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PROSPECTS FOR THE USE OF 3D BIOPRINTING TECHNOLOGIES FOR REGENERATIVE THERAPY OF SKIN DAMAGE

Anastasiia Baranovska[1]
nasty.bar23@gmail.com
Tetiana Lutsenko[1,2]:
lutsenko.tetiana@lll.kpi.ua
1 National Technical University of Ukraine
"Igor Sikorsky Kyiv Polytechnic Institute", Kyiv, Ukraine
2 LLC "PRO-PHARMA UNIVERSAL AGENCY", Kyiv, Ukraine
Corresponding author's e-mail

Abstract. *Until recently, rapid tissue regeneration, replacement of damaged organs, and restoration of their functions were the dreams of doctors and patients. The advent of tissue engineering and regenerative medicine makes this possible. The main tasks of tissue engineering are the combination of cells in nutrient scaffolds to create components for the restoration of damaged edges and tissues. Regenerative medicine, in turn, combines tissue engineering techniques and various strategies, such as gene therapy, immunomodulation, tissue therapy to implement functional restoration, reconstruction of tissues and organs. The shortage of organs and tissues for transplantation is a global problem [1]. In addition to the long wait for donor organs, the results of transplantation are unpredictable, as a large proportion of operations end in failure, either immediately or within 10 years after transplantation, in addition, the recipient becomes obliged to take immunosuppressive drugs for life, which increase the risk of infection. The development of automation technologies and the creation of new biomaterials has accelerated research into the production of preclinical models and bioartificial organs. One of such automated technologies is 3D printing, which has been widely developed over the last dozen or so years and has not lost the interest of scientists due to its simplicity and the ability to create complex structures using a wide range of biomaterials. In the field of transplantology, there is a need not only to develop new strategies for restoring the functioning of internal organs, but also to develop methods for obtaining skin protection, because in the world there are millions of people suffering from chronic skin diseases or suffering from skin lesions as a result of injuries or burns*
Keywords: *3D bioprinting, skin diseases, biomaterials, bioartificial organs, transplantology.*

I. INTRODUCTION

The field of bioprinting has made significant progress over the past decade, with many innovations making 3D bioprinting one of the most exciting and promising technologies with the potential to impact a wide range of medical applications. Scientists, using bioprinting technology, will be able to print living organs de novo, such as heart, liver, kidney, lung and skin, thus reducing the shortage of transplantable organs [1]. At the same time, cells, that are obtained from patients, will ensure that immune system attacks and organ rejection cases are eliminated. Another exciting industrial application for 3D bioprinting is in the pharmaceutical industry. Similar to in vitro, in vivo models can be printed using human cells, and living organs or organ systems can be created and used for preclinical drug testing as alternatives to animal organs [2].

II. THE AIM OF THE STUDY

The purpose of this study is to analyze literature data on the potential of using 3D printing technology to produce materials for the regenerative treatment of skin lesions.

III. METHODS

An analytical review of literature data was carried out using the analysis of information

from the databases of PubMed, Web of Science and Scopus, Google Scholar and the Cochrane Central Register of Controlled Trials (CENTRAL) and other sources up to and including 2023, using the keywords: "3D bioprinting", "skin diseases". ", "biomaterials", "bioartificial organs", "transplantology".

IV. BIOPRINTING AND ITS APPLICATION IN REGENERATIVE MEDICINE

3D printing technology uses computer-aided design (CAD) to sequentially combine layers of two-dimensional medical images, such as CT scans, MRIs and others, into three-dimensional models. These models are stored as digital files and can be printed into physical 3D structures. 3D printing technology is widely used in various fields of medicine for surgical planning, educational modeling, manufacturing implantable medical devices, and tissue and organ regeneration [3, 4].

It is important to clearly distinguish between 3D printing and 3D bioprinting as the two are used interchangeably in the scientific community. Both processes involve creating a 3D object layer by layer using a 3D model. However, 3D bioprinting uses cellular bioinks and other biological products to form living tissue, while 3D printing technologies do not use any of that. It is important not to confuse 3D printing of porous polymer scaffolds for cell seeding with bioprinting of cellular bioink [5].

Conventional 3D printing and additive manufacturing methods are used to create cell-free scaffolds for subsequent implantation in surgery. Many traditional 3D printing processes, such as selective laser sintering (SLS), stereolithography (SLA), and fused deposition modeling (FDM), are also actively used in tissue engineering and regenerative medicine. These traditional methods create solid scaffolds using thermoplastics or resins as biomaterials. These systems can polymerize a liquid resin, heat a filament as it passes through a nozzle, or sinter the material in powder form.

The basic principle of traditional tissue engineering is stated as follows: isolated cells are attached to pre-formed solid scaffolds, which are then placed in a bioreactor and implanted in patients.

3D printing technology can meet the requirements for hollow organs, but there are some limitations, such as uneven seeding of cells in the structure, the location of different types of cells in certain places, that prevent the reproduction of complex 3D organs. Uneven distribution of cells in the scaffold can lead to incomplete or ineffective healing. High temperatures and the use of toxic solvents can affect cell survival rate. Increased period for cell proliferation can also slow down the treatment process. Thus, the improvement of existing 3D technologies for tissue engineering leads to the emergence of more efficient 3D bioprinting methods [6]. The development of 3D bioprinting means a shift from the traditional process of creating 3D printed scaffolds and then seeding them with cells to simultaneously create a 3D bioprinted matrix and seed cells [3].

In recent years, a number of new advances have been made in the field of bioprinting, with various types of tissue being printed and tested. The human body is composed of multiple organ systems that interact to ensure homeostasis and normal functioning of the organism. Each organ system comprises of different organs, tissues and anatomical structures aimed at performing a specific function. The human body has eleven systems, including skeletal, muscular, nervous, lymphatic, endocrine, reproductive, cutaneous, respiratory, digestive, urinary and circulatory systems. Let's consider the latest advances in 3D bioprinting in some of these areas of application [5].

- Skeletal system. There is an extremely high demand for functional bone grafts, with more than two million patients around the globe undergoing bone defect repair operations annually, around 500,000 of which are performed in the United States [7]. Therefore, bioprinting of skeletal tissues such as bone and cartilage is one of the major areas of interest in the field of tissue engineering and regenerative medicine.

Nowadays, one of the most effective strategies for facilitating osseointegration is the method for hard tissue replacement with multifunctional implants.

3D printed metals, due to their bioinert properties, usually require bioactive surface modifications after printing, regardless of the type of implant. Physicochemical modification methods, such as changing the surface roughness, wettability and hardness, are used to improve properties of metals. Additionally, biocompatible coatings (e.g., polymer coating) on metal implants can promote biomimetic cellular responses (adhesion, proliferation, differentiation) after implantation. Unlike bioinert metals, ceramics have a high osteogenic capacity. Functional strategies for 3D-printed ceramic implants focus on the development of biomimetic structures and the implementation of various functions (photothermal, osteogenic, antibacterial), which together enhance the effectiveness of bone regeneration. The properties of polymers depend on the structure of their monomers, so polymer implants are often chemically modified to improve osteogenesis. Given the various advantages of polymers, the use of synthetic and natural polymers in combination with 3D printing can be a powerful method for the manufacturing of multifunctional implants for hard tissue replacement [8].

• Vascular system. Tissue engineering techniques were a success for creating functional thin skin grafts. However, organs with a high metabolic rate, such as the liver, heart and kidneys, that are produced using tissue engineering, are unable to carry out adequate oxygen and nutrient exchange. The absence of biologically functional capillary networks in thick tissues (≥ 200 μm thick) undoubtedly limits the development of tissue engineering in the field of organ regeneration and transplantation. The way for combining microvascular networks with thick tissues is a hot topic and direction for future development [9].

Cardiovascular disease is the most common cause of death worldwide. The annual number of deaths is expected to reach 23.3 million by 2030 [10].

Transplantation is currently the only effective treatment for terminal heart failure. Thus, 3D stem cell bioprinting approaches can help to achieve the necessary results in regenerative medicine, for the modelling and treatment of heart disease and heart failure, as well as in toxicological studies and personalised drug testing [11].

Separate processing methods were used to create blood vessels in the past, However, the vessels produced by these processes could not accurately reproduce the complex structure and functions of natural small-caliber blood vessels. Conventional 3D bioprinting technology has a limitation in resolution of several tens of microns. This prevents the effective creation of a nanoscale structure of the extracellular matrix (ECM), which makes it difficult to reproduce the microenvironment for blood vessel cells [12].

A team of researchers from the University of Edinburgh has developed a hybrid device that combines bioprinting and electrospinning. This device, equipped with a bioprinting head and two electrospinning heads, can be used to create tubular structures made of electrospin nanofibers and layered hydrogel structures. These structures not only improve the mechanical properties of the hydrogel effectively, but also mimic the two-layer structure of natural blood vessels. Using the electrospinning method to create a framework for the inner layer of blood vessels helps endothelial cells to adhere to and proliferate in it [13].

In another study, Hassan and colleagues developed a new method to use gelatin hydrogel to create multilayered blood vessels on a microfluidic device. The researchers successfully reproduced the physical structure of blood vessels while ensuring the correct placement and growth of endothelial cells in the vessel walls during the three to five days of maturation [13].

Bertassoni and his colleagues also succeeded in using agarose in a cross-linked hydrogel to create a printed blood vessel that was cultured with endothelial cells in vitro [14].

• Covering system. A variety of severe skin injuries have traditionally been treated with grafts obtained from donors or the patient's own body. Innovative 3D bioprinting technology makes it possible to quickly and efficiently create skin grafts for patients in less time and at lower cost.

There are two different approaches to skin bioprinting: in situ bioprinting and in vitro bioprinting. Apart from pressure points and organizational maturity, the two approaches are similar. *In situ* bioprinting involves the direct printing of pre-cultured cells at the site of injury to heal the wound, allowing the tissue to mature at the site of injury. Using *in situ* bioprinting for burn wound repair has several advantages, including precise placement of cells within the wound, avoidance of expensive and time-consuming *in vitro* differentiation, and elimination of multiple surgical procedures. During *in vitro* bioprinting, produced skin matures in a bioreactor, which is transplanted to the wound site afterwards [15, 16].

Fibroblasts are widely used to create 3D bioprinted skin structures. These cells are essential for skin formation and wound healing. The extracellular matrix (ECM) is formed in the presence of appropriate stimuli such as transforming growth factor beta β-1, platelet-derived growth factor, and insulin-like growth factor (IGF-1). In most studies, two types of bioink is used for skin printing: keratinocytes (keratinocytes of the human epidermis) alone or keratinocytes and fibroblasts. Human dermal fibroblasts are most rapidly used in bioprinting [17].

Currently, interest in the use of 3D printing technology with stem cell research continues to grow. According to reports, bone marrow stem cells, embryonic stem cells and adipose tissue stem cells demonstrate "bioink" properties, working as "bioink" directly on substrates, including skin regeneration. Stem cells have the potential for multilineage differentiation and self-renewal, which allows them to form accessory skin structures such as hair follicles and sweat glands. The applications of stem cells also includes regeneration of skin tissue with the formation of a vascular network, creation of cells and cell and tissue biology research [18].

Insufficient concentrations of nutrients and oxygen in transplanted skin are often a critical limitation for the clinical implementation of bioprinting-based wound care. In their work, Xiaocheng Wang and colleagues used a single-celled microalgae (Chlorella pyrenoidosa), which performs oxygen photosynthesis, as a component of bioink to promote sustained oxygen production under light conditions. The encapsulated live microalgae in the created scaffolds effectively and controllably provided oxygenation, which supported the processes of proliferation, migration and differentiation [19].

V. BIOINKS AND REQUIREMENTS FOR THEIR COMPONENTS

Bioprinting is an innovative approach that ensures high accuracy and reproducibility in the manufacturing of structures in an automated manner, opening up the potential for high-throughput production. Bioprinting uses a solution of a biomaterial or a combination of several biomaterials in the form of a hydrogel to create a tissue structure. This hydrogel is used to encapsulate the desired cells, which are called bioink. After bioprinting, the structure derived from the bioink can be fixed or stabilised, giving the structure its final shape. Bioinks can be created from natural or synthetic biomaterials, either on their own or in combination with each other hybrid materials. In some cases, cellular aggregates can be used for bioprinting processes without additional biomaterials [20, 21].

Bioink for bioprinting can be made from natural or synthetic biomaterials. The main advantage of natural materials for bioprinting, such as collagen, gelatin, chitosan, alginate, fibrin, hyaluronic acid, is their bioactivity, which is usually manifested in high similarity to the extracellular matrix and excellent biocompatibility. However, natural biomaterials often show poor mechanical properties, even after crosslinking [22]. Synthetic materials, such as PCL, PLA, PEG, PEEK, Pluronic, have better mechanical properties because they can be tailored to specific physical characteristics and have greater homogeneity compared to natural materials. However, the use of synthetic materials for 3D bioprinting is associated with problems such as poor biocompatibility, toxic products of material degradation, and lack of bioactive ligands [23]. That is why the use of single-component bioinks (either natural or synthetic) is very limited. Such bioinks do not have the necessary biochemical and biophysical

characteristics similar to natural tissues, and therefore do not have high print quality [24, 25].

Multicomponent bioinks are used to overcome the limitations of using single-component bioinks for printing. The introduction of additional components leads to both an improvement in biofunctionality and an increase in the mechanical stability of the resulting bioink, which contributes to the preservation of its shape [26].

Every created bioink must meet a number of requirements. They must be adapted to specific bioprinting technologies to create living structures with appropriate biological and mechanical characteristics. Key properties of ideal bioink may include:

- printability, i.e. fluidity or deformability with precise control in three dimensions;
- biocompatibility to create an environment that is not cytotoxic to cells, ensuring that cellular functions are maintained after printing;
- biomimicry, which is based on understanding the composition of endogenous material to develop the desired structural and functional properties;
- mechanical integrity and stability to maintain shape and biocompatibility with cells;
- biodegradability, which corresponds to the rate of decomposition of the cells of their own extracellular matrix.

The development of ideal bioinks often requires compromise solutions, as it is difficult to create a material that includes all listed properties [27, 28].

The ability to apply or form stable and viable volumes of material using bioink printing is key to the manufacturing process. In order to attain the best outcomes, a comprehensive comprehension of bioprinting characteristics is essential, along with the optimization of its properties, such as controlling viscosity and ensuring shear thinning of the bioink. It is important that the bioink remains stable and holds the desired shape and architecture after printing according to the model design. Irrespective of whether physical or chemical crosslinking techniques are employed, the structure should be suitable for living functional cells and capable of sustaining the cell culture lifespan or an in vivo biological setting. Extensive research has been conducted on the influence of bioink viscosity in 3D bioprinting, revealing it to be a crucial parameter in the formulation of bioprinting strategies.

Bioinks commonly used in bioprinting often include basic hydrogels, a decellularized matrix element, microcarriers, tissue spheroids, filaments, cell pellets, and/or more sophisticated options like multi-material bioinks, interpenetrating network (IPN) bioinks, nanocomposite bioinks, and supramolecular bioinks. Hydrogels are the most prominent class of materials for bioink due to their ability to provide a viable environment for cell attachment, growth and proliferation [29]. Natural hydrogels are more biologically active, but their synthetic counterparts are generally more economical and provide more stable material properties.

Nowadays, various bioink solutions have been commercialised in a variety of biomedical applications (Table 1) [29].

Table 1. **Commercial bioinks**

Product	**The company produces**	**Materials**	**Advantages**
CELLINK A CELLINK A-RGD	CELLINK, Gothenburg, Sweden	Alginate peptide L-arginine-glycine-L-aspartic acid	Cartligae, bone and mesenchymal stem cells, can be used for drug delivery and cell differentiation
PhotoHA®. Lifeink® 200 collagen	Advanced BioMatrix, Carlsbad, California	Methacrylated hyaluronic acid Type I collagen	Used in cartilage tissue applications Excellent cytocompatibility, supports cellular remodelling, high biomimetics

Synthetic peptide hydrogel bioink functionalised with fibronectin	Regemat 3D, Granada, Spain	fibronectin	Form a nanofibrous network that mimics the extracellular matrix, adjustable mechanical and chemical properties
3D bioplotter HT PCL	EnvisionTEC, Gladeck, Germany	Polycaprolactone	Versatile thermoplastic, bone and cartilage regeneration, biodegradable, excellent mechanical stability, allows for controlled drug release
GelMA Bio Conductink GelMA A	CELLINK, Gothenburg, Sweden	Gelatin methacrylate GelMA and carbon nanotubes Gelatin methacrylate and alginate	Created for nerve, heart, and muscle cells, enhances electrical potential through photo crosslinking

VI. USE OF 3D BIOPRINTING TECHNOLOGY FOR THE PRODUCTION OF SKIN MEDICAL DEVICES

Severe skin injuries, including severe mechanical trauma, unavoidable surgical procedures or extensive burns, can be life-threatening due to the potential for hemorrhagic shock, severe fluid loss and multiple infections. Regeneration of soft tissues is the main defence of the human body against adverse environmental conditions when skin injury occurs, but this process is always time-consuming and complex [30]. Recently, 3D bioprinting technology has attracted considerable attention as a new area of research in medicine. The diverse uses of this technology in creating structures that imitate natural tissues or serve as substrates for biosensors hold great potential for advancing the treatment of different diseases, such as skin burns and persistent wounds, promising a positive outlook for the future.

The advantage of bioprinting technology is a precise deposition of cells and biomaterials in 3D orientation. Clinical application of this approach for manufacturing appropriate wound dressings promises a favourable alternative to skin regeneration for large defects compared conventional approaches [31].

Instances of employing 3D bioprinting in the production of skin products include the research of Visscher D.O. and colleagues, who developed customised neck splints made on a 3D printer for the treatment of post-burn wounds on the neck and demonstrated successful clinical results in improving the treatment of this area [32].

Another example of the use of 3D bioprinting is the research of Pourchet L.J. and his colleagues, who created a skin model that mimics the dermis and epidermis with its cellular, molecular and other characteristics. The bioink for this model consisted of a mixture of gelatin, alginate and fibrinogen. Each component of the bioink had a specific role in the bioprinting of the skin. Gelatin provided the appropriate rheology during the extrusion process, strength during printing on the cooled substrate, and solubility for dissolving in subsequent steps. The alginate gave the structure rigidity and stability by forming a calcium-based hydrogel. The fibrinogen, in turn, promoted cell maturation and provided structural stability by crosslinking with the alginate. The presented bioprinting process is the first report abandoning pre-printing scaffolds, allowing the creation of full-thickness skin constructed from primary human skin cells. The skin was printed in the form of a viable 5 mm thick dermis in a matter of minutes, and this is the main advantage of the method. The presented model can be expanded to include other types of skin cells, such as endothelial cells, adipocytes and melanocytes, in order to reproduce more complex skin functions within the bioprinted skin model [33].

There are a huge number of wound dressing materials that are currently being studied for using in different treatment approaches on types of wounds. The selection of dressing depends on crucial factors such as the type, depth, and location of the wound, along with considerations of the injury's extent, the quantity of wound exudate, and the presence of infection at the wound site. Traditional dressings such as cotton bandages or gauze are ineffective as they absorb moisture from the wound, which in turn leads to dehydration of its surface and, as a result, a slower healing rate. Researchers led by Andriotis E.G. and colleagues have successfully created an innovative wound dressing system utilizing polymers in the form of films, foams, or gels. This alternative dressing, based on natural and non-toxic materials like pectin, honey, and propolis, ensures optimal conditions for wound healing. The dressing maintains moisture at the wound site, offers relief to patients, and provides an occlusive environment to protect against infections and contaminants. Pectin, a key component, acts as a hydrophilic agent, forming a soft gel on the wound bed when it reacts with wound fluid. This gel aids in the removal or control of exudate, and the resulting pectin solution's acidity enhances the system's barrier properties against bacteria or viruses. Honey has several bioactive properties related to the wound healing process and shows broad-spectrum antibacterial effects with varying. Propolis is generally studied for its antiseptic, antibacterial, antifungal, astringent, antispasmodic, anti-inflammatory, anesthetic, antioxidant, antifungal, antiulcer, antitumour and immunomodulatory effects. The effectiveness of propolis in expediting the recovery of damaged tissue has been validated, indicating a potential connection between flavonoid compounds' ability to diminish lipid peroxidation and the prevention of cell necrosis. A study conducted ex vivo demonstrated robust wound healing capabilities when 5% propolis complexes were added, revealing accelerated cell migration inhibition and healing with higher concentrations. Comparable outcomes were observed with 3D-printed propolis-alginate scaffolds, exhibiting potent antimicrobial activity against *Escherichia coli, Staphylococcus aureus,* and *Candida albicans* strains [34].

Today, wound dressings are the gold standard for the treatment of severe skin injuries, as they protect the wound from the external environment, while providing the necessary moisture level and accelerating the healing process. The incorporation of medications, including pain relievers and non-steroidal anti-inflammatory drugs, contributes to pain reduction and consequently enhances the quality of patient care [35].

A work by Jingjunjiao Long and colleagues is an example, where a wound dressing made of a biopolymer chitosan-pectin hydrogel for the delivery of lidocaine was investigated. For this purpose, hydrogels were obtained by physically crosslinking polysaccharides. Scaffolds were created through 3D printing using an extrusion-based printer equipped with a mechanical positive displacement dispensing system, followed by lyophilization. The hydrogels produced through this 3D printing process exhibited excellent printability, maintained dimensional integrity, and demonstrated self-adhesion to the skin. The incorporation of lidocaine into the hydrogel did not compromise its functional stability. In vitro drug release studies conducted over a 6-hour period consistently aligned with the Korsmeyer-Peppas model. This research illustrates the feasibility of utilizing a 3D printed hydrogel as a promising option for wound dressings [36].

Another exciting approach to wound healing is the use of self-healing hydrogels, consisting of natural monomers or amino acid derivatives that are linked by amide bonds with a stable secondary structure similar to natural proteins. These materials are non-toxic, biodegradable, hydrophilic, and have low immunogenicity, while being prone to non-covalent interactions [37].

The increasing occurrence of wound infections resulting from antibiotic-resistant bacteria poses a significant challenge for contemporary medicine. In response to this challenge, a solution has been devised by integrating antimicrobial metals like zinc, copper, and silver into a polymer known as

polycaprolactone (PCL), thereby creating filaments suitable for 3D printing. The metals have been shown to help fighting infections, inhibit the development of bacteria and thus prevent them from developing resistance. Mouwaffaq and others incorporated metals into extruded polycaprolactone (PCL) filaments, which were then used to print wound dressings. The filaments, consisting of Ag, Cu and Zn at concentrations ranging from 10 to 25%, were processed using fused deposition modelling to produce dressings in the shape of the scanned nose and ear. The findings unequivocally indicate the efficacy of hot melt extrusion as an innovative approach for incorporating antimicrobial elements such as Ag, Cu, and Zn into polycaprolactone filaments, facilitating the 3D printing of individualized wound dressings. The 3D printed dressings exhibit distinct advantages over traditional flat dressings in terms of anatomical conformity and antibacterial characteristics, making them suitable for promoting wound healing [38].

Diabetic foot ulcers represent a prevalent and serious complication of diabetes, exhibiting distinct pathophysiological characteristics compared to other chronic wounds due to their association with a metabolic disorder. A key distinction lies in the elevated glucose microenvironment, a consequence of hyperglycemia, a hallmark of diabetes. Research demonstrates a positive correlation between glucose levels in the skin tissue microenvironment and the plasma glucose levels in diabetic individuals. This heightened glucose microenvironment poses a significant impediment to effective wound healing across various stages, resulting in unfavorable outcomes for patients.

The impact of elevated glucose levels extends to the physiological activity of diverse skin cell types, including keratinocytes, fibroblasts, macrophages, and endothelial cells. This interference leads to delayed or non-healing wounds. Current treatments often involve human skin substitutes cultivated by culturing keratinocytes and fibroblasts on biocompatible scaffolds. However, diabetic wounds exhibit reduced pro-angiogenic signals, preventing simplified scaffolds from vascularizing or integrating with host tissue. Consequently, transplanted cells face challenges in long-term survival.

In efforts to enhance vascularization and tissue integration, 3D bioprinted skin substitutes have been developed. These substitutes feature layers of neonatal human dermal fibroblasts and epidermal keratinocytes, along with human dermal microvascular endothelial cells (ECs) embedded in a fibrin-collagen bioink [39].

In another study, a team of scientists produced an antibiotic-coated scaffold model using extrusion-based bioprinting technologies to treat diabetic foot ulcers. The bioink used was a pre-made polycaprolactone powder manufactured by Ingevity (South Carolina, USA), which was mixed with the antibiotic levofloxacin (LFX) in different concentrations (0.5, 1, 1.5, 2, 2.5, 3 %). This broad-spectrum fluoroquinolone antibiotic is employed for the treatment of various ailments, such as urinary tract infections, eye infections, and skin infections. In previous studies, LFX led to successful wound healing results in case of diabetes. It was formed in a nanoemulsion gel for topical use that provided infection control, reduced inflammation and promoted wound healing. After conducting a large number of tests on the printed scaffolds, it was found that 3D bioprinted ones promote the gradual release of the antibiotic and therefore promote wound healing [40].

A significant amount of research has been directed towards the treatment of wounds and diabetic ulcers, with a specific emphasis on utilizing autologous platelet-rich plasma (PRP). This approach is known for accelerating the healing process swiftly and without triggering immunological rejection. However, PRP gel still has its disadvantages, such as the rapid release of growth factors (GFs) and the need for frequent injections, which leads to reduced wound healing efficacy, higher cost, and greater discomfort for patients. Qiwei Huang and his team of researchers have developed a PRP-loaded bioactive multilayer hydrogel-based. The resulting hydrogels showed excellent water absorption and water retention capacity, good biocompatibility, and broad-spectrum antibacterial action. Compared to clinical PRP gel, these bioactive fibrous

hydrogels demonstrated prolonged release of growth factors, reduced frequency of injections by 33%, and more prominent therapeutic effects, such as effective reduction of inflammation, in addition to promoting granulation tissue growth and angiogenesis [41].

Scientists are actively incorporating stem cells into the treatment of ulcers and wounds, as stem cell-based therapies show great promise in the field of regenerative medicine. These therapies work by promoting angiogenesis, alleviating neuroischemia and inflammation, and facilitating collagen deposition. Composite hydrogels are emerging as promising materials for tissue engineering due to their ability to impart specific properties, such as size, shape, surface activity, biodegradability, and biocompatibility. By carefully adjusting these characteristics, hydrogel scaffolds can offer a precise mechanical and biological environment to support cell growth and tissue regeneration.

A recent study revealed that using rat tail collagen type I hydrogel to deliver mouse BMSCs and adipose-derived mesenchymal stem cells (ADMSCs) noticeably modulates immune and inflammatory responses at wound sites [42]. These findings underscore the potential of 3D bioprinted cellular constructs in wound healing, addressing issues like revascularization to enhance the long-term viability of on-skin constructs and skin substitutes. Nevertheless, further research and optimization are necessary. The application of 3D bioprinting to generate intricately designed cellular constructs with specific cell types at precise densities and spatial distribution is crucial for developing targeted treatments for diabetic foot ulcers and other chronic wounds.

VII. CONCLUSIONS

Nowadays, bioprinting technology is developing rapidly and has great potential to revolutionise the medical sciences, creating an invaluable basis for tissue and organ transplantation, pharmaceutical research and regenerative medicine. Due to the commercialisation of bioprinting technologies, this industry is moving forward at an ever-increasing pace.

3D bioprinting using stem cells has demonstrated significant progress in the study of many organ systems. Methods of bioprinting skin tissue using stem cells still needs improvement, including reproduction of the external characteristics of the skin, bioprinting of skin appendages such as sweat glands and hair follicles.

A review of the research described in this article shows that bioprinting is an effective approach to help create wound healing materials. Printed patches and skin equivalents can be of great help for patients with burns of varying severity and deep wounds, reducing healing time and the pain levels, as well as improving the appearance of the affected area. The process of bioprinting skin and skin-based constructs still has a lot of unresolved issues and needs to be improved, but advances in manufacturing, materials science, biology and medicine will help the industry to move forward to meet the need for rapid skin repair and wound healing.

Despite everything mentioned above, the development of high-quality bioinks and tissue manufacturing remains a challenge. Maintaining the livability of the cells contained in bioinks and protecting them from damage during printing requires new developments in bioinks, new cell sources and printing technologies.

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ORCID ID and Author Contributions

0009-0004-2292-1887 (A, B, C, D) Baranovska Anastasiia

0000-0002-6023-0428 (A, E) Tetiana Lutsenko

A - Conceptualization and design,
B- Data analysis,
C- Responsibility for statistical analysis,
D- article writing,
E- Critical review,
F- Final approval of the article

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ПЕРСПЕКТИВИ ВИКОРИСТАННЯ ТЕХНОЛОГІЙ 3D БІОДРУКУ ДЛЯ РЕГЕНЕРАТИВНОЇ ТЕРАПІЇ ПОШКОДЖЕНЬ ШКІРИ

***Анастасія Віталіївна Барановська*[1]**
nasty.bar23@gmail.com
***Тетяна Миколаївна Луценко*[1,2]**
lutsenko.tetiana@lll.kpi.ua
1 Національний технічний університет України
«Київський політехнічний інститут імені Ігоря Сікорського»,
м. Київ, Україна
2 ТОВ «ПРО-ФАРМА УНІВЕРСАЛЬНЕ АГЕНТСТВО»,
м. Київ, Україна

Анотація. *До недавнього часу швидка регенерація тканин, заміна пошкоджених органів і відновлення їх функцій були мріями лікарів і пацієнтів. Поява тканинної інженерії та регенеративної медицини робить це можливим. Основними завданнями тканинної інженерії є поєднання клітин у поживні каркаси для створення компонентів для відновлення пошкоджених країв і тканин. Регенеративна медицина, у свою чергу, поєднує методи тканинної інженерії та різні стратегії, такі як генна терапія, імуномодуляція, тканинна терапія для здійснення функціонального відновлення, реконструкції тканин і органів. Дефіцит органів і тканин для трансплантації є глобальною проблемою [1]. Крім тривалого очікування донорських органів, результати трансплантації непередбачувані, оскільки велика частина операцій закінчується невдачею відразу або протягом 10 років після трансплантації, крім того, реципієнт змушений довічно приймати імунодепресанти, які підвищують ризик інфікування. Розвиток технологій автоматизації та створення нових біоматеріалів прискорив дослідження виробництва доклінічних моделей та біоштучних органів. 3D-друк є однією з таких автоматизованих технологій, яка отримала широкий розвиток протягом останніх десятків років і не втратила інтересу вчених завдяки своїй простоті та можливості створювати складні конструкції з використанням широкого спектру біоматеріалів. У сфері трансплантології існує потреба не тільки в розробці нових стратегій відновлення функціонування внутрішніх органів, а й у розробці методів отримання шкірних покривів, оскільки у світі мільйони людей страждають від хронічні шкірні захворювання або мають пошкодження шкіри внаслідок травм або опіків.*
Ключові слова: *3D біодрук, шкірні захворювання, біоматеріали, біоштучні органи, трансплантологія.*