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Alternative Therapies in Transplantology as a Promising Perspective in Medicine

Authors' Contribution:
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Manuscript Preparation E
Literature Search F
Funds Collection G

E 1 Natasza Michalska
E 1 Ewa Totoń
E 2 Przemysław Kopczyński
E 3 Magdalena Jankowska-Wajda
A 1 Błażej Rubiś

1 Department of Clinical Chemistry and Molecular Diagnostics, Poznań University of Medical Sciences, Poznań, Poland
2 Centre for Orthodontic Mini-Implants at the Department and Clinic of Maxillofacial Orthopedics and Orthodontics, Poznań University of Medical Sciences, Poznań, Poland
3 Faculty of Chemistry, Adam Mickiewicz University in Poznań, Poznań, Poland

Corresponding Author: Błażej Rubiś, e-mail: blazejr@ump.edu.pl
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Despite continuous and rapid progress in the transplantation of cells, tissues, and organs, many patients die before receiving them. This is because of an insufficient number of donors, which leads to a significant disproportion between the need for donors and their availability. This review aims to present the possibilities offered by alternative therapies. We use the term "functional transplantology" to describe such alternative methods of transplantation that could help change the current state of transplantation medicine. Its purpose is not to replace a defective or removed organ with another but to replace its functions using complementary biological, mechanical, or biomechanical structures or devices. Implementation of many innovative solutions shown in the work for clinical applications is already a fact. In the case of others, it should be considered a future vision. We hope that the role of a defective or damaged tissue or a group of tissues will be taken over by different structures that are functionally complementary with the organ being substituted. Undoubtedly, developing the described methods based on functional transplantology will change the face of transplantation medicine. Thus, we show current trends and new directions of thinking and actions in transplantation medicine that combine technology and transplantology. The review considers the latest technologies, including 3D bioprinting, nanotechnology, cell encapsulation, and organoids. We discuss not only the advantages of new approaches but also the limitations and challenges that must be overcome to achieve significant progress in transplantation. That is the only option to provide a safe and efficient way of improving the quality of life of many patients.

Keywords: **Bioprinting • Cell Encapsulation • Organoids • Cell Transplantation • Organoids • Nanotechnology**

Abbreviations: **ESCs** – embryonic stem cells; **iPSCs** – induced pluripotent stem cells; **ASCs** – adult stem cells; **iBAKi** – implantable bioartificial kidney; **T1D** – type 1 diabetes; **SNM** – silicon nanopore membrane; **MEMS** – microelectromechanical systems; **TNF-α** – tumor necrosis factor-α; **IFN-γ** – interferon-γ; **IL-1β** – interleukin-1β; **RCP** – recombinant peptide; **MSCs** – mesenchymal stem cells; **PLL** – poly-L-lysine; **PA** – polyamide; **ECM –** extracellular matrix

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Introduction

Transplantation is a surgical or medical procedure involving grafting cells, tissues, or organs from one person (or body part) to another, thereby substituting or repairing the damaged, missing, or diseased cells, tissues, or organs. Organ transplantation offers not only improved quality of life but also improved long-term survival for many patients suffering from renal, hepatic, cardiac, or pulmonary failure. However, despite the constant progress made in transplantology, many patients still die without receiving a transplant due to various factors. The main problem is the insufficient number of donors. In addition, although the application of immunosuppressive drugs has contributed to improving short-term survival and graft function, the long-term effects are still unsatisfactory [1]. Based on the genetic variations between the recipient's and donor's tissues, the most common transplantation types are being distinguished: xenograft, allograft, isograft, and autograft [2]. Currently, alternative approaches are supported by novel technologies (eg, based on stem cells or nanotechnology), genetic engineering (an option to use genetically modified and adopted animal organs) [3], and robotics, which provides automatic and minimally invasive cardiac surgery that is safe and feasible although not standardized yet [4].

All current transplantation methods are based on the approach that provides replacing a damaged or dysfunctional organ with an organ either derived from stem cells or a graft obtained from another person or an immunocompetent animal. However, enormous efforts are being expended to develop alternative methods for replacing vital organ functions. That would lead to replacing and substituting an organ function with other biological, mechanical, or biomechanical structures or devices. Another example, one of the latest is a 3D bioprinting technology that enables the formation of organ-like structures that are capable of substituting a damaged or missing organ, providing compatible functions. Further development of new technologies seems to be the only way to offer a normal lifestyle for patients with advanced organ failure [5,6].

The Current Status and Challenges in Organ Transplantation

Transplantation

By adopting different division criteria, individual classifications of transplant procedures can be made. Regarding the genetic differences between the donor and the recipient, different types of transplantation are distinguished:

a) autologous, when the donor and the recipient are the same person;
b) isogenic (syngeneic), when the donor and recipient are different people but genetically identical (identical twins);
c) allogeneic, when the donor and recipient belong to the same species but are genetically different;
d) xenogeneic, when the donor and the recipient belong to 2 different species [7].

Similarly, depending on the origin of the transplant material, different types of transplantation are distinguished:

a) ex vivo, when the material is taken from a living donor, who may be related or unrelated to the recipient;
b) ex mortuo, when the material is collected from a deceased donor when the death occurred due to brain death or irreversible cardiac arrest [8].

Transplantation Statistics

The development of transplant medicine enables an increase in the number of transplants and expands the spectrum of transplanted tissues and organs. According to data reported by the "Global Observatory on Donation and Transplantation," over the last 12 years, from 2010 to 2021, there has been an increase in the total number of transplants of kidneys, liver, heart, lung, pancreas, and small intestine by 35% (106 879 in 2010 and 144 302 in 2021) (**Figure 1A**). However, despite the observed general upward trend, the number of transplants performed annually is less than 10% of the global demand [9]. A significant decrease in the number of transplants was observed in 2020, which was correlated with the COVID-19 pandemic [10].

The significant disproportion between the number of transplants performed and the number of patients waiting for this type of treatment remains an unsolved problem in transplantology. Although the number of donors from whom organs were collected after death (deceased donors) worldwide increased by 64% from 2010 to 2021 (24 280 in 2010 and 40 036 in 2021) (**Figure 1B**), the donation rate (ie, the number of donors per million population) remains low, with 3.49 in 2010 and 5.11 in 2021 [11].

For several years, the United States and Spain have been the global leaders in the number of transplants carried out annually and the number of donors per million inhabitants [11].

Organs successfully transplanted include the heart, kidneys, liver, lungs, pancreas, intestine, thymus, and uterus. Tissues include bones and tendons (both referred to as musculoskeletal grafts), cornea, skin, heart valves, nerves, and veins. The kidneys are the most commonly transplanted organs worldwide, followed by the liver and heart. Cornea and musculoskeletal grafts are the most commonly transplanted tissues.

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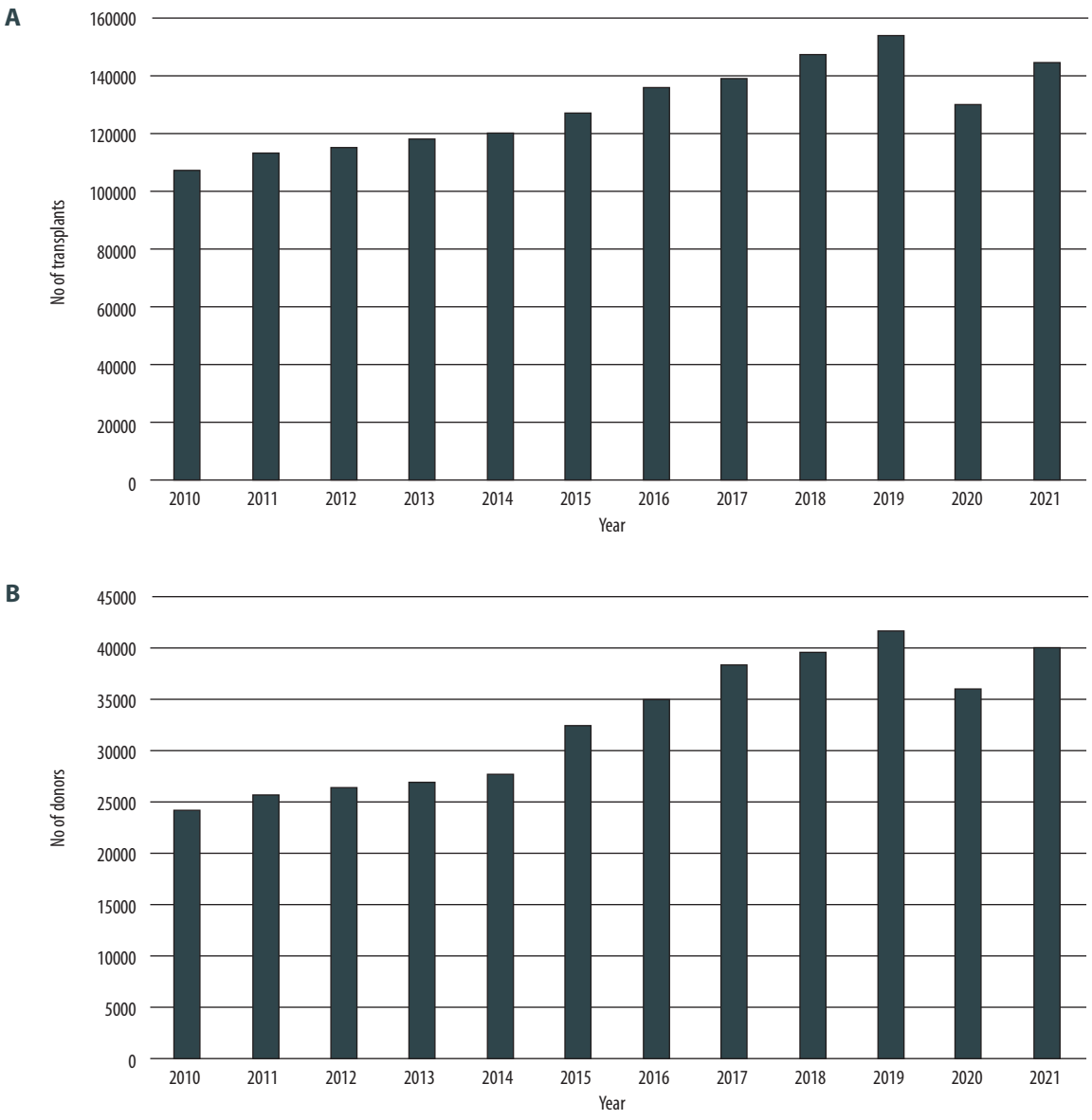

Figure 1. Number of organ transplants (**A**) and donors (**B**) worldwide in 2010-2021 (kidney, liver, heart, lung, pancreas, small intestine) [1,9].

The primary challenge in transplantation today for all organ types is the disproportion between organ demand and availability. Additional challenges involve several ongoing studies in these areas. There are, however, some specific challenges associated with the transplantation of individual organs that make the solution less universal and more complex. It seems that xenotransplantation can solve many problems associated with organ deficiency and storage, but some unsolved physiological, microbiological, and immunological problems are still associated with this type of transplantation [12].

Xenotransplantation

The practical application of xenotransplantation may be a promising approach to solving the donor shortage problem. Cross-species transplantation would expand the range of transplanted tissues and organs. In the initial stages of xenotransplantation research, the primary focus was using donor organs from non-human primates (NHPs). However, despite the close phylogenetic relationship between NHPs and humans, it was revealed that they were not suitable for several reasons. These reasons included ethical concerns, high costs, challenges in implementing genetic modifications, and

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concerns related to biosafety [13]. Currently, pigs are considered the optimal donors because their physiology and organ size are comparable to humans. They are easy to breed, reproduce quickly, can be bred relatively free of pathogens, and, most importantly, can be subjected to programmed genetic manipulations [14]. However, this does not change the fact that the pig is phylogenetically quite distant from humans, which causes immunological complications, including hyperacute vascular rejection [15]. In 2021, The New York Times disclosed the outcomes of an experimental pig-to-human xenotransplantation conducted at New York University. With the family's consent, a kidney from a pig with a knockout of the alpha 1,3-galactosyltransferase gene was transplanted into the femoral vessels of an organ donor who had experienced brain death. The transplanted organ was closely monitored for 54 hours, and it exhibited urine production and clear creatinine levels and showed no apparent signs of rejection [16]. In the past decade, research efforts have shifted towards creating donor organs from pigs using CRISPR technologies to edit various genes [13]. In 2022, a pig's heart was transplanted (after modulation of 10 genes) into a human at the University of Maryland Medical Center [17]. Significantly, the xenograft immediately performed its function, and the use of extracorporeal membrane oxygenation (ECMO) was stopped after a few days. Unfortunately, this intervention ended in the patient's death due to multiorgan failure after 2 months. Nevertheless, it is evident that hyperacute rejection was successfully overcome, and the xenograft played a crucial role in extending the life of this patient, who had no other viable options. A significant challenge in successful xenotransplantation is alleviating the risks of immune rejection of the xenotransplant. It is essential to conduct further intensive research so that interspecies transplantation becomes not only a vision but a viable treatment option in the future [18].

New Era – the Future of Functional Transplantology

Worldwide, there is a significant disproportion between the number of donors of cells, tissues, and organs for transplantation and the number of patients waiting for them. The reason for this is, among other things, lack of consent of the family to collect the material from the deceased, which may result from the reluctance of many people to make decisions about becoming a potential donor after death [19]. Another worrying factor is the underuse of living donor donation. This is also significantly affected by the aging of societies; therefore, in many cases it is necessary to refrain from collecting tissues or organs from potential donors due to their inadequate quality [1].

The effectiveness of transplantation is limited by the graft rejection process, which is classified as hyperacute, acute, or chronic according to the pathomechanism of its formation. It occurs within minutes or hours (hyperacute), days or weeks (acute), or months or years (chronic) after transplantation. Antibodies directed against blood group antigens or histocompatibility antigens of the donor are involved in the immunopathogenesis of hyperacute rejection; T cells and antibodies specific for alloantigens of the transplant in acute rejection; and alloantibodies, T cells, and inflammations in chronic rejection [20]. Various immunosuppressive therapies are used to prevent or eliminate the symptoms of transplant rejection. Their implementation (for the first time in 1960 in the form of the drug azathioprine) significantly improved the short-term survival of patients and the durability of transplants [21]. However, it is necessary to search for new methods of this type of treatment because long-term effects are still unsatisfactory [22-24].

In the face of the current challenges in transplantology, it is necessary to look for alternative methods to help solve this crisis. The goal of alternative organ transplantation methods (ie, functional transplantology) is to substitute a defective or removed organ, not in the context of physical, but functional replacement. Thus, the role of a given tissue or group of tissues is taken over by visually different but functionally complementary structures.

The paper discusses 4 innovative research areas: 3D bioprinting, nanotechnology, cell encapsulation, and organoids (**Figure 2, Table 1**) [25-29].

Alternative Approaches – 3D Bioprinting

One alternative approach to transplanting and replacing damaged organs is 3D bioprinting, based on the precise layer-by-layer application of biological materials, biochemical compounds, and living cells to produce 3D biostructures [30]. The invention of the 3D printer based on stereolithography in 1984 by Christian Hull is considered the beginning of the 3D printing technique. The idea of bioprinting was first described by Klebe in 1988, who used a standard thermal inkjet (HP) printer to print collagen and fibronectin. In the following years, 3D bioprinters based on various technologies were constructed, and the already known systems were improved, allowing for this field's dynamic development. There are 3 major types of 3D bioprinting techniques: inkjet bioprinting, extrusion bioprinting, and laser-assisted bioprinting.

3D bioprinters require bioinks. Bioinks consist of living cells or living cells combined with carriers (most often biomaterials), whose task is to provide the cells with an appropriate environment for proliferation, differentiation, migration, maturation, and protection during the printing process [31].

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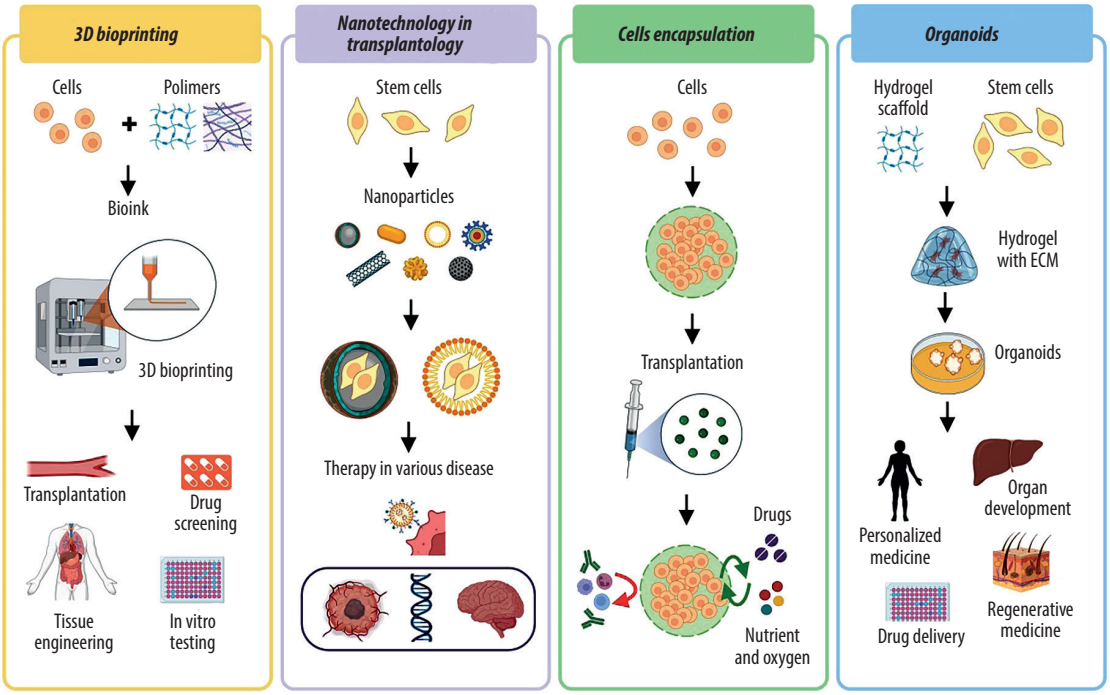

Figure 2. Current alternative transplantology technologies.

Bioinks should have the following biophysical properties: optimal viscosity, high stability and mechanical integrity, biocompatibility, cytocompatibility, biodegradability, non-immunogenicity, non-toxicity, and the ability to promote cell adhesion and proliferation [32].

Individual bioink parameters need to be adjusted to the 3D bioprinting technology used and the cell type to enable the generation of tissues and organs that precisely and closely reproduce the structure and functions of their in vivo counterparts. Currently, the most popular class of biomaterials used as bioink components is hydrogels. Their attractiveness for this type of application is related to their biocompatibility, mechanical and structural similarity to the extracellular matrix (ECM) of many tissues, high permeability to oxygen and nutrients, and the ability to provide an environment favorable for cell adhesion and proliferation [33].

Autologous cells are the best source of cells for printing tissues and organs. Their use allows for minimizing the risk of transplant rejection and eliminating the need for patients to take immunosuppressive treatment after surgery. Two main types of cells are used in 3D bioprinting technology: primary cells (PCs) and stem cells (SCs) [34].

3D bioprinting of tissues and organs is widely regarded as a groundbreaking solution in transplantology. The dynamic development of this technology offers hope for its more comprehensive clinical application in the future. Indeed, examples of the application of 3D bioprinting have already been documented in the literature in various medical fields, such as dermatology, cardiology, and otology. Chronic skin wounds resulting from injuries (most often burns), surgery, or disease are a severe health problem that affects many millions of patients around the world. Currently, their treatment methods include autotransplantation procedure or the use of artificial skin substitutes such as Integra®, Biobrane®, and Dermagraft®, which, despite promising results at the stage of clinical trials, are characterized by a lower structure complexity than normal skin, which makes it impossible to reproduce all its functions (including sensation, secretion, thermoregulation, and protection against UV radiation). A promising alternative to this type of solution is 3D bioprinting technology. There are 2 approaches to skin bioprinting: in situ and in vitro bioprinting. The first involves the precise deposition of bioink directly at the site of injury, while the second involves printing the skin in vitro, its maturation in a bioreactor, and subsequent transplantation at the wound site [35]. A pivotal moment in advancing research on skin transplants was developing a way to print living skin cells in a 3D format that were provided with blood vessels [36].

Bioprinting in Cardiovascular Diseases

Cardiovascular diseases are the leading cause of death all over the world. Currently, the only treatment option for end-stage

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Table 1. Potential of alternative transplantology technologies.

	3D bioprinting [25,26]	Nanotechnology in transplantology [27]	Cells encapsulation [28]	Organoids [29]
Applied technique	Bioprinting is a technology where bioinks and biomaterials, mixed with cells, are 3D printed to construct living tissue models. Construction of many tissues/organs (skin, blood vessel, adipose tissue, bone/cartilage, heart, liver, kidney, muscle, and nerve)	Nanotechnology in stem-cell-based therapy is applied in neurodegenerative disease, anti-tumor, and gene delivery	Cell encapsulation technology involves immobilization of cells within a polymeric semi-permeable membrane. Therapeutic applications (diabetes, cancer, liver and pancreatic disease, heart diseases, monoclonal antibody therapy)	Organoids are self-organized three-dimensional tissue cultures that are derived from stem cells. Ideal model for preclinical drug toxicity evaluation. Application in regenerative medicine (repair damaged tissues and organs)
Resolution	30-200 µm	1-100 nm	Capsule permeability <1 µm	>500 µm
Materials used	Hydrogels, decellularized matrix components, tissue spheroids and strands, cell pellet, and nanocomposites	Non-toxic and biodegradable nanomaterials such collagen nanofiber, carbon nanofiber, graphene, Quantum dots, gelatin-hydroxyapatite, gold nanoparticles, liposomes.	Microcapsules made of polimer (alginate), cellulose sulphate, collagen, chitosan, gelatin, and agarose	Stem cells are seeded on matrices of biological origin (matrigel, hydrogels)
Cell viability	>90%	No data available.	<50%	80-90%
Cost/ease of operation	Low/medium	High/medium	Mediumlow	Low/medium
Implemantation potential/ applicable	High	Medium	High	Medium
Selected disadvantages	Functionalization is the core factor of 3D bioprinting. Bioinks need to possess good biocompatibility and mechanical property	High concentrations of reagents may cause artifacts. Barriers to clinical implementation of nanoparticles	Inflammatory response, and consequently, to rejection of the transplant	Heterogeneity of cultured organoids. Potential tumorigenicity of using matrix gel in organoid culture. Organoid cultivation is time- and labor-intensive
Future perspective	Future bioprinters could be made clinician-friendly, easy to use and maintain, and customized for specific types of tissues	Personalized immunosuppressive regimens to avoid graft rejection. Cell-specific drug targeting in therapy diseases	Cell encapsulation could the former allows a sustained and controlled delivery of therapeutic molecules that prevent immune response while permitting easy in vivo transplantation	Good preclinical model for human disease research and drug development – personalized medicine

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heart failure is transplantation. 3D bioprinting technology is a promising alternative, enabling avoidance of the problem of donor shortage and transplant rejection. Cardiac extrusion bioprinting is the most commonly used method to create three-dimensional structures of blood vessels and muscle tissue. Bioinks under development are mainly based on gelatin methacrylate, gelatin, and alginate. The source of cells is primarily human umbilical vein endothelial cells (HUVEC), vascular smooth muscle cells, blood vessels, fibroblasts, cardiomyocytes, and in recent years, more and more often, also mesenchymal stem cells (MSCs), human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs), and human-induced pluripotent stem cell-derived endothelial cells (hiPSC-ECs). One of the biggest challenges in creating complex, three-dimensional organs, such as the heart, suitable for transplantation is ensuring proper vascularization [37]. For the first time, the vascularized heart was printed using a 3D bioprinter by scientists from the University of Tel Aviv in 2019, but it was not fully functional [38].

Bioprinting in Otology

American 3DBio Therapeutics started a clinical trial on August 9, 2021, whose aim was to assess the safety and effectiveness of the implant AuriNovo™ for ear reconstruction in 11 patients with unilateral grade microtia II-IV (congenital disability consisting of partial absence of auricles). The exact details of the procedure generation of this implant are unknown, and the estimated end date of the study is September 2029 [39,40].

Prospects for using 3D bioprinting technology in regenerative medicine are broad, and it presents a potential breakthrough for transplantology. However, scientists still encounter numerous challenges in finding practical solutions. Key obstacles include the search for new sources of biomaterials, optimization of the bioprinting process to make it less harmful to cells (without negatively affecting their lifespan), the production of bioprinters with enhanced resolution and speed, and the development of a method for replicating a natural vascular system in bioprinted constructs. It is worth noting that the advancement of 3D bioprinting technology also raises specific bioethical and legal concerns [41].

Nanotechnology in Transplantology

Nanotechnology involves the development of materials called nanoparticles (NPs), which are defined to range from 1 to 100 nm in at least 1 dimension. The major classes of NPs under clinical study include natural/organic materials (eg, liposomes, polymers, proteins) or inorganic materials (eg, gold, iron oxide, quantum dots) [42]. Combining nanotechnology and transplantology sets a new direction in transplantation medicine in creating artificial organs. The role of nanotechnology is primarily the creation of new immunosuppressive drugs and optimization of the pharmacokinetics of existing drugs, improving tissue protection and organs intended for transplantation, and supporting the generation of artificial organs [43].

Nanotechnology in Immunosuppression

Currently, there are numerous strategies for targeted and controlled drug delivery nanotechnology-based immunosuppressants that may contribute to minimizing the adverse effects of these drugs and increasing their therapeutic potential. In 2018 Bahmani et al developed a PLGA-based nanoparticle (poly(lactic-co-glycolic acid)), a copolymer of lactic and glycolic acid as an anti-CD3 monoclonal antibody carrier (drug immunosuppressive). They covered it with mAb MECA79, which recognizes peripheral node addressin (PNAd) to increase its accumulation in lymph nodes (MECA79-anti-CD3-NP). Scientists have investigated the effectiveness of the synthesized nanoparticle in suppressing cardiac allograft rejection using a mouse model [44].

To reduce the dose of immunosuppressive drugs, minimize toxicity and adverse effects, and improve the effectiveness of treatment, it is important to control the release of a given drug. This effect can be achieved by the application of implantable devices equipped with nanochannel membranes, enabling drug delivery within a specific therapeutic range and according to zero kinetics order (only then is it possible to achieve a constant drug concentration in the body for a longer time) [45]. In 2019 Trani et al developed a subcutaneous implantation method using a remote-controlled drug-release device. Using standard techniques for producing silicon semiconductors, they have created a nanofluid membrane, on whose surface there are 2 platinum electrodes. Drug diffusion occurs by changing the applied electric field. This system runs on a battery, and the drug release is regulated via Bluetooth technology. Scientists verified the operation of this system based on 2 drugs – enalapril, used in treating hypertension, and methotrexate, used to treat rheumatoid inflammation joints. They confirmed its effectiveness for controlled delivery and biocompatibility in in vivo tests on rats and macaques. Further studies aim to reduce energy consumption and thus extend the "lifetime" of this device [46].

Nanotechnology in Organs Conservation

Conservation of organs (ie, ensuring appropriate conditions for their storage and continuous perfusion using appropriate equipment) is an essential stage before their transplantation. A promising research direction is combining nanotherapy with machine perfusion [43]. In 2017 Zhu et al developed micelles for encapsulating an immunosuppressive drug – rapamycin – that was followed by its modification with cyclic moieties arginine-glycine-aspartate (cRGD) specific for alpha V beta 3 (αVβ3)

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integrins. Scientists showed that adding TRaM (targeted rapamycin micelles) nanoparticles to the standard UW solution (University of Wisconsin solution) intended for preserving organs in cold storage helps prevent organ dysfunction in mice (trachea and aorta) and also limits the occurrence of vasculopathy, which is characteristic of chronic graft rejection [47].

Nanotechnology in Creating Artificial Organs

Currently, the most advanced work is observed in kidney engineering. Worldwide, more than 2 million people suffer from end-stage renal disease, and the only treatments available to them are transplantation (limited by the availability of donors) and long-term dialysis (associated with the occurrence of comorbidities or an increased risk of kidney cancer). A group from the University of California, San Francisco (UCSF), in collaboration with the Vanderbilt University Medical Center (VUMC), are the originators of "The Kidney Project," which aims to create a small implantable bioartificial kidney called iBAK. This device uses microelectromechanical systems technology and consists of 2 main components: a hemofilter (HemoCartridge) and a bioreactor (BioCartridge). The hemofilter is made of a silicon nanopore membrane, thanks to which filtration and removal of toxins are possible only by using the patient's blood pressure, eliminating the need for additional pumps or power supply. The bioreactor provides optimal conditions for cultivating kidney tubule cells and metabolic functions, such as vitamin D production, and can process the ultrafiltrate and concentrate it into urine. This device, implanted in the patient's body, would be anastomosed to the iliac vessels to provide blood flow and to the bladder to allow the removal of toxins from the body. The device should also contain built-in sensors to detect possible failures and monitor blood flow, urea clearance, and electrolyte balance. Animal studies have shown that both elements work together as intended, which opens the clinical trials pathway that is supposed to be finished by the end of 2030 [48-50].

Another project developed by this team is the development of the "iHemo" implantable dialysis system, which consists of a hemofilter with a silicon nanopore membrane. The system is placed in the patient's abdomen and connected to the patient's circulatory system on one end and to an external pump on the other. Preclinical animal studies have been successful. The most significant advantage of this device for patients would be the ability to perform dialysis at home without requiring frequent hospital visits, improving their comfort and quality of life [51].

Nanotechnology in Corneal Therapy

One of the applications of medical nanotechnology is corneal therapy. According to the World Health Organization, corneal diseases are the fifth-leading cause of blindness worldwide. Nanomaterials used for research on corneal keratoprosthesis include hydroxyapatite, graphene oxide, and zinc sulfide. Nanofabrication methods that have demonstrated potential in corneal tissue regeneration applications are electrospinning and 3D-bioprinting [52]. Researchers from Virginia Commonwealth University have developed dexamethasone sodium phosphate (DSP)- loaded dicarboxyl-terminated poly(lactic acid) nanoparticle (PLA DSP-NP) formulations. DSP is one of the most commonly used corticosteroids for treatment of various ocular diseases, such as ocular inflammation, non-infectious uveitis, macular edema, and corneal neovascularization. In the preclinical corneal graft rejection model, single nanoparticle dosing prevented corneal graft rejection for 6 months. By using the nanoparticles to control the release of the medicine over time, patients would require only 1 injection right after the corneal transplantation surgery, without frequent eye drops. In addition, because the medicine is released slowly and directly where it is most needed, the approach requires much lower doses than current standard eyedrop treatment while providing better efficacy and safety profiles [53].

Nanotechnology in Skin Regeneration

Nanotechnology has several uses in skin regeneration. In wound healing, there are 2 main nanomaterials: nanomaterials that exhibit intrinsic properties beneficial for wound treatment and nanomaterials employed as delivery vehicles for therapeutic agents. It was demonstrated that pure silver nanoparticles could treat inflammation through cytokine modulation and induce wound healing with decreased scar formation. Nanostructures can act as carriers for therapeutic agents [54]. In 2015 Nurhansi et al synthesized NO-releasing poly(lactic-co-glycolic acid) (PLGA)–polyethylenimine (PEI) nanoparticles for assessment of healing activity in wounds infected by methicillin-resistant *Staphylococcus aureus* (MRSA) [55]. Nanoscale delivery systems have shown several advantages for the wound-healing process, including decreased cytotoxicity of drugs, administration of poorly water-soluble drugs, enhanced skin penetration, controlled release properties, antimicrobial activity, protection of drugs against light, temperature, enzymes or pH degradation, stimulation of fibroblast proliferation, and decreased inflammation.

Perspectives in Nanotechnology

More and more scientific reports confirm the importance of conducting research on the development of nanotechnology-based solutions for overcoming current problems in transplantology. However, barriers still exist, hindering their clinical implementation. First of all, there is a lack of data on the short- and long-term toxicity of nanoparticles. Some experiments found that their accumulation in various organs, including the

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liver, lungs, spleen, and kidneys, can lead to inflammation and cell necrosis, while other studies found no toxicity at all [42]. Predicting the behavior of nanotherapeutics in vivo is difficult due to existing differences between the animal and human models that may affect their distribution, bioavailability, and targeting efficacy [42,56].

Cells Encapsulation

Encapsulation of transplanted cells is a strategy to isolate cells and protect them from the host immune response. Various biomaterials are currently being studied for cell encapsulation, the most popular of which are hydrogels. They show optimal properties for this type of application, such as high water content, softness, flexibility, porosity, and permeability [57]. This method is a promising solution to the problem of transplant rejection, reducing the need for long-term immunosuppressive therapy. Research has focused primarily on its use as an alternative to pancreatic islet transplantation in treating type 1 diabetes (T1D). This technology consists of enclosing cells inside a matrix made of a semi-permeable membrane, which allows free diffusion of nutrients, oxygen, and metabolic products while protecting cells from components of the host's immune system [58]. The increased interest in this area began with Lim's work published in 1980, on production of a hybrid artificial pancreas [59]. Lim placed pancreatic islets in a shell of sodium alginate cross-linked with calcium ions. *In vivo,* studies in diabetic rats showed that after transplantation of encapsulated cells, the glycemic level returned to normal after 4 days, and the normoglycemia was maintained for 20 days until the end of the study, while after transplantation of islets that were not encapsulated, the glycemic level also returned to normal after 4 days but then increased and reached baseline by day 10 [59].

In 2016, Song et al developed a semi-permeable silicon nanopore membrane (SNM) to encapsulate pancreatic islets. The membrane was based on microelectromechanical systems (MEMS) technology and had a pore size of 7 nm. In vitro studies showed that glucose and insulin ultimately passed through the SNM (sieving coefficient at 6 hours was 1), while transport of cytokines (TNF-α, IFN-γ, and IL-1β) was impeded (sieving coefficients at 6 hours were 0.16, 0.27, and 0.27, respectively) [60].

In 2018, Stephens et al developed a strategy for macro-encapsulation of pancreatic islets with oligomeric collagen type I. In vitro studies showed that the encapsulated islets had better viability and morphology than islets maintained in conventional suspension culture, and positive immunostaining for insulin and glucagon confirmed the preservation of their normal cytoarchitecture and functions. In vivo, studies in a mouse model showed rapid reversal of diabetes mellitus (within 24 hours) after subcutaneous islet transplantation, and normoglycemia was maintained for 14 days (immunodeficient mouse model), 90 days (syngenic mouse model), and 14 days (allogenic mouse model). Histological analyses showed no inflammation markers or foreign body reactions. Further studies are needed to optimize the subcutaneous pancreatic islet transplantation method, as its effectiveness is limited by poor oxygen pressure and inadequate vascularization in the subcutaneous space [61].

In 2020, Kogawa et al performed pancreatic islet transplantation in diabetic mice using a combination of 3 elements: microencapsulated islets, the MSC CellSaic platform, and a nylon mesh filled with a silicone plate. The CellSaic (cell- and scaffold-forming mosaic) platform is a three-dimensional structure created by combining cells with bioresorbable, recombinant protein RCP (recombinant peptide). Unlike spheroids, spaces between RCPs in this platform enable the free transport of nutrients to cells and the removal of unnecessary metabolic products, improving their viability. Mesenchymal stem cells (MSCs) show revascularization and immunomodulatory functions, and when transplanted together with pancreatic islets, they improve their functions. The islets were encapsulated with sodium alginate and coated with poly-L-lysine (PLL). A silicone plate in a nylon mesh was placed in the peritoneal cavity of the mouse, which was removed 4 weeks after the tissue reaction had subsided and blood vessels had formed. The pockets created in mice were transplanted with islets, microencapsulated islets, and microencapsulated islets, together with MSC CellSaic. The MSC CellSaic platform improved the function of microencapsulated pancreatic islets by inducing angiogenesis and inhibiting the inflammatory response [62].

However, using conventional polymer membranes for cell encapsulation has limitations, including limited cell viability, lack of support for blood vessel formation, and suboptimal pore size. The condition of cells depends on many factors, including sufficient oxygen and nutrients, the transport of which through hydrogel membranes is often ineffective. Too large a pore size prevents effective isolation of cells and protection against immune system components, leading to its activation and, consequently, to transplant rejection. Conventional polymer membranes with pores smaller than 1 μm can effectively block immune cells (≈10 μm in diameter). However, retaining smaller particles, such as TNF-α (3.80 nm), IFN-γ (interferon-γ; 3.67 nm), IL-1β (interleukin-1β; 3.81 nm), is impossible, negatively affecting the long-term viability and function of grafts. The solution to this problem may be using membranes with nanometer-scale pore sizes [60].

Another innovative approach with high clinical potential is the ability to implant a cell encapsulation device directly into the body. In 2020, Paez-Mayorga et al created the NICHE (neovascularized implantable cell homing and encapsulation) platform

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to encapsulate vascularized cells with local immunosuppression [63]. It was made using a 3D printing method – selective laser sintering using biocompatible polyamide PA 2200. Its dimensions are 25×14.6×5 mm. This system has 2 tanks. The central reservoir of cells is surrounded by a U-shaped drug reservoir from which the immunosuppressant is permanently released through 2 nanoporous nylon membranes. These membranes are attached with a silicone adhesive, and the silicone plugs serve as venting and charging ports for transdermal drug replenishment. Nylon nets surround the cell reservoir – the inner net provides mechanical support, while the outer net allows penetration of blood vessels and retention of immune cells. Nylon was chosen because it is an SLS-compatible biomaterial. It also has high tensile strength and flexibility and is readily commercially available, facilitating reproducible system development. This platform integrates in situ vascularization along with local immunosuppression. To create a vascularized environment, in the first step, NICHE is loaded with a hydrogel containing MSCs and implanted subcutaneously. MSCs secrete angiogenic factors that enable blood vessel formation and modulate the microenvironment to mitigate the immune response. This study demonstrated that the platform was biocompatible and mechanically stable. In an in vivo histological analysis in a rat model, the biointegration of NICHE with the subcutaneous tissue and visible blood vessels was observed after 6 weeks.

Interestingly, allogeneic subcutaneous Leydig cell transplantation was performed in immunocompetent rats, and the drug reservoir was loaded with the immunosuppressive agent CTLA4Ig [63]. Placing NICHE directly under the skin allows easy access to drug reservoirs and cells for on-demand replenishment, which can be done in a minimally invasive way. Over the 31-day study period, local release of CTLA4Ig enabled the transplanted Leydig cells to be protected from destruction by the immune system and reduced systemic exposure to the drug by 12-fold, reducing its adverse effects. The limitation of this study is undoubtedly the short period of observation of the allograft in vivo. However, its results are so promising that scientists plan to develop this technology, seeing its potential, especially in the transplantation of cells sensitive to hypoxia, such as pancreatic islet cells [63].

A promising way to overcome the donor shortage may be xenotransplantation of encapsulated pancreatic islets from pigs. Pigs are a preferred source of islet cells due to the ability to obtain high numbers of islets at low cost and the lack of concerns about potential carcinogenicity (observed in the case of embryonic stem cell transplantation and induced pluripotent stem cells). However, each interspecies transplant is associated with a high risk of rejection due to the strong activation of the immune system's defense mechanisms. Therefore, encapsulating immunoisolating islets may increase this technique's therapeutic potential. In 2023, Ajima et al developed a device to encapsulate porcine pancreatic islets. The islets were encapsulated with a sodium alginate solution and then sealed in a semi-permeable cellulose acetate membrane bag. The devices were implanted into the abdominal cavity of immunocompetent diabetic mice without using any immunosuppressive agent. There was a marked and rapid reduction in blood glucose levels, good long-term glycemic control (over 1 year in some mice), and no adverse effects on cell survival.

Furthermore, the devices functioned correctly when recovered and transplanted into new immunocompetent diabetic mice. However, this study showed many limitations. First, encapsulated islets are less permeable to glucose, insulin, and oxygen than naked islet cells, which may lead to a delay in insulin response that, although not observed in mice, may occur in humans. Although immunohistochemical analysis did not reveal invasion of immune system cells, suggesting that the device was effectively isolated from immune reactions, diffusion of smaller particles such as cytokines was not investigated. In addition, the transplantation method requires refinement since intraperitoneal implantation of this type of system in humans may be associated with damage to other organs and a strong foreign body reaction [28].

Interestingly, Papas from the University of Arizona, together with other scientists (within the Juvenile Diabetes Research Foundation grant), is developing the concept of creating an implantable system called "Tea Bag" to treat type 1 diabetes. The idea is to place pancreatic islets inside a device resembling a tea bag, which would allow the free transport of insulin to the outside while protecting cells from components of the immune system. The details of this project are currently unknown. However, its perceived potential will probably lead to the start of clinical trials [29].

Organoids

Organoids are three-dimensional structures obtained in vitro that mimic some aspects of the anatomy and functional properties of tissues and organs. Currently, they are widely used primarily for disease modeling and drug testing. The possibility of their application in regenerative medicine is an attractive field for research; however, it is still in the initial development phase [64]. Two types of stem cells are used to create organoids – pluripotent stem cells (including both embryonic stem cells and induced pluripotent stem cells) and adult stem cells. These cells are cultured under appropriate conditions to maintain their ability to self-renew and differentiate. After isolation, these cells are seeded on selected matrices of biological origin, such as Matrigel or gels, based on components of the extracellular matrix (ECM) or synthetic origin (mainly hydrogels). During cultivation, it is essential to ensure appropriate

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physical conditions to effectively deliver nutrients to the cells and remove metabolism products [65], which is a significant challenge in controlling the maturation process of organoids. Organoids do not have all the cell types characteristic of a given tissue and do not reflect the complexity of native organs, often due to the lack of vascularity, innervation, microbiome, or immune system. Moreover, different types of cells have different proliferation rates and requirements for specific growth factors and even oxygen availability, making it difficult to optimize their (co-) culture protocols. Organoid culture can also lead to unpredictable cell differentiation, which means that the organoids may contain different cell types that are not specific to a given organ. The limited ability to control the heterogeneity of organoids leads to significant variability in their formation efficiency, morphology, and function. Organoid cultivation is time- and labor-intensive. Moreover, as mentioned above, research is needed on the durability of organoids and their safety and effectiveness before their potential clinical use [64,65]. Despite these challenges, organoids have great potential in transplantology and may contribute to a revolution in the treatment of diseases. The first promising applications of organoids were shown in studies involving the kidney, liver, and intestine. Specifically, organoid technology was shown to be efficient in generating a functional small intestinalized colon by replacing the native colonic epithelium with ileum-derived organoids [66], which revealed a feasible regenerative potential for short bowel syndrome treatment.

Conclusions

Undoubtedly, transplantology in its current form is in crisis. The list of patients waiting for a transplant operation is constantly growing, while the list of donors does not increase proportionally to the demand. Although the currently used immunosuppressive drugs contributed to a decrease in the rejection rate in the early period after transplantation, they did not improve patient survival and graft function in long-term follow-up. Therefore, it is necessary to develop alternative methods to replace defective organs with modern technologies, including functional transplantology, which aims to replace a defective or removed organ as a substitution that is functional, not physical. A breakthrough solution for transplantology may be the 3D bioprinting of tissues and organs. Examples of the vast clinical potential of this method are the first 3D heart created in 2019 by scientists from Tel Aviv, the clinical trials of the bioprinted AuriNovo™ implant for ear reconstruction in patients with unilateral microtia, and the successful bionic pancreas preclinical trials of Polish researchers [67].

A new direction of thinking and action in transplantation medicine may be the combination of nanotechnology and transplantology. Nanotechnology allows optimizing the pharmacokinetics of immunosuppressive drugs by modifying them with nanoparticles, which may improve long-term patient survival and transplant function. Platforms for targeted delivery of immunosuppressive drugs are being created at the nanoscale, and artificial organs are being generated, such as the bioartificial kidney, which is the subject of The Kidney Project.

Cell encapsulation is a good alternative, especially for pancreatic islet cell transplantation. An attractive approach is to create devices similar to the NICHE platform, which enable cell encapsulation and local immunosuppression when implanted into the patient's body. The use of organoids in transplantation medicine is an increasingly common research topic. Although they are still in the early stage of development, the first clinical trials, such as the transplantation of an organoid in a patient with ulcerative colitis by a team of scientists from the University of Tokyo, show their significant clinical potential.

All the solutions mentioned above have limitations and still pose many challenges for scientists and clinicians to overcome. However, it seems that the development of these study areas may soon change modern transplantology and give a chance for a "new life" helping patients whose diseases have been incurable so far or who would be on the waiting list for many years, often not having undergone transplantation.

All the technologies currently studied or developed may show some limitations, and there may be no universal solution. Their efficacy may depend on the characteristics of a person, the type of organ being transplanted/injured, comorbidity, immunology, severity of adverse effects, and much more. It seems that bioengineering and biotechnology could solve these problems, but even in the case of the most modern technologies like CRISPR, it eventually appears that there are some nonspecific and random effects, which may limit the use of such an approach. However, as these technologies are being improved, it is possible that the use of autologous organs, modified to resist underlying disease, could avert the need for lifelong immunosuppression. However, these technologies are still expensive, and adjusting an organ on demand takes money and time. The creation of a bank of spare parts or body parts on demand is intriguing, but at present it seems a very futuristic vision.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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