

Bioprinting in the Russian Federation: Can Russians Compete?

Peter Timashev^{1,2,3}, Vladimir Mironov^{1,4*}

¹Institute for Regenerative Medicine, Sechenov University, Moscow, Russia

²Department of Chemistry, Lomonosov Moscow State University, Moscow, Russia

³Department of Polymers and Composites, N.N. Semenov Institute of Chemical Physics, Moscow, Russia

⁴3D Bioprinting Solutions, Moscow, Russia

Abstract: Bioprinting is a rapidly emerging biomedical research field. Three-dimensional bioprinting is defined as a robotic additive, layer-by-layer biofabrication of functional tissues and organs from living cells, and biomaterials according to a digital model. Bioprinting can revolutionize medicine by automated robotic production of human tissues and organs suitable for transplantation. Bioprinting is based on sophisticated high technology, and it is obvious that only technologically advanced countries can make a real contribution to this rapidly evolving multidisciplinary field. In this paper, we present main Russia's achievements in bioprinting. Here, we also discuss challenges and perspectives of bioprinting research and development in Russia. Russian researchers already made some impressive contributions with long-lasting impact and they have capacities, potential, and ambitions to continue contribute to the advancements of bioprinting.

Keywords: Russia, Three-dimensional bioprinting, Bioinks, Tissue engineering, Laser-induced forward transfer

*Corresponding Author: Vladimir Mironov, The Laboratory of Biotechnological Research, 3D Bioprinting Solutions, Kashirskoe Roadway, 68/2, Moscow, Russian Federation; vladimir.mironov54@gmail.com

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1 Introduction

Bioprinting is defined as an additive biofabrication of three-dimensional (3D) tissues and organs from living cells and biomaterials according to digital design. Bioprinting is a rapidly emerging biomedical technology which promises to solve the urgent and yet unsolved problem of the shortage of human organ for transplantation, once and for all. In the past two decades, many research groups around the world became involved in systematical research in this multidisciplinary field. There are a lot of original papers, influential reviews^[1-3], and even textbooks^[4-6] which have already been

published. There are several new societies (such as International Society for Biofabrication) and new journals (such as Biofabrication, Bioprinting, and International Journal of Bioprinting) with impressive impact factors. The commercialization of bioprinting technology is also under way. There are more than 100 bioprinting companies in the world. Thus, bioprinting is already a global phenomenon. In this context, it will be extremely interesting and even potentially useful to investigate comparative landscape of bioprinting research and development in different countries around the world, to identify specific directions in research as well as strength and weakness in

dominated approaches, and to outline potential perspectives. In this review, we focus our attention on bioprinting research and development in Russia. To date, Russia still represents a sufficiently big player with strong research infrastructure, traditions, research schools, and impressive educational and training system. Thus, the focus of this paper is to illustrate how Russian research community can address new research challenges and explore a perspective in high technology areas such as 3D bioprinting and to estimate how competitive is bioprinting research in Russia now and the potential of Russian contribution to this new field in the future.

2 Four Russian bioprinting success stories

Conventionally, to show contribution of specific country to the development of emerging research field, quantitative scientometric analysis was used. However, we believe that it is a basically formal approach and that the presentation of so-called success stories sometimes provides much more valuable qualitative information about competitive potential of the analyzed research community. Here, we will present four most impressive Russian bioprinting success stories which reflect a strong creative and competitive potential of Russian bioprinting research community.

2.1 Development of the first Russian original commercial 3D bioprinter

A 3D bioprinter is a robotic device that carries out layer-by-layer biofabrication of 3D human tissues and organs from living cells and hydrogels according to a digital model^[7]. Development of commercial 3D bioprinters certifiable for clinical use will enable bioprinting 3D human tissues and organs that are suitable for implantation. The capacity to develop an original 3D bioprinter is also a direct evidence of the competitiveness of a particular country on a global level. Fabion is the first Russian original commercial multifunctional 3D bioprinter of extrusion type that is suitable for robotic biofabrication of 3D human tissues and organs and potentially certifiable for clinical use. The development of Fabion is not only an

important milestone but also a manifestation of competitiveness of Russian bioprintists.

Multifunctional commercial clinical 3D bioprinter “Fabion” of extrusion type has been not only designed and developed, but some of its most essential functionalities have been also tested^[7]. The main principle constructive feature of a 3D bioprinter is a separation of a cell printing process from hydrogel spraying, which allows the use of photosensitive hydrogel with ultraviolet-induced polymerization without cell damage. The 3D bioprinter enables extrusion and precision placing of (i) hydrogel filaments with or without living cells, (ii) continuous cellular rods, and (iii) separated tissue spheroids as well as (iv) independent spraying of biocompatible hydrogels based on different principles of induced polymerization. The “built-in” multifunctionality of the Russian 3D bioprinter allows the layer-by-layer additive biofabrication of complex 3D human organ constructs using tissue spheroids as building blocks. The use of only disposable and sterilized components in the multinozzle system made the 3D bioprinter Fabion suitable and certifiable for clinical use^[7].

According to independent rating, bioprinter Fabion is one of the top 5 world best commercial bioprinters. The development of an original certifiable clinical multifunctional 3D bioprinter is an important step toward practical implementation of desirable organ printing technology in Russia.

2.2 Development of the first Russian laser-assisted 3D bioprinter

To date, laser-assisted bioprinting is one of the actively developing techniques in bioprinting and developed based on a nozzle-free laser-induced forward gel microdroplet transfer helping to remove nozzle-associated side effects^[8]. One of the pioneers who introduced this technique was Boris Chichkov. However, it was mostly exploited outside Russia (mainly in Germany and France) for a long period of time. In 2019, the research team from Institute for Regenerative Medicine (Sechenov University) and Institute of Photon Technologies (Federal Research Center Crystallography and Photonics) announced that they had constructed

the first Russian laser-assisted bioprinter BioDrop and initiated studies on fabrication of tissue-engineered constructs using it for their further clinical applications. This bioprinter has the same advantages as foreign setups. Taking into account that there is only one commercial laser-assisted bioprinter on the global market, it can become a good alternative after its commercialization.

2.3 Bioprinting of functional and vascularized animal organ

The best possible demonstration of functionality of a 3D bioprinter is its capacity to bioprint functional and vascularized 3D tissues and organs. We define bioprinting in more narrow sense as an additive biofabrication of 3D tissues and organ constructs using tissue spheroids as building blocks. In this approach, the self-assembling properties of tissue spheroids have been explored. The endocrine organs such as the thyroid gland, a relatively simple endocrine organ without complicated ductal system is more suitable for testing using the proposed bioprinting technology. The 3D bioprinting of a functional vascularized mouse thyroid gland construct from embryonic tissue spheroids as a proof of concept has been recently reported^[9]. The thyroid tissue has been generated from thyroid spheroids and allantoic spheroids as a source of thyrocytes and endothelial cells. The closely placed embryonic tissue spheroids fused into a single vascularized tissue construct. Radiatively ablated mice were used as an animal model of thyroid gland hypofunction. The cultured bioprinted construct was functional as it could normalize blood thyroxine levels and body temperature after grafting under the kidney capsule of hypothyroid mice^[9]. Bioprinting of the functional vascularized mouse thyroid gland construct represents an important milestone and impressive advance in the development of bioprinting technology.

2.4 Bioprinting in space

Magnetic levitational bioassembly of 3D tissue constructs represents a novel rapidly emerging scaffold-free and label-free approach as well as

alternative conceptual and experimental advance in tissue engineering. However, implementation of magnetic levitation on Earth requires the use of relatively toxic paramagnetic medium that, in most cases, contains gadolinium salts. The magnetic levitational bioassembly under the conditions of space microgravity can be implemented at low non-toxic concentrations of gadolinium salts. A new magnetic bioassembler has been designed, developed, and certified for life space research. To the best of our knowledge, 3D tissue constructs have been biofabricated for the 1st time in space under microgravity from tissue spheroids consisted of human chondrocytes using magnetic levitational bioassembly at low non-toxic concentrations of paramagnetic medium^[10]. Bioassembled 3D tissue constructs demonstrated good viability and advanced stages of tissue spheroid fusion processes. These data strongly suggest that scaffold-free, label-free, and nozzle-free formative biofabrication using magnetic fields is a feasible alternative to traditional scaffold-based approaches. It opens a new perspective avenue of research which could significantly advance tissue engineering. Magnetic levitational bioassembly of 3D tissue constructs in space can also advance space life science and space regenerative medicine^[10]. It is another impressive example of important contribution of Russian bioprinting research community which capitalized on strong existing Russian expertise in space research^[11].

3 Education and training bioprintists in Russia

However, as bioprinting is developing and there is an increasing demand for specialists with multidisciplinary background, new educational and training programs focused on bioprinting and related fields have been appearing. This mostly becomes possible after the foundation of first two institutes for regenerative medicine in two biggest and recognized universities (Sechenov University and Lomonosov Moscow State University) in 2016. For instance, Institute for Regenerative Medicine of the Sechenov University launched a new discipline called the “Introduction to Regenerative Medicine” for medical students in

2017 and introduced a training program called “Tissue Engineer,” first of its kind in Russia, for the final year students majoring in General Medicine and Pharmacy in 2018. The first Russian textbook “3D Printing in Medicine” has recently been published^[10].

To date, there is an increasing number of both national and international student exchange programs supported by the government, universities, and national and international foundations. Most of such programs are developed to increase international academic mobility and cover almost all expenses, giving a unique chance for students to broaden their background in top research teams from all around the world. Since the frequencies of international student exchanges are constantly increasing, young Russian researchers can also attend established training courses on bioprinting and biofabrication in the USA, The Netherlands, Australia, etc.

Moreover, 3D Bioprinting Solutions, a private Russian company, offers 3-week training courses on bioprinting for young Russian students and researchers. Comics “Adventure in Bioprinting Laboratory” has also been developed.

Thus, there are real possibilities to get education and training in bioprinting in Russia. There are also certain undeniable advantages of carrying out research in Russia on which the emerging community of Russian bioprintists can capitalize: (i) There are new grant schemes and funding organizations; (ii) Russian scientists can participate in conferences, workshops, meetings, and congresses abroad without any restrictions; (iii) young Russian researchers can now receive training in foreign countries; (iv) access to foreign literature and patent databases is not a problem anymore; and (v) foreign researchers are welcomed to Russia to build a research laboratory.

4 Can Russian bioprintists compete?

Russian scientists can indeed compete and be very successful. Breakthrough pioneering works of Prof. Boris Chichkov who is a Russian scientist in laser-based bioprinting technologies

(Hannover, Germany) is the best evidence. In addition, Vladimir Mironov, one of the authors of this paper, was awarded the prestigious Senior Investigator Award from the International Society of Biofabrication for his pioneering contribution to the development of bioprinting technology in 2018.

The bioprinting success in Russia depends on not only the scientist *per se* but also many other factors. We believe that to guarantee success and optimize competitiveness of Russian bioprintists community, several highly desirable aspects require our utmost attention; they include: (i) Organization of center(s) of excellence and/or National Bioprinting Research Center or Institute; (ii) training of young scientists in the best bioprinting research centers around the world; (iii) recruitment of foreign scientists to work in Russia; (iv) increasing collaborations with the world’s best bioprinting research scientists, research groups, and bioprinting research centers; (v) increasing publications in top journals; (vi) increasing application for patents; (vii) developing start-up companies in bioprinting; and (viii) clinical translation.

Today, Russia’s successes are also proven by the increase in bioprinting activity and the establishment of the society on regenerative medicine in 2013 (President Prof. Vsevolod Tkachuk; Honorary President Prof. Gennadiy Sukhikh). It is also noteworthy that Russia was invited by the International Society on Tissue Engineering and Regenerative Medicine to be a Guest Nation on TERMIS-EU Chapter 2019 (May 27–31, 2019). The increasing visibility of Russia on the world TERM map is also due to the organization of world class events such as Sechenov International Biomedical Summit (<https://sechenov-sibs.confreg.org/>) and National Congress on Regenerative Medicine (<https://congress.regenerative-med.ru/>) where leading scientists (Anthony Atala, James Yoo, William Wagner, etc.) from the USA, Italy, Germany, France, Iran, the Netherlands, China, Ireland, etc., present their recent achievements.

In view of the bioprinting success stories such as the creation of the world’s first animal organ

in Russia and the establishment of bioprinting research infrastructure in several Russian universities and research organizations, it is logical to assume that Russia may take the lead to bioprint the world's first human organ and also achieve the first successful clinical transplantation of bioprinted human organ in Russia. Hence, Russian researchers and engineers can compete and compete successfully.

5 Conclusion and outlook

3D bioprinting is a rapidly emerging biomedical technology that promises to transform the landscape of organ transplantation. Russian contribution to global development of this technology cannot be understated; at least five main achievements of Russian bioprintists deserve the attention of the global research community: (i) Development of new software for bioprinting based on function representation (see paper in this issue); (ii) development of natural bioinks (see papers in this issue); (iii) development of original 3D bioprinters (see papers in this issue); (iv) bioprinting of the world's first functional and vascularized organ construct – mouse thyroid glands^[9]; and (v) magnetic levitational bioassembly of 3D tissue constructs in the condition of microgravity in space (accepted for publication in *Science Advances*).

For the next decade, it is logical to expect further contribution of Russian researchers in traditional areas of Russian expertise. First, bioprinting in space at the Russian segment of the International Space Station will continue to advance^[12]. Second, new type of bioprinters especially laser-based bioprinters will be developed in Russia due to the traditional strong expertise in laser research. Third, Russian bioprintists can capitalize on their initial success with bioprinting the world's first functional and vascularized animal organ and have chances to bioprint and test *in vivo* the world's first functional and vascularized human organ. There are attempts to advance education and training young generations of specialists in the field of bioprinting. The first Russian textbook in 3D printing in medicine and bioprinting has been already

published^[10], and several universities introduced programs on 3D bioprinting technology. Recently, Russian bioprintists also contributed to one of the most comprehensive textbooks on 3D printing and biofabrication^[13]. Moreover, the commercialization and clinical translation of 3D bioprinting will need to be supported. It remains to be seen how competitive will Russian bioprintists be and how successfully established Russian research potential, expertise and infrastructure in bioprinting field will be commercialized and clinically translated.

The special issue “**Bioprinting in Russia**” published in the *International Journal of Bioprinting* demonstrates the broad potential of Russian bioprintists research community which includes the development of novel software based on principle of function representation, novel bioinks based on natural polymers such as fibrin and collagen, new types of 3D bioprinters, laser-based bioprinting and magnetic levitational bioprinting in space, as well as ethical aspects of bioprinting and emerging business models in bioprinting. We believe that the selected papers will demonstrate quality and perspectives of bioprinting research in Russia and will support our opinion that Russia will continue to be an important and highly competitive player in the advancements of bioprinting technology.

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Conflict of interest

The authors declare no conflict of interest.

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