https://doi.org/10.30702/transpaorg/08_20.0112/108-115/77
УДК 004.383.4:61:616-77

Sid E. V.
Zaporizhzhia Medical Academy of Postgraduate Education of Ministry of Health of Ukraine, Zaporizhzhia, Ukraine

Prospects of the Artificial Organs Structures 3D Printing Technology

Abstract. Transplantation technologies are now highly effective modern methods of medical care for patients with irreversible stage of chronic diseases of vital organs. The success of transplantology allowed to start solving the problems of improving the quality of patients' life who live with transplanted organ, their adaptation to society, return to work, to authentic family relationships.

The aim of the study is to perform analysis of modern literary sources related to the prospects of application of artificial organs structures bioprinting 3D technology.

The shortage of donor organs for transplantation, the high cost of traditional transplantation and the problem of immunocompatibility of donor tissues led to the search for alternative, cost-effective and efficient organ replacement technologies. There are different methods of making 3D structures, each of which has its advantages and disadvantages. The technology is selected depending on the properties of the material, the desired characteristics of the finished structure and its application. To date, bioprinters are able to print bone and cartilage implants quickly enough.

Thus, 3D bioprinting is now becoming a real breakthrough in regenerative medicine. Every day there are more and more different techniques to improve this technology.

Keywords: 3D bioprinting; rapid prototyping; biofabrication; tissue engineering.

Actuality. Transplantation technologies are now highly effective modern methods of medical care for patients with irreversible stage of chronic diseases of vital organs. The accumulated world experience of organ transplantation, the improvement of surgical technologies and anesthetic service, the achievements of modern immunology and the creation of the legal framework of donation, allowed to develop the basic principles of donors and recipients selection, options for surgical treatment, as well as to develop patient management protocols in the remote period after transplantation [1, 2, 3].

The main problems limiting the life expectancy and quality of the recipients are, on the one hand, immunocompatibility of donor and recipient tissues, manifested by acute or chronic graft rejection, on the

other hand, undesirable consequences of immunosuppression. Given that immunosuppressive drugs, used for the prevention and treatment of rejection, have a narrow therapeutic range, to reduce the risk of undesirable drug interactions in patients with transplanted organ, special care is taken regarding the issue of validity, safety of additional drug administration [4, 5].

The success of transplantology allowed to start solving the problems of improving the quality of patients' life who live with transplanted organ, their adaptation to society, return to work, to authentic family relationships. However, the development of an integrated approach to improving the clinical results of transplantation remains an crucial task [6].

But even modern transplantation infrastructure can become a non-effective tool in the absence of by-law regulations regulating the process of obtaining donor organs for transplantation. Even with a good level of identification of potential donors, the existing donor potential cannot be fully utilized due to the discrepancy between the requirements of by-law regulations and the actual conditions for obtaining and using donor organs in clinical transplantation. It is necessary to modernize the current legislation on the statement of human death on the basis of the brain death diagnosis [7].

No less urgent question is about the necessity of special regulation of infectious safety of organ and tissue transplantation from the standpoint of a clear distinction of the infections list in the group of absolute contraindications for organ donation, relative contraindications and infections that are not a contraindication for organ and tissue donation. By all means, administrative capacity is needed to address these issues. Therefore, the high-tech medical technology supported by state budgetary funds is of great importance both for stable operation and for increasing the volume of transplant care [8].

The aim of the study is to perform analysis of modern literary sources related to the prospects of application of artificial organs structures bioprinting 3D technology.

Review of literature. Every year, 100 thousand organ transplantations and more than 200 thousand human tissues and cells are performed in the world. Up to 26 thousand of them account for kidney transplantation, 8-10 thousand – for liver, 2.7-4.5 thousand – heart, 1.5 thousand – lungs, 1 thousand – pancreas. The leader among the countries of the world in the number of transplants are the United States. Every year, American doctors perform 10 thousand kidney transplants, 4 thousand – liver, 2 thousand – heart. This figure is hundreds of times lower than the need for these operations. According to the study of American experts, the estimated need for the number of organ transplants per 1 million people per year is: kidney – 74.5;

heart – 67.4; liver – 59.1; pancreas – 13.7; lung – 13.7; complex heart-lung – 18.5 [9, 10, 11].

The lack of donor organs available for transplantation, the duration of waiting for the operation, the urgency of its implementation after the removal of the organ create the necessary prerequisites for scientific research. One of the directions of which is to increase the donation of organs of the deceased, to make transplantation more accessible to more candidates. In particular, new strategies for managing the pool of potential donors are proposed [12].

The shortage of donor organs for transplantation, the high cost of traditional transplantation and the problem of immunocompatibility of donor tissues led to the search for alternative, cost-effective and efficient organ replacement technologies. There are different methods of making 3D structures, each of which has its advantages and disadvantages. The technology is selected depending on the properties of the material, the desired characteristics of the finished structure and its application [13, 14].

The new most modern, non-contact and non-destructive method used for the manufacture of 3D structures is bioprinting with the creation of three-dimensional structures in layers and involves the imposition of cells on each other in a special biological medium. The term bioprinting is considered from several points of view, but in general it can be described as a method of creating models of organs, bone tissue and other body fragments on a cellular basis using 3D printers, for which the requirement to preserve the survival and functioning of cells is established [15, 16].

The development of this technology began with the fact that it became possible to produce external non-critical elements of the body, parts of the skull, dental implants, etc. Currently, the replacement of bone and cartilaginous tissue is already a solved problem. Moreover, the practice of bioprinting of various functional and cosmetic prostheses for people who have undergone various surgical interventions to remove tumors or amputation of limbs has increased in popularity. However, this technology is still at an early stage of development, as this process is more complex than simple 3D printing of plastic products [17, 18].

The bioprinting method is based on inkjet printing technology, it makes it possible to form 3D structures with a predetermined shape. «Bio-ink» in this methodology are biopolymers for the formation of the matrix, living cells, proteins, and as a substrate the «bio-paper» is used, which provides stabilization of the formed structures and their existence. The bioprinting method has no drawbacks in comparison with traditional methods of matrix formation, which makes it possible to directly set the final structure of the organ. Due to the accuracy of the

method and its high reproducibility, it is possible to carry out layer-by-layer printing, as well as to apply growth factors and cytokines to the obtained design, which are necessary for cell adhesion and differentiation [19, 20].

Next, the manufactured organ is placed in a bioreactor or incubator, where, while maintaining optimal conditions, the matrix is fixed, and cell proliferation occurs, which leads to the germination of cell structures into the matrix. This equipment provides the necessary conditions for cell proliferation, differentiation and functioning [21, 22].

The development of additive 3D printing technologies allowed to materialize virtual 3D models, applying the layer-by-layer principle of objects creating, when a thin layer of material is applied to the horizontal surface, then the next layer is applied until a complex object is completely created. One of the varieties of 3D printers are bioprinters. These devices are able to create organs and tissues, applying biological material layer by layer. To date, bioprinters are able to print bone and cartilage implants quickly enough [23, 24].

This technology is developing faster than you can imagine, but there are many unresolved problems at the moment, such as the lack of suitable software to create the ideal and most natural organs. An important task is to develop the technology of reproduction of blood vessels in the created organs, as it is vital for them to have working arteries, veins and capillaries to deliver oxygen and nutrients to the blood, which are the key to their viability [25, 26].

Currently tissue and organ designers, created with the help of bioprinters, are small in size and too fragile for human implantation. In addition, they are deprived of blood vessels, that is why their size is determined by the limit of diffusion of oxygen and nutrients, which is 200 microns. The root of the problem consists in their physiology, blood vessels are almost not a subject to successful printing. At present, despite the progress of 3D bioprinting technology, the main problem of transplantation of artificially regenerated organs is the difficulty of maintaining their viability, as tissues with a thickness of more than 0.2 mm lack oxygen and nutrients [27, 28].

Created today artificial organs are able to maintain efficiency for several weeks, as the viability of cells in existing matrices in most cases does not exceed 30 days. For example, an artificial liver functioned for 42 days «printed» by biology company «Organovo» in 2014 [29].

Perhaps the application of the latest innovations in this field, the generation of living tissue permeated by microchannels, will improve the diffusion of oxygen and nutrients. The tissue, which has a spongy base, allows nutrients and neural networks to penetrate into its structure, which makes it possible to maintain the physiological function and viability of an artificially created organ [30].

Recently, companies have emerged in order to use this industry as a business. There are about 60 organizations in the world that directly sell bioprinters and equipment for research laboratories, and they produce biomaterials for use in printers. All of these companies are based on their unique value proposition of providing bioprinting services or partnerships for the production of functional fabrics. Leading commercial companies are gradually forming 3D bioprinting standards, improving technologies that require less time for the production of organs, as well as reducing their cost to patients [31, 32].

Thus, 3D bioprinting is now becoming a real breakthrough in regenerative medicine. Every day there are more and more different techniques to improve this technology.

Conclusions

Analysis of the above literature allows us to make a conclusion that:

– 3D-technology in medicine is a promising direction, the development of which is associated with the improvement of methods of diagnosis and treatment;

– perhaps this is a dead-end way of development of medicine and technology, and currently 3D bioprinting is imperfect, but the existing technologies are applicable in the creation of prostheses and implants.

Prospects for further research. Very high cost of equipment, its maintenance, the price of raw materials, entail a corresponding high cost of research on this topic. In order to solve the important problem of maintaining the life and health of citizens, it is necessary to involve state structures in the financing of research and new developments.

Conflicts of interest: author has no conflict of interest to declare.

Сідь Є. В., канд. мед. наук, доцент каф. медицини невідкладних станів
ДЗ «Запорізька медична академія післядипломної освіти Міністерства охорони здоров'я України», м. Запоріжжя, Україна

Перспективи технології 3D біодруку структур штучних органів

Резюме. Трансплантаційні технології на сьогодні є високоефективними сучасними методами медичної допомоги хворим з необоротною стадією хронічних захворювань життєво важливих органів. Успіхи трансплантології дозволили розпочати вирішення проблем підвищення якості життя пацієнтів, які живуть із трансплантованим органом, їх адаптації в соціум, повернення до трудової діяльності, повноцінних сімейних відносин.

Метою дослідження було проведення аналізу сучасних літературних джерел, пов'язаних з перспективою застосування технології біодруку 3D структур штучних органів.

Дефіцит донорських органів для трансплантації, дорожнеча традиційної пересадки і проблеми імуносумісності донорських тканин призвів до пошуків альтернативних, економічних і ефективних технологій органозаміщення. Існують різні методи виготовлення 3D структур, кожен з яких має як свої переваги, так і недоліки. Технологію обирають залежно від властивостей матеріалу, бажаних характеристик готової конструкції та сфери її застосування. На сьогодні біопринтери здатні досить швидко надрукувати кісткові і хрящові імплантати.

Отже, нині 3D біодрук стає справжнім проривом і в регенеративній медицині. З кожним днем з'являється все більше і більше різних методик для удосконалення цієї технології.

Ключові слова: 3D біодрук, швидке прототипування, біофабрикація, тканинна інженерія.

REFERENCES

1. Никоненко АС. Состояние и перспективы развития трансплантации в Украине. Сучасні медичні технології. 2011;3-4:12-14.

Nikonenko AS. [The state and prospects of development transplantation in Ukraine]. Suchasni medychni tekhnolohii. 2011;3-4:12-14. Russian.

2. Багненко СФ, Резник ОН. Ключевые проблемы развития трансплантологии и задачи высшего медицинского образования. Трансплантология. 2017;9(3):192-210.

Bagnenko SF, Reznik ON. [Key Problems of Transplantation Development and the Objectives of Higher Medical Education]. Transplantologiya. The Russian Journal of Transplantation. 2017;9(3):192-210. Russian. https://doi.org/10.23873/2074-0506-2017-9-3-192-210

3. Bezinover D, Saner F. Organ transplantation in the modern era. BMC Anesthesiol. 2019 Mar 4; 19(1):32. doi: 10.1186/s12871-019-0704-z

4. Sethi S, Choi J, Toyoda M, Vo A, Peng A, Jordan SC. Desensitization: overcoming the immunologic barriers to transplantation. J Immunol Res. 2017;2017:6804678. https://doi.org/10.1155/2017/6804678

5. Allison TL. Immunosuppressive Therapy in Transplantation. Nurs Clin North Am. 2016 Mar;51(1): 107-20. https://doi.org/10.1016/j.cnur.2015.10.008

6. Готье СВ. Трансплантология XXI века: высокие технологии в медицине и инновации в биомедицинской науке. Вестник трансплантологии и искусственных органов. 2017;19(3):10-32.

Gautier SV. [Transplantology of the 21st century: High technologies in medicine and innovations in biomedical science]. Russian Journal of Transplantology and Artificial Organs. 2017;19(3):10-32. Russian. https://doi.org/10.15825/1995-1191-2017-3-10-32

7. Шульга ВМ. Державне регулювання у сфері трансплантації органів та інших анатомічних матеріалів: поняття та сутність. Аспекти публічного управління. 2017;5(3-4(41-42)):26-35.

Shulga VM. [State regulation in the field of transplantation of organs and other anatomical materials: concept and nature]. Public administration aspects. 2017;5(3-4(41-42)):26-35. Ukrainian. https://doi.org/10.15421/1520176

8. Haidar G, Singh N. Viral infections in solid organ transplant recipients: novel updates and a review of the classics. Curr Opin Infect Dis. 2017 Dec;30(6):579-588. https://doi.org/10.1097/QCO.0000000000000409

9. Михель ДВ, Резник ОН. Дефицит донорских органов как глобальная проблема: культурные различия, неравенства и альтернативные стратегии самообеспечения. Социогуманитарные проблемы органного донорства: междисциплинарные исследования: сб. науч. ст. Под ред.: Резник ОН. Москва: 4Принт;2018. С. 11-58.

Mikhel DV, Reznik ON. [Shortage of donor organs as a global problem: cultural differences, inequalities, and alternative strategies of self-sufficiency]. In: Reznik ON, editor. Socio-humanitarian problems of organ donation: interdisciplinary research. Moscow:4Print;2018. p. 11-58. Russian.
10. Капитонова ЕА, Романовская ОВ, Романовский ГБ. Правовое регулирование трансплантологии: монография. Москва: Проспект;2016.
Kapitonova EA, Romanovskaya OV, Romanovskii GB. [Legal regulation of transplantation]. Moscow: Prospekt; 2016. Russian.
11. Matesanz R, Mahillo B, Alvarez M, et al. International figures on donation and transplantation-2014. Newsletter Transplant. Spain: Organización Nacional de Trasplantes. 2015;20:1-64.
12. Girlanda R. Deceased organ donation for transplantation: challenges and opportunities. World J Transplant. 2016 Sep 24;6(3):451-9. https://doi.org/10.5500/wjt.v6.i3.451
13. Хенч Л, Джоунс Д. Биоматериалы, искусственные органы и инжиниринг тканей. Пер.: Цвирко ЮЛ, Лушникова АА. Москва: Техносфера; 2007.
Hench L, Jones D. [Biomaterials, artificial organs and tissue engineering]. Moscow: Tehnosfera; 2007.
14. Штильман МИ. Биоматериалы - важное направление биомедицинских технологий. Вестник Российского государственного медицинского университета. 2016;5:4-15.
Shtilman MI. [Biomaterials are an important area of biomedical technologies]. Bulletin of Russian State Medical Universit. 2016;5:4-15. Russian.
15. Горбатов РО, Романов АД. Создание органов и тканей с помощью биопечати. Вестник Волгоградского государственного медицинского университета. 2017;3(63):3-9.
Gorbatov RO, Romanov AD. [Bioprinting of organs and tissues]. Journal of Volgograd State Medical University, 2017;3(63):3-9. Russian. https://doi.org/10.19163/1994-9480-2017-3(63)-3-9
16. Медведев МП, Фомина МА. 3D-печать как новая эпоха в медицине. Новая наука: От идеи к результату. 2016;4(11):16-19.
Medvedev MP, Fomina MA. [3D printing as a new era in medicine]. Novaya nauka: Ot idei k rezultatu. 2016; 4(11):16-19. Russian.
17. Пысина ЛМ. Искусственные органы. Инновационные методы. Новая наука: Проблемы и перспективы. 2016;53(79):27-29.
Pisina LM. [Artificial organ. innovative method]. Novaya nauka: Problemi i perspektivi. 2016;53(79):27-29. Russian.
18. Zhang YS, Yue K, Aleman J, Moghaddam KM, Bakht SM, Yang J, et al. 3D bioprinting for tissue and organ fabrication. Ann Biomed Eng. 2017 Jan;45(1):148-163. https://doi.org/10.1007/s10439-016-1612-8
19. Murphy SV, Atala A. 3D bioprinting of tissues and organs. Nat Biotechnol. 2014 Aug;32(8):773-85. https://doi.org/10.1038/nbt.2958
20. Wang Q, Xia Q, Wu Y, Zhang X, Wen F, Chen X, et al. 3D-printed atsttrin-incorporated alginate/hydroxyapatite scaffold promotes bone defect regeneration with TNF/TNFR signaling involvement. Adv Healthc Mater. 2015 Aug 5;4(11):1701-8. https://doi.org/10.1002/adhm.201500211
21. Миронов ВА. 3D-биопечать: любые органы на заказ. Инициативы 21 века. 2013;4:94-100.
Mironov VA. [3D same results for bioprinting: organs on any order]. Initsiativi XXI veka. 2013;4:94-100. Russian.
22. Derby B. Printing and prototyping of tissues and scaffolds. Science. 2012 Nov 16;338(6109):921-6. https://doi.org/10.1126/science.1226340
23. Jungling MK, Wood PA, Koike Y. MedTech: 3D Printing – A Solution for Innovation. Morgan Stanley, Blue Paper. 2013 Sept 5.

24. Шмарин НВ, Карелина АА. 3D-биопринтер - печать донорских органов и тканей для трансплантологии. Сборник статей V Международной научно-практической конференции «Инновационное развитие современной науки: проблемы, закономерности, перспективы»: 10 декабря 2017; Пенза, Россия. С. 334-336.
Shmarin NV, Karelina AA. [3D-bioprinter-printing of donor organs and tissues for transplantology]. Innovatsionnoe razvitie sovremennoi nauki: problemi, zakonomernosti, perspektivi: Proceedings of the 5th International Scientific and Practical Conference; 2017 Dec 10; Penza, Russia. p. 334-336. Russian.
25. Hesuani YD, Pereira FD, Parfenov V, Koudan E, Mitryashkin A, Replyanski N, et al. Design and implementation of novel multifunctional 3D bioprinter. 3D Printing and Additive Manufacturing. 2016; 3(1):64-68. https://doi.org/10.1089/3dp.2015.0040
26. Ozbolat IT, Moncal KK, Gudapati H. Evaluation of bioprinter technologies. Additive Manufacturing. 2017;13:179-200. https://doi.org/10.1016/j.addma.2016.10.003
27. Фадеева СА, Ситдикова ИД, Мешков АВ и др. Актуальные проблемы биосовместимости материалов медицинского назначения в аддитивных технологиях. Сборник статей XV международной научно-практической конференции «Advances in Science and Technology»; 31 июля 2018; Москва, Россия. С. 28-30.
Fadeeva SA, Sitdikova ID, Meshkov AV, Kamaletdinova AA, Gordeeva AV, Vasileva EV, et al. [Actual problems of biocomposition of materials of medical purpose in additive technologies]. Advances in Science and Technology: Proceedings of the 15th International Scientific and Practical Conference; 2018 Jule 31; Moscow, Russia. Moscow; 2018. p. 28-30.
28. Richards D, Jia J, Yost M, Markwald R, Mei Y. 3D bioprinting for vascularized tissue fabrication. Ann Biomed Eng. 2017 Jan;45(1):132-147. https://doi.org/10.1007/s10439-016-1653-z
29. Neff EP. Printing cures: Organovo advances with 3D-printed liver tissue. Lab Anim (NY). 2017 Feb 17;46(3):57. https://doi.org/10.1038/laban.1203
30. Khademhosseini A, Camci-Unal G, editors. 3D Bioprinting in Regenerative Engineering: Principles and Applications. 1st ed. Boca Raton:CRC Press;2018. https://doi.org/10.1201/b21916
31. Choudhury D, Anand S, Naing MW. The arrival of commercial bioprinters - Towards 3D bioprinting revolution. Int J Bioprint. 2018 Jun 17;4(2):139. https://doi.org/10.18063/IJB.v4i2.139
32. Токарев БЕ, Токарев РБ. Анализ рыночных перспектив технологий 3р-биопечати. Интернет-журнал Науковедение. 2016;2(8). Режим доступа: http://naukovedenie.ru/PDF/33EVN216.pdf
Tokarev BE, Tokarev RB. [Market outlook analysis of the 3D bio-printing technologies]. Internet-zhurnal Naukovedenie [Internet]. 2016 [cited 2020 Aug 01];2(8):[about 16 p.]. Available from: http://naukovedenie.ru/PDF/33EVN216.pdf. Russian.

Стаття надійшла в редакцію 29.08.2020 р.