gebruik maken van TE-producten.

In *hoofdstuk 2* brachten we ethische problemen gerelateerd aan TE in kaart zoals die in de wetenschappelijke literatuur besproken zijn. Problemen die het debat bleken te domineren waren het gebruik van humane embryonale stamcellen en therapeutisch kloneren. Daarnaast werden diverse andere ethische aspecten genoemd, gerelateerd aan de verschillende fasen in de ontwikkeling van het veld. Vervolgens bespraken we een aantal ethische problemen die nog onvoldoende aan de orde komen in de literatuur, waaronder informed consent van donoren, de behoefte aan adequate diermodellen, de problemen rond klinische studies in TE, rechtvaardige verdeling van de TE-producten en de wenselijkheid van niet-medische toepassingen.

Om adequaat en tijdig te reageren op huidige en toekomstige ethische problemen in het EuroSTEC-project en ten aanzien van TE in het algemeen, is een prospectieve en anticiperende ethische analyse essentieel. In *hoofdstuk 3* streefden we naar het identificeren van de ethische problemen die experts betrokken bij onderzoek naar soft-TE voor sluitingsdefecten verwachten tegen te komen tijdens de verschillende fasen van het EuroSTEC-project. Met dit doel hebben we de Delphi-methode gebruikt. De professionals die direct betrokken waren bij het EuroSTEC-project zijn gevraagd naar hun ideeën over mogelijke ethische problemen. De eerste ronde leverde 27 ethische problemen op, waarna de respondenten in de tweede ronde gevraagd werd deze te prioriteren. In de fundamentele onderzoeksfase werden privacy en informed consent van de weefseldonor het meest belangrijk gevonden. In de dierexperimentele fase werden drie problemen genoemd (op volgorde van afnemend belang): het lijden van dieren, het instrumentele gebruik van dieren, en de beperkte adequaatheid van diermodellen. Problemen die het meest belangrijk werden gevonden in de klinische (studie)fase waren gerelateerd aan het afwegen van risico's en voordelen voor de foetus/het kind en de zwangere vrouw.

Op basis van de resultaten van de vorige twee ronden van de Delphi-studie onder EuroSTEC-projectleden selecteerden we twee onderwerpen om in focusgroepen te bespreken: ethische

problemen gerelateerd aan (1) de bron van cellen en (2) donatie van cellen en weefsels. In *hoofdstuk 4* presenteerden we de resultaten van deze focusgroepen, te verdelen in drie clusters: weefsel, donor, en wetenschapper. Ten aanzien van het onderwerp weefsel bespraken deelnemers de bron van het materiaal dat gebruikt wordt in TE, en het concept leven in relatie tot embryonale stamcellen. Ten aanzien van het onderwerp donor bediscussieerden deelnemers onder andere het idee “helpen” en problemen rond controle over het gebruik van gedoneerd materiaal. Waar de vorige twee clusters — weefsel en donor — grofweg overeenkomen met de resultaten van de vorige ronden, was het derde onderwerp nieuw, maar werd het besproken in beide groepen: de rol van de wetenschapper in het TE-proces. Ten aanzien van dit onderwerp hadden de deelnemers het over de toekomst van wetenschap, de relatie tussen wetenschapper en samenleving, en reflecteerden zij op de wetenschapper als persoon.

TE zou in potentie elegante oplossingen kunnen bieden voor urogenitale defecten, maar heeft tot op heden haar beloftes niet waargemaakt. In experimentele studies naar blaas- en urethrareconstructies zijn twee klinische toepassingen beschreven, maar uitbreiding van deze technieken naar de bredere urologische patiëntenpopulatie heeft tot op heden niet plaatsgevonden. In *hoofdstuk 5* hadden we als doel het identificeren van de ethische problemen in de klinische evaluatie van humane TE-producten (HTEPs) voor kinderurologische aandoeningen binnen de reguleringen van de European Medicines Agency en de Food and Drug Administration, om uiteindelijk strategieën aan te bevelen om deze te overwinnen. Het gebruik van HTEPs om kinderen met aangeboren urogenitale defecten te behandelen zorgt voor uitdagingen in de klinische testfase verbonden met drie kenmerken van de toepassing van deze behandeling in deze patiëntengroep: (1) gerelateerd aan het product, namelijk de meervoudige complexiteit van de HTEP; (2) gerelateerd aan de procedure, namelijk, het gebrek aan een in een gerandomiseerde gecontroleerde studie geteste gouden standaard om de nieuwe behandeling mee te vergelijken en problemen rondom standaardisatie van het behandelprotocol; en (3) gerelateerd aan de jonge leeftijd van de patiënt en problemen ten aanzien van mogelijke langetermijneffecten en het informed consent-proces. Door deze problemen is een conventionele gerandomiseerde gecontroleerde studie niet de meest geschikte methode om deze behandeling in deze patiëntengroep te testen. De onvoorspelbaarheid van HTEPs maken strikte langetijd follow-up en -registratie noodzakelijk om de veiligheid van patiënten die met deze producten behandeld zijn te garanderen.

In hun artikel uit 2007 identificeren Swierstra en Rip karakteristieke patronen van morele argumentatie in het debat over de ethiek van nieuwe en opkomende wetenschap en technologie (oftewel “NEST-ethiek”). In *hoofdstuk 6* gebruiken we hun NEST-ethische structuur als startpunt om het debat rond TE te beschouwen en te beargumenteren welke aspecten deel uit zouden moeten maken van een rijk en kwalitatief sterke debat over TE.

Het debat rond TE bleek voornamelijk een debat onder experts. Bij het beschouwen van de NEST-ethische argumenten die direct met technologie te maken hebben, kunnen we in het algemeen concluderen dat consequentialistische argumenten veruit het meest voorkomen in discussies over TE. Daarnaast bespreken veel artikelen principes, rechten en plichten relevant voor aspecten van TE, zowel in positieve als kritische zin. Rechtvaardigheidsargumenten en “goed leven”-argumenten werden slechts sporadisch gebruikt.

Onderwerpen die ontbraken in de discussie, in ieder geval vanuit NEST-ethisch perspectief, waren de “tweede niveau”-argumenten — die te maken hebben met technomorele verandering door TE. Momenteel richt het debat rond TE zich voornamelijk op de zogenaamde harde impacts — kwantificeerbare risico's en voordelen van de technologie. Haar zachte impacts — effecten die minder makkelijk te kwantificeren zijn, zoals veranderingen van ervaringen en gewoontes — verdienen meer aandacht.

In *hoofdstuk 7* beschouwden we het concept hype en haar rol in het TE-discours, en keken we naar een praktisch voorbeeld van het instrumentele gebruik van hype en de mogelijke valkuilen daarbij: het discours rond de implanteerbare bioartificiële nier.

Verwachtingen over de toekomst van een technologie hebben wat men noemt een performatieve en genererende invloed in het heden. Het hypen van een technologie zoals TE kan leiden tot verschillende problemen. Daarom zouden wetenschappers af moeten zien van het aangeven van een termijn wanneer ze zelf weten dat deze onrealistisch is. In plaats daarvan zouden ze bescheidener moeten zijn in hun claims, en concrete stappen aangeven op de weg naar het bereiken van het uiteindelijke doel.

De dubbelrollen van sommige TE-wetenschappers — wetenschapper/ondernemer en wetenschapper/arts — laten zien dat hoewel het toenemende beroep op de ondernemingstalenten van wetenschappers hen kan verleiden om hun werk te hypen, de confrontatie met patiëntverhalen kan dienen als tegenwicht voor deze verleiding.

Hoofdstuk 8 bespreekt de hoofdimplicaties van het werk in dit proefschrift. Voor de meeste toepassingen van TE is er nog steeds een substantiële kloof tussen het laboratorium en de patiënt, en tussen vroege klinische experimenten en wijdverbreid succes op de markt. Hoewel het langetermijnsucces van de resultaten van het EuroSTEC-project nog onduidelijk is, lijkt de samenwerking tussen de actoren en hun wederzijdse begrip van de benodigheden en grenzen van elkaars werk tussenstappen te bieden om het translationele gat te dichten dat zo vaak een probleem is gebleken in TE-onderzoek.

Publiek vertrouwen in de wetenschap kan fragiel zijn en wordt gemakkelijk beschadigd door problemen die een technologie veroorzaakt. De intieme en irreversibele verbinding van mensen met technologie in TE maakt ethische reflectie over de impact van technologieën zoals TE nog belangrijker. Reflecteren op deze impact moet gedaan worden door de ontwikkelaars van de technologie in dialoog met haar uiteindelijke gebruikers. Een tijdige en

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rijke reflectieve analyse, zowel in termen van inhoud als deelnemers, zou problemen kunnen voorkomen.

Curriculum vitae

Anke Oerlemans (1983) startte in 2001 met de studie Biomedische Wetenschappen aan het UMC St Radboud te Nijmegen. In 2004 behaalde zij haar bachelortitel en begon aansluitend aan de masteropleiding Biomedische Wetenschappen met de afstudeerrichting Health Technology Assessment.

Na stages bij de afdeling Ethisiek, Filosofie en Geschiedenis van de Geneeskunde (UMC St Radboud) en het Rathenau Instituut studeerde zij in 2006 af bij de afdeling Medical Technology Assessment (UMC St Radboud) met een scriptie over nachtelijk inzetten van de traumahelikopter getiteld "Helicopter Emergency Medical Services in the Netherlands. The HATCH trial."

De stage bij de afdeling Ethisiek, Filosofie en Geschiedenis van de Geneeskunde wakkerde haar interesse voor medische ethiek aan. In 2006 verhuisde ze naar België voor de masterstudie Applied Ethics aan de Katholieke Universiteit Leuven. Hier studeerde ze in 2007 cum laude af met een scriptie over de technologische imperatief in bevolkingsonderzoek naar kanker getiteld "Mass screening for cancer. The imperative character of medical technology."

Ze keerde vervolgens terug naar de afdeling Ethisiek, Filosofie en Geschiedenis van de Geneeskunde, later een sectie van het Scientific Institute for Quality of Healthcare (IQ healthcare). Hier startte zij met haar promotieonderzoek binnen het EuroSTEC-project, waarvan de resultaten in deze dissertatie beschreven zijn. Daarna volgde bij dezelfde afdeling een onderzoek naar ethische dilemma's van zorgverleners rond de zorg voor intensive care-patiënten. Momenteel is zij als postdoctoranderzoeker verbonden aan de afdeling IQ healthcare en doet onderzoek naar de ethische problemen van professionals die bij neonatale hielprikscreening betrokken zijn.

Daarnaast is zij als docent betrokken bij onderwijs aan het UMC St Radboud, de Radboud Zorgacademie en de Hogeschool van Arnhem en Nijmegen.

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