3D BIOPRINTING: ISSUES OF BIOETHICS

Khokhlov AL[1] ✉, Belousov DYu[2]

[1] Yaroslavl State Medical University, Yaroslavl, Russia

[2] Center for Pharmacoeconomics Research, Moscow, Russia

Scientific development of 3D bioprinting is rapidly advancing. Bioprinting is expected to be actively implemented within the healthcare industry producing a revolutionary impact on transplantation. However, the innovative biotechnology involves numerous ethical and regulatory issues. Special attention is given to ethical issues associated with the use of embryonic cells, storage of personal data, obtaining informed consent, and peculiarities of clinical trials. The issues of safety and quality are reviewed. Equal access to technologies and use of biotechnologies to 'enhance a human being' are addressed. The issues of culture and religion are separately discussed within the context of this technology. It is stressed that as far as the issue of ethical estimation and legal regulation goes, 3D bioprinting can't be completely assessed with the help of regular clinical trials or acting regulatory requirements. In particular, no suitable regulatory system or special documents regulating 3D bioprinting of tissues and organs and their subsequent transplantation are currently available in Russia or globally. Thus, it's necessary to develop requirements to safety, quality and effectiveness of technological processes and end products obtained with the help of 3D bioprinting with the best interests of generally acknowledged human rights.

Keywords: bioprinting, 3D bioprinting, bioethics, biotechnology, informed consent, tissue engineering, transplantation, regenerative medicine

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✉ **Correspondence should be addressed:** Alexander L. Khokhlov
ul. Revolutsionnaya, 5, Yaroslavl, 150000, Russia; al460935@yandex.ru

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ТЕХНОЛОГИЯ 3D-БИОПЕЧАТИ: ВОПРОСЫ БИОЭТИКИ

А. Л. Хохлов[1] ✉, Д. Ю. Белоусов[2]

[1] Ярославский государственный медицинский университет, Ярославль, Россия

[2] ООО «Центр фармакоэкономических исследований», Москва, Россия

Научные разработки 3D-биопечати стремительно развиваются. Ожидается, что биопечать активно внедрится в здравоохранение, произведя революцию в трансплантологии. Вместе с тем данная инновационная биотехнология включает множество этических и нормативных вопросов. Особое внимание уделено этическим проблемам, связанным с применением эмбриональных клеток, сохранением персональных данных, получением информированного согласия, особенностями клинических исследований. Уделено внимание вопросам безопасности, а также качества продукции. Затрагиваются аспекты равного доступа к технологиям, применения биотехнологии для «улучшения человека». Отдельно обсуждены в контексте данной технологии темы культуры и религии. Подчеркивается, что проблема этической оценки и правового регулирования заключается в том, что 3D-биопечать не может быть полностью оценена с помощью стандартных клинических исследований или действующих нормативных требований. В частности, в настоящее время как в России, так и во всем мире, нет ни подходящей нормативной базы, ни специальных нормативных документов, регулирующих трехмерную биопечать тканей и органов и их дальнейшую трансплантацию. В силу этого встает задача разработки требований к безопасности, качеству и эффективности технологических процессов и конечной продукции, получаемой с помощью 3D-биопечати, с максимальным учетом общепризнанных прав человека.

Ключевые слова: биопринтинг, биопечать, 3D-биопринтинг, биоэтика, биотехнология, информированное согласие, тканевая инженерия, трансплантация, регенеративная медицина

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✉ **Для корреспонденции:** Александр Леонидович Хохлов
ул. Революционная, д. 5, г. Ярославль, 150000, Россия; al460935@yandex.ru

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From time to time there appear news about 3D printed organs. Researchers from around the world have only initiated working upon different technological solutions: from a group that printed a miniature kidney [1] and such technological solutions as BioAssemblyBot [2] to completely new methods that enable printing cardiac tissues for certain patients.

The bioprinting technology can help overcome limitations of modern methods in tissue engineering, including the long wait for transplants. In the nearest future, bioprinting can satisfy the needs both of the elderly and children with the bioprinting tissue or organ being capable of growing along with the patient.

However, the innovative biotechnology involves numerous ethical and regulatory issues. Just like any new technology, 3D bioprinting is associated both with capabilities and risks. Thus, simultaneous solution of various scientific and ethical issues is required. Some of them will be discussed in this article.

3D BIOPRINTING TECHNOLOGY

Traditional 3D printing means building three-dimensional solid objects from CAD-files (computer aided design files) by adding layer by layer. The most common type heats plastic or any other material and adds every layer of it onto a platform until an object is completely shaped.

Printed organs imply a slightly higher level of complexity. Three-dimensional (3D) bioprinting technology creates tissues and organs from aggregates of cells similar to a construction set. 3D bioprinters are specifically developed for this creation or bioprinting. They are used just like 3D printers for fitting

different figures together to compose a 3D model one layer at a time.

At the beginning of the 2000s, researchers have found out that living cells can be diffused through the nozzles of jet printers without any damage. However, having only cells is not enough, and culture medium is required. For this, gelatin microgel is currently used. It contains vitamins, proteins and other essential compounds.

Cartridges for printers are loaded with spheroids or cell suspension. Inside cellular spheroids, cells connect to each other through cell adhesion receptors (from Latin stem of *adhaesio*). Tissue spheroids are fused like two drops of oil in water driven by surface tension and due to cell reaggregation and migration. When fused, tissue-specific spheroids form tissue- and organ-specific structures with 'normal' morphology. Spheroids are incorporated into biomedical scaffolds (made of biodegradable polymers or collagen), yielding 3D structures, where they can turn into a completely functional tissue. One printed layer of cellular spheroids is covered with another one, and the layers are fused together. This is how a 3D living object (tissue or organ) is obtained [3].

Let's take a urinary bladder, a less complex organ, consisting just of two types of cells. First researchers scan the organ to determine its patient-specific shape and form. Then 3-dimensional scaffolds are created and patient's cells are added to the scaffolds. The thorough and hard work can last for up to eight weeks. Finally, a bioreactor system provides an optimal environment for cells to grow into the organ. When doctors transplant the organ, the scaffold has already disintegrated and will vanish following a surgery.

Ideally, all types of cells need to be included. For instance, while printing the kidney, nervous, granular cells, and cells of the lymphatic system can be excluded as basic renal functions (filtration and reabsorption) can be fulfilled without the cells [3].

Bioprinting of more complicated organs strongly depends on effective vascularization. Innervation of a printed organ or tissue is definitely desirable but not obligatory, at least during the first stages. Moreover, postimplantation reinnervation is possible in theory. Printed organs can't be preserved. Their vitality is supported due to a specific solution in the so-called perfusion bioreactor systems. The organ expires within several days prior to transplantation. After it has been transplanted, it is best used till the end of the patient's life [3].

Several companies specializing in bioprinting of tissues or implants but not organs already have some products ready for sale at their disposal. The products include Organovo [4], CELLINK [5], 3D Bioprinting Solutions [6], Particle3D [7], Aspect Biosystems [8], ROKIT Healthcare [9], Viscient Biosciences [10], Dimension Inx [11], and Poietis [12].

LEGAL FUNDAMENTALS

The Russian legislation lacks guidelines regulating creation and implantation of bioprinted human organs [13]. The current edition of Federal Law No. 180-FZ 'About biomedical cellular products' [14] can't regulate the use of human biological organs yet, as the Law doesn't consider the issues of organ transplantation. At the same time, Law of the Russian Federation No. 4180–1 'About transplantation of human organs and (or) tissues' [15] can't regulate the use of 3D bioprinted organs as they are artificial [13].

However, both 3D printers, and bioprinted organs and tissues obtained herewith, can be classified as medical devices, because the relations concerning their use are directly associated with health protection of citizens (art. 38 of Federal Law No. 323 'On fundamental healthcare principles in the Russian Federation', [16], GOST 31508–2012 Medical products. Classification in accordance with potential risk of using. General requirements [17]).

It should be noted that specialized software is also categorized as a medical device by the legislator. Thus, special permission must be obtained not only to conduct clinical trials, produce and implant bioprinted human organs, but also to create their templates (CAD-files) using special software.

Trials of 3D bioprinters and special software, clinical trials of bioprinted organs and tissues should be regulated by Order of the Ministry of Healthcare of the Russian Federation as of January 9, 2014 No. 2н 'On approval of the order of assessing compliance of medical devices in the form of technical trials, toxicological studies, clinical trials for state registration of medical devices' [18].

3D BIOPRINTING — NEW ETHICAL ASPECTS

Possible manufacture of living tissues for research and therapeutic purposes, including tissue restoration and replacement, results in previously unknown ethical issues without clearly established regulatory pathways. For instance, if all human organs can be artificially created and replaced, can the human being still be considered as a holder or an object of rights?

The type of used cells plays a key role in characterizing tissues with bioprinting. During transplantation of allogenic cells, we come across donorship-associated classical ethical issues:

- donor's confidentiality;
- donor's informed consent;
- ownership of donor cells.

Stem cells are commonly used as 'construction blocks' for bioproduction of human tissues and organs. The principal ethical issue of stem cells is represented by their 'source'. The use of human embryonic stem cells (ESC) was heavily criticized and has some limitations. The limitations are both of legal (like in Federal Law as of June 23, 2016 No. 180-FZ 'On biomedical cellular products' [14]) and ethical origin [19]. The principal cell source is represented by embryos or fetuses. That's why the issue of ESC obtaining is at the intersection of bioethical problems of determining the moral 'embryonal status', legal abortions and experiments involving human participants.

Another source of cells for bioprinting is represented by xenogeneic cells. In this case, social and religious aspects of using animal cells should be considered. Patients who underwent xenografting can have psychosocial personality-related problems. Moreover, it can happen that religious beliefs won't allow some patients to use cells taken from certain animals [20].

Emerging opportunities of differentiated cell reprogramming and creation of induced pluripotent stem cells (IPSC) eliminate ethical problems of using ESC or xenogeneic cells. IPSC can be persistently differentiated to any certain types of adult cells (from skin cells to cardiac muscle cells and neurons). Nevertheless, 3D printing of human organs using autologous IPSC is not neutral from an ethical point of view [21].

Cell reprogramming is far from being perfect as well. Our current principal issue is to develop methods of correct differentiation of all stem cells prior to transplantation. The risk of oncogenicity poses a serious problem while using IPSC [22]. To make IPSC-based therapy safe, genetic testing of stem cell lines for potential clinical application should be conducted [23]. However, this results in additional ethical and legal issues associated with collection, storage and use of personal genetic data [21].

DIGITALIZATION

Another aspect that should be considered in ethical assessment of bioprinting states that the technology is set by the digital model. 3D printing technology digitalizes material objects, eliminating the borders between the physical world and digital space. If 3D printing digitizes material objects, then bioprinting digitizes a human body. A person acquires dependence on digital embodiment of an own body or separate organs through the respective electronic 3D models [13]. Printed organs manufactured with biotechnologies on the basis of digital models will replace natural ones. It means that models will replace nature. Thus, a question is raised about the liability for development, estimation of 3D models (CAD-files), getting and use of legal rights.

PERSONAL DATA

Human digitalization makes the issues of confidentiality and privacy relevant, as digital 3D model of bioprinting will represent personal data. This requires special rules that regulate obtaining consent to storage, processing and use of the data in accordance with Federal Law No. 152-FZ 'On personal data' [24].

INFORMED CONSENT

The principle of voluntary informed consent is the fundamental principle of protection of human rights in biomedical research. During 3D bioprinting, problems can arise while obtaining informed consent in urgent situations, when the patient can't express his/her informed consent. Obtaining informed consent can be difficult when a participant can't take a decision about donorship (for instance, some patients can stay at intensive care units) [25].

CLINICAL TRIALS

Clinical trials are required to implement 3D bioprinting into routine clinical practice and eliminate associated risks [25]. As 3D bioprinting is developed within the paradigm of personalized medicine, every biotechnological product is manufactured on an individual basis and can require additional changes in the experimental design in every particular case. Thus, standard approaches to clinical trials such as double-blind randomized control trials can't be applied to 3D bioprinting [21]. Though biomaterials are personalized, procedure criteria and protocols can be standardized based on the first clinical trials [21].

Management of experimental trials of 3D bioprinting of human organs is a complex task as effectiveness and safety of custom-made organs can't be tested on other people. Thus, every person is the first test subject [21]. Issues about the risk-benefit ratio, inclusion criteria, for instance, participation of terminally ill patients in experiments, have been raised [21].

Unlike regular clinical trials with, for instance, possible slow dose adjustment, patients who participate in 3D bioprinting trials can have difficulties to exercise their right to withdraw from a trial following implantation of an artificial bioprinted organ. Interfering with 3D bioprinting can be limited as far as reversibility of the procedure goes (removal of a graft and all cells that grew out of it), and attempts of reimplantation can lead to subsequent damage of patients' health. Besides, a patient can lose a chance for alternative treatment due to participation in bioprinting research [25].

SAFETY

As 3D bioprinting is still a clinically unverified technology, any new treatment with 3D printers is risky. That's why patients must be well aware of health consequences.

The majority of trials were successful in the immediate future. Nevertheless, long-term trials *in vivo* are required to understand whether adverse events can arise. It is obvious that need in the source of cells for bioprinting raises ethical issues associated with embryonic stem cells in accordance with more widely spread ethical debates about their use. Just like in donorship of organs, cells must be similar at a genetic level. Otherwise, the future organ will be rejected by a body. Human stem cells must be used to manufacture an organ for a certain patient. To advance this technology, medicine should find a way to check and standardize manufacturing of the organ.

Moreover, there are risks of teratoma and cancer, graft displacement and migration, which are probably irreversible.

QUALITY

Key aspects of bioprinting management include liability for product quality. Consequently, quality control, service and working safety liability, and quality assurance issues can be essential.

EQUAL ACCESS TO TREATMENT

As 3D bioprinting will soon become a reality, it raises ethical issues concerning treatment of diseases in low-income earners.

Bioprinting is an expensive innovative solution which can probably contribute to the good of some members of a certain subgroup only. So, accessibility of this medical aid is highlighted.

3D bioprinting is another solution that doesn't change rules of game for everyone. It is not intended for the majority. In spite of the promise that organs will be printed at the request and provided to everyone in need, social disintegration of biological manufacturing is likely to arise, when only those who can pay for organs will benefit.

Multi-level system of therapeutic organ replacement is acceptable for those who can pay for a more durative life of own organs. They will probably have a significantly higher quality of life, as bioprinted organs help avoid negative effects of immunosuppressive drugs. At the same time, whereas some patients will wait for a donor organ to be transplanted, and take immunosuppressive agents for the rest of their lives to prevent graft rejection, those with low income will be content with worn-out organs taken from a living or deceased donor wherever they are available.

Bioprinting is focused on individual medical aid, but not on development of a universal treatment plan for all patients. Personalized medicine is costly; it widens the gap between the rich and the poor.

Ownership of printed bio-objects. Lawyers believe that bioprinting opens up a new territory which is different from the former legal regulation of medicine or traditional 3D printing as far as legal ideas of a body go. Thus, issues concerning belonging of implanted bioprinted organs, right and/or possibility to grow own organs are raised.

«HUMAN ENHANCEMENT»

Bioprinting can be used to improve human working capacity, force, speed and endurance. For instance, bioprinting allows

to produce stronger and more flexible structures that imitate natural human bones. 3D bioprinters can also improve working capacity of muscles.

«Human enhancement» will produce a dangerous, but unbelievable effect on the society; bioprinting can create a culture without diseases and imperfections. An ethical issue associated with possible printing of a unique human organ is raised, as this is related to a superhuman.

LEGISLATION

Bioprinting faces serious challenges on the part of technological, financial and regulatory practice. Bioprinted goods must be subject to state regulation.

As bioprinted organs don't correspond to the current rule of clinical trials, the existing rules need to be reconsidered and probably revised to guarantee safety of the products.

Moreover, bioprinting is a new topic to be examined and rules of biosafety in this area haven't been established yet. Adverse events in bioprinting were rarely taken into consideration, including such issues as degradation of biomaterials and tissue integration, biocompatibility and continuous tissue synthesis during material decomposition.

PROTECTION OF PERSONAL DATA

Exchange of data for research purposes increases a number of people who can get access to personal genomic data. In its turn, this improves the probability of data leakage and misuse, including for commission of an offence.

Management and conduct of human genome research and activity of the respective genetic companies are not regulated by the Russian legislation. Requirements to donor's consent to the research and requirements to processing and transfer of genetic data as a special category of personal data are not provided for in the acting legislation [26]. Moreover, the existing legislation provides for no turnover of biological materials withdrawn from donors for research, and neither protects donors' rights nor regulates obligatory preliminary consent of the research by ethics committees [27].

Bioprinting will have to select between limited and open use of the technology. An unregulated bioprinting market can lead to thriving black markets.

Moreover, there exist obstacles for commercialization and use of ESC-based 3D printing technologies. Thus, according to subpar. 3, par. 4, art. 1349 of the Civil Code of the Russian Federation 'the use of human embryos for industrial and commercial purposes… is excluded from patentability' [28].

CONCLUSIONS

1. 3D bioprinting is an extremely complicated technology with numerous social, legal and ethical problems. Researches and technological capabilities are developed much faster than our comprehension of ethical and legal consequences thereof. There is currently no system or specific documents regulating 3D bioprinting of tissues and organs and their subsequent transplantation neither in Russia, nor globally.
2. The problem of ethical assessment and legal regulation of 3D bioprinting is that the technology can't be completely estimated using standard clinical trials or acting regulatory requirements.
3. Rules of clinical trials need to be accepted to make 3D bioprinting more accessible. Informed consent to donation, manipulation with materials, their storage and subsequent use for commercial and research purposes is required.
4. Requirements to safety, quality and effectiveness of technological processes and end products obtained using 3D bioprinting must be developed taking into account human rights and dignity.
5. It is necessary to establish the rules of circulation and limits of commercialization of 3D bioprinting of human organs and tissues, and possible sanctions against illegal trade of artificial organs.

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