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Biofabrication

TOPICAL REVIEW

Ethical considerations in the translation of regenerative biofabrication technologies into clinic and society

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Abstract

Biofabrication technologies have the potential to improve healthcare by providing highly advanced and personalized biomedical products for research, treatment and prevention. As the combining of emerging techniques and integrating various biological and synthetic components becomes increasingly complex, it is important that relevant stakeholders anticipate the translation of biofabricated 3D tissue products into patients and society. Ethics is sometimes regarded as a brake on scientific progress, yet from our perspective, ethics in parallel with research anticipates societal impacts of emerging technologies and stimulates responsible innovation. For the ethical assessment, the biofabrication field benefits from similarities to regenerative medicine and an increasing ethical awareness in the development of tissue-engineered products. However, the novelty of the technology itself, the increase in attainable structural complexity, and the potential for automation and personalization are distinguishing facets of biofabrication that call for a specific exploration of the ethics of biofabrication. This review aims to highlight important points of existing ethical discussions, as well as to call attention to emerging issues specific to 3D biofabrication in bench and bedside research and the translation to society.

Introduction

The aim of restoring impaired function by repair, replacement or regeneration of cells, tissues or organs using a combination of converging technologies is central to the interdisciplinary field of regenerative medicine [1]. One approach herein is the engineering of biological substitutes through the use of living cells, extracellular matrix components, bioactive molecules, and biomaterials [2]. Although promising advances have been achieved in the generation of biological tissue derivatives using traditional tissue engineering approaches, the need to accurately mimic the native architecture of tissue is underscored by our increasing knowledge of the structure/function relationship in both healthy and pathological conditions [2]. Three-dimensional (3D) printing, patterning and assembly techniques allow for a greatly enhanced control over the spatial positioning of biomaterials. The incorporation of multiple materials into constructs with highly defined external and internal geometries has the potential to achieve increasingly complex structural organizations that more closely mimic native tissues in their structure and function [3]. This superior structural organization attainable with 3D biofabrication compared to traditional tissue engineering techniques is believed to improve tissue development, quality and functionality [4].

A main objective of biofabrication for tissue engineering and regenerative medicine is the creation of functional tissues and organs suitable for transplantation, with the ultimate aim of alleviating shortages in tissue grafts and donor organs [5]. However, the output of the technology is not limited to this considerable goal. Tissue-engineered products are also increasingly applied in fundamental research, pharmaceutical drug testing, analysis of biological and chemical agents, and cancer and disease models [6]. Biofabrication machinery can allow automated, cost-effective mass production of tissue-engineered

products, whereas the ability to create custom spatial designs and incorporate autologous-derived materials paves the way for highly personalized clinical treatments [7]. A 3D bioprinted ear-shaped implant for auricular reconstruction is an illustrative example of such a personalized treatment [8].

The rapid progress in biofabrication technologies has sparked great enthusiasm and hope for the future of regenerative medicine applications. As the combining of emerging techniques and integrating various biological and synthetic components becomes increasingly complex, it is important that relevant stakeholders anticipate the translation of biofabricated tissue products into patients and society [9]. In particular, in translational medicine, dynamic interactions between scientists, clinicians, ethicists, patients, and other members of society are instrumental in enabling effective scientific progress [10]. Hence, a timely exploration of the ethical and societal impacts of biofabrication technologies is essential to promote responsible interdisciplinary innovation. Ethics is sometimes regarded as a brake on science, yet in our perspective, ethics provides moral guidance and the incentive to continuously refocus on the scientific direction and its impact.

For the ethical assessment, the biofabrication field benefits from similarities to regenerative medicine and an increasing ethical awareness in the development of tissue-engineered products [11]. However, the novelty of the technology itself, the increase in attainable structural complexity, and the potential for automation and personalization are distinguishing facets of biofabrication that call for a specific exploration of the ethics of biofabrication. This review aims to highlight the important points of existing ethical discussions, as well as to call attention to emerging issues specific to 3D biofabrication in bench and bedside research and the translation to society.

Bench

In the bench arena, ethical issues revolve predominantly around the use of both animal and human materials. The ethical challenges of biofabrication highlighted in this section, regarding animal experimentation, cell source and biobanking, are similar to those in regenerative medicine.

In regenerative medicine, animals are used as a source of cells for studying fundamental processes, or as a model to test new innovations [12]. The justifiability of using animals for laboratory experiments is an overarching debate in all biomedical fields, and the use of animals for research is only considered justifiable under strict conditions [13]. Animal studies contribute to a solid base of preclinical data when a relevant animal model is chosen. Nevertheless, the selection of animal models that predict outcomes in humans as closely as possible can still be a challenge [14]. Through the principle of 'modest translational distance', only good animal models contribute to the evidentiary threshold required to move fundamental research into a clinical research phase [15–17]. These considerations count for all biomedical research, including biofabrication. Although laboratory animals may never become obsolete, there is clear potential to reduce animal experimentation by using regenerative medicine, which envisions the use of *in vitro* tissue models or organs-on-chips as alternatives [18]. Biofabrication can contribute to this goal as it can rapidly mass produce pieces of tissue for testing, create custom bioreactors, and fabricate chips with intricate architectures.

Stem cells are often key building materials for biofabricated products. Hence, the ongoing debate on the origin, collection, and use of (stem) cells, though common to biofabrication and other biomedical research, is relevant for discussion in this context. In particular, the use of human embryonic and fetal tissues for research has been controversial, though considered morally acceptable under strict conditions in many quarters of the world [19]. Human materials are very valuable for research purposes, and increasingly also for clinical applications. A readily available source of human material is residual tissue, which is obtained during clinical care and would otherwise be discarded. Biobanking is the organized collection and storage of such biological specimens and their associated information for research purposes [20, 21]. The ethical debate regarding biobanking has largely focused on the appropriate type of consent and privacy. The key here is the realization that, even in the bench phase, the use of human materials necessitates some form of consent, where the donor either gives explicit approval (opt-in) or explicitly objects (opt-out) [21]. Consent can be given for the use of material for a defined research purpose (specific consent), or for a yet unspecified range of research topics with only a few restrictions based on the donor's preferences (broad consent) [22]. Although in the latter case a specific research question may be absent, a tissue donor can still be informed about the governance structures of the biobank, such as its ethical oversight procedures, privacy policy and information management; this has been posed as 'broad consent for governance' [23]. One important issue in data management is privacy protection as specimens are usually linked to phenotypic and identifying data. Using anonymous samples is favorable from a privacy perspective, but then clinically relevant unsolicited findings cannot be returned to the donor [24]. Moreover, one could question whether complete anonymization is still possible in this era of genomics research and big data [25]. Another issue is whether, if at all, a person retains ownership of the donated tissue once it is separated from the body [26]. This can become a serious issue once the research has yielded a product that is commercialized, as per the example of the immortal HeLa cell line, originating

from the residual tissue of the unwitting patient, Henrietta Lacks [27].

The responsible use of animal and human materials can be justified by social value. This means that the research conducted should add to the body of knowledge that has the potential to improve the wellbeing of patients, individuals in society, or society itself [28]. It is, therefore, good practice for scientists to regularly question what their experiments will lead to, and in what way they can ensure that the results from their research can be exploited in subsequent steps.

Bedside

The translation from bench to bedside requires a timely and thorough ethical reflection, as premature trials could compromise patient safety and damage public perception of the field [10]. Although results from basic research are sometimes moved to the clinic through compassionate care, surgical innovation or even inappropriate use, the clinical trial is the most rigorous approach to evaluate preclinical results in a clinical perspective. First-in-human trials are an exciting and important step in bridging successful bench experiments and bedside application. However, the novelty, complexity and invasiveness of emerging technologies require specific refinement of the standard ethical, legal and regulatory framework of clinical trials [10, 29]. Many of the ethical issues identified for regenerative medicine in previous literature are also applicable to the biofabrication field. Yet, biofabrication adds another layer of complexity by truly converging emerging technologies, such as stem cell technology and 3D (bio)printing. Whilst every aspect in clinical research ethics deserves consideration, the discussion for biofabrication is especially interesting with regards to balancing risk/benefit, design challenges, and obtaining informed consent.

It is generally agreed that risks to participants of clinical trials must be proportionate to the anticipated benefits to science, society, and/or the individual. Early phases of clinical research are likely to generate more benefits to science than to the participant, while individual risks and burdens are present at all stages [28]. The dynamic interaction between the body and the tissue-engineered product is regarded as the major challenge in determining the possible outcomes [11]. In principle, the regenerative implant becomes integrated with the body and it will be virtually impossible to remove it or reverse its effects [30]. Due to the lack of prior comparators in tissue engineering to base anticipated risks and benefits on, as well as the variability and complexity of the product, the uncertainties and (un)known unknowns are substantial [31]. The known risks of tissue-engineered products are that cells may exhibit a tumorigenic potential and biomaterial interactions may cause undesirable effects. First, there is the risk of transferring pathogens or instigating an immunogenic rejection response to non-autologous cells [12]. Second, after providing the inductive cues, the tissue engineer renders complete control to the implanted cells and the host body. The capacity of stem cells to endlessly self-renew and differentiate into multiple lineages may pose a considerable risk of tumor development, especially since adult cells may already have encountered DNA damage or other detrimental chromosomal or cellular changes precipitating tumorigenesis [32]. In addition, the bioprinting process may harmfully impact the cells through mechanical, thermal and oxidative stresses. Third, the scaffold material used for the biofabrication of tissue-engineered products may elicit unwanted effects. Since every item intended for implantation in the human body must comply with certain safety standards, it is essential to evaluate the biocompatibility and safety of biomaterials in the short and long term. Biofabrication of tissue-engineered products demands biomaterials with improved biological functionality, as well as specific printing properties, such as shear thinning and mechanical strength [33]. Since even residues of used reagents can be toxic or can elicit undesirable functional responses in the patient [34], the development of novel biomaterials should take into account the presence of potential toxins, as well as the interactions between the material, the cells, and the body. Does the novelty and potential of the field grant acceptance of higher risks and more uncertainties? For early trials, it has been suggested to balance risk versus potential value instead of individual benefits [28]. As such, benefits of a trial can also include reciprocal value, in which insight is generated into the working mechanism of the evaluated product and the interaction with the body. This type of value is especially important in young innovative fields like biofabrication.

A well-designed randomized controlled clinical trial is generally the most appropriate way to gather robust clinical data. Although adding a control group makes the research scientifically more valid, this is not always practically or ethically possible. The invasiveness of biofabrication applications would require sham procedures in the control groups, which carry inherent risks and burdens and are, therefore, ethically challenging [35]. In some cases of future biofabrication-based applications, such as auricular reconstruction in children, the route of innovative surgery seems more appropriate. It is important to realize that normative considerations may play as essential a role in the study design as scientific validity. In any case, such novel products require complementation of the study with a long follow-up program since tissue-engineered products have many uncertainties and unknowns, and the long-term effects of biofabricated implants with regenerative potency are especially unknown. Compared to pharmaceutical phase I trials, participant selection in clinical studies with regenerative biofabricated products is also more complex. Since this approach is aimed at restoring damaged, degenerated

or diseased tissue, selecting healthy volunteers as trial participants is not suitable. In comparison to end-stage patients, stable patients with alternative treatment options may experience fewer benefits and higher risks from a novel intervention. However, end-stage patients with no alternative options may be especially vulnerable to therapeutic misconception [30], which is a misunderstanding of patients regarding the purpose of the study [36].

An important imperative in clinical research ethics is that patients make informed decisions about their participation in a clinical study. Hereto, informed consent is essential in avoiding exploitation of vulnerable patient groups and empowering participants [37]. The many uncertainties of biofabricated products may make it difficult to appropriately disclose information and it may be very challenging to ensure that participants sufficiently understand the risks and benefits. High expectations of the field may cause people to regard biofabrication as the magical solution for difficult medical problems. In particular, patients with no alternative treatment options or younger patients with undesirable prognoses (e.g. cartilage injury progressing to osteoarthritis) are prone to therapeutic misconception [31].

Society

A set of repeating moral patterns of argumentation has been identified that is applicable to any new biomedical technology, where emphasis is often placed on the hard, quantifiable consequences of the technology on the wellbeing of living beings. The debate generally misses explications on the moral changes fostered by technology, such as changes to experience, habits and perceptions, often referred to as soft impacts [38]. Crucial in this discussion is the public perception of the biofabrication field. Another important societal aspect is the relationship of biofabrication technologies to views on human enhancement.

Emerging technologies and scientific progress generally spark excitement and expectations. The positive portrayal of a new biotechnology—in both media and research proposals—seems increasingly necessary in order to garner attention, attract actors, and secure scarce funding. However, overselling a product raises societal expectations and nurtures therapeutic misconception, often leading to public disillusionment as a field fails to deliver. Unrealistic promises can severely damage a field's reputation and the public's trust [39]. The Gartner hype cycle [40] visualizes how a technology can go through phases of inflated expectations and subsequent disillusionment before it matures and enters the stage of productivity and application. A relevant illustration of this cycle is the story of tissue engineering, which received widespread attention after the spectacular sight of the 'Vacanti mouse'. In this experiment, engineered cartilage in the shape of the human auricle was subcutaneously implanted on the back of a nude mouse [41]. The first successes in tissue engineering indeed sparked hope for the treatment of damaged tissues and failing organs. In their excitement, scientists made bold statements to highlight the potential of tissue engineering, overestimating the possible benefits of an intervention or giving unrealistic timelines for it to reach the clinic in order to attract funding [42]. However, the field could not deliver on its initial promises and the translation was further hampered by the complicated search for appropriate regulations for the Advanced Therapy Medical Product guidelines. As a result, public enthusiasm and trust waned as clinical application seemed to be too far away to ever become reality. Presently, biofabrication technology is well on its way up the slope of expectations and is marked as a research field with great potential. What the stories of tissue engineering and other high-potential fields can teach us is that modesty in claims may prevent structural public disappointment and a damaged reputation. Public trust can be earned by presenting concrete steps on the way to the proverbial flag on the hill, the ultimate goal [39]. In this modern day and age, scientific citizenship—the ideal that the public is well informed and able to make decisions regarding scientific research—is becoming increasingly important [43]. A public that is sufficiently aware of the potential impact of a technology on their lives, on a realistic timeline, can provide the researcher with valuable input on the degree of public acceptance, the aspects of the technology people are resistant to, and how a technology can be refined so it will be truly successful upon implementation [38]. It is the moral duty of the researcher to rightly inform the stakeholders, and how research results are portrayed in the media is crucial in forming the public's perception. Although journalists may have a tendency to blur the distinction between what is being experimentally done and what is clinically possible, scientists still have a responsibility to temper such expectations.

The potential of biofabrication may raise concerns of human enhancement practices as the technology allows control over the architectures of tissues. Yet, body modification has been deeply embedded in our cultures and is actually a product of the evolution of our species. Evolution has caused our species to develop the intellectual capacity to influence our own development, and through our scientific progress we gain more and more control over this so-called 'neo-evolution' [44]. By treating or preventing disease, we are continuously altering our natural evolution. Although regenerative medicine, to which biofabrication contributes, has the intention of restoring tissues and organs to a (near-)normal state [1], the technology could significantly alter and possibly enhance the form, function, and lifespan of an individual. As Fineberg elegantly states, 'the same engine of science that can produce the changes to prevent disease, will also

enable us to adopt superior attributes' [44]. Enhancement by repair paves the way for enhancement of the natural features of our body—to not only fix what is broken, but to improve on our exterior, physiological and cognitive features [45]. Human enhancement is not inherently ethically wrong; in fact, we practice it daily by studying to increase our intellectual capacity, by training to become a better athlete, or by wearing glasses to improve our eyesight [46, 47]. Rather, the type of enhancements under debate are those that improve human form or functioning *beyond* what is necessary to restore or sustain health [47]. Aesthetic enhancements, for example, are deemed problematic because they can be intended for the sake of vanity [45]; yet in reconstructive surgery, such adaptations are rather made for functional or psychosocial reasons [8]. Highly functionalized tissue-engineered constructs could give rise to performance enhancement intended for greater athletic competitiveness [45], but could just as well have medical applications (e.g. a 3D-printed bionic ear where biological tissue is combined with functional electronics for human hearing [48]). A current ethical discussion in regenerative medicine concerns increasing lifespan and longevity by treating conditions due to ageing [10]. Biofabrication-based strategies are currently being investigated as interventions for the prevention or treatment of degenerative diseases. Taken together, biofabrication technologies have the potential to contribute to changes made to the human body that stir up discussions on human enhancement.

Discussion

Biofabrication is an emerging technology with great potential for increasing the complexity of tissue-engineered products. Developing biofabrication technologies has the potential to improve healthcare by providing highly advanced and personalized biomedical products for research, treatment and prevention. The impacts of emerging technologies on society receive relatively little attention in scientific discussions. However, the inherent relationship between humans and technology [49] requires an integral approach to biomedical innovation. Striving towards coproduction involves a constructive dialogue between science, technology, ethics and society [10]. Involving ethics early in the developmental stages of an intervention allows joint reflections on the objectives, design and impact of the product.

In this review we have highlighted ethical aspects of the translation of regenerative biofabrication technologies from a bench, bedside and societal perspective. This identification of key ethical topics is meant to serve as an impetus towards a more comprehensive analysis of the ethical implications of biofabrication technologies. Not surprisingly, it appears that there is substantial overlap with the fields of regenerative medicine and tissue engineering, although biofabrication can be set apart by its potential to mass generate highly functionalized and personalized constructs with improved internal and external architectures. In each research stage there are ethical aspects to consider in the development of biofabricated tissue products. In summary, in bench research it is important to consider consent for the use of human materials and the choice of relevant animal models. Upon moving biofabrication technologies towards the clinic, the novelty, complexity and invasiveness of biofabricated products cause substantial uncertainties and risks. It may be preferable to balance risks with potential value instead of individual benefits. In first-in-man trials with biofabricated products, it may be challenging to select appropriate patients and sufficiently inform them of the risks. An important aspect to consider is how the technology affects society. Besides concerns of inappropriate human enhancement and public perception of biofabrication, there are general aspects of introducing any new biomedical technology that are absolutely relevant to consider here too. An expensive innovative technology impacts equity, for example. It is important to develop technologies and products that do not increase social injustice, but have the potential to reduce it.

In ethical discussions on societal impacts of a new technology, emphasis is often placed on the hard, quantifiable consequences. However, our lives are constantly shaped by our changing morals and routines, and influenced by science and technology. The potential of biofabrication technologies for the creation of tissue-engineered products may, for instance, change perceptions of the ownership of human materials, of (the boundaries of) the human body, of the responsibility towards our bodies [38]. It appears that scientists and physicians do not consider themselves as having the power to alter these impacts [50]. In the constructivist view on technology and society, stakeholders together shape the design of the technology and thus its impact on society [10]. Therefore, it is important that scientists and physicians actively take up their role as an actor, and drive responsible technological innovation in the biomedical field in bench, bedside and society.

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