Bioprinting: Paving the Way for the Future of Regenerative Medicine

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ABSTRACT

Regenerative medicine has seen significant advancements with the introduction of bioprinting technology. Bioprinting, a novel approach in regenerative medicine, involves the precise deposition of biomaterials, cells, and growth factors to create 3D structures that mimic natural tissues and organs. By integrating bioprinting into regenerative medicine, researchers and clinicians have been able to design and fabricate personalized tissues and organs for transplantation and drug testing, offering new avenues for enhanced therapies, organ transplantation, and disease modeling. Recent advancements in bioprinting have demonstrated its transformative impact on regenerative medicine, enabling the creation of complex, multi-cellular structures with precise spatial control. The versatility of bioprinting spans across precision medicine, organ-on-a-chip models, drug discovery, drug delivery, and regenerative medicine, showcasing its potential to revolutionize healthcare. As bioprinting technology continues to advance, particularly with the integration of artificial intelligence and modern biotechnology, the future of regenerative medicine holds immense promise. With the ability to manufacture complex organs on demand and redefine the landscape of healthcare, bioprinting is poised to shape the future of regenerative medicine in more ways than ever before.

Keywords: Bioprinting, Regenerative medicine, Personalized medicine

Introduction

Regenerative medicine, a cutting-edge interdisciplinary field, focuses on harnessing the body's natural ability to repair, replace, or regenerate damaged tissues and organs. It encompasses various branches of science and medicine, including stem cell research, tissue engineering, biomaterials science, and cellular therapies, all working together to revolutionize healthcare.[1–3] The ultimate goal of regenerative medicine is to restore normal function by stimulating the body's healing and growth mechanisms,[4] offering hope for patients with a wide range of conditions.

The applications of regenerative medicine are vast and continue to expand rapidly. From treating chronic diseases like diabetes[5] and heart failure[6] to repairing tissues damaged by injury or aging,[7] regenerative medicine holds immense promise. It also includes techniques for growing organs and tissues in the laboratory for transplantation,[8] leading to a potential solution for the shortage of donor organs.

Bioprinting, a novel technology in regenerative medicine, involves the precise layer-by-layer deposition of biomaterials, cells, and growth factors to create 3D structures that mimic natural tissues and organs.[9] While 3D printing emerged in the 1980s from the successful work of Hideo Kodama, followed by Chuck Hull a few years later, the 3D printed approach using biological materials perplexed scientists for years to follow.[10] 3D printing still played a role in the field of medicine even before the addition of biologics to the printed material. Replacement knees, hips, and even portions of the spine were generated using the 3D printing technique. A 3D printed spinal disc replacement used to treat degenerative disc disease can be found in Figure 1. The concept of bioprinting was first introduced in the early 2000s when Thomas Boland invented the first viable bioprinter in 2003,[11] with significant advancements in recent years enhancing its feasibility and efficacy in tissue engineering and regenerative medicine.[12] This innovative approach offers a customizable and scalable method for creating complex biological constructs with high precision.

The integration of bioprinting into regenerative medicine has propelled the field forward, enabling researchers and clinicians to design and fabricate personalized tissues and organs for transplantation and drug testing.[13] Its ability to recreate intricate tissue architectures and microenvironments has opened doors for more effective treatments and therapies across various medical disciplines. The potential applications of bioprinting extend beyond regenerative medicine, with implications for advancing drug discovery, disease modeling, and personalized medicine.

The convergence of regenerative medicine and bioprinting represents a groundbreaking shift in healthcare innovation. By combining the principles of regenerative medicine with the precision of bioprinting technology, researchers and healthcare professionals are poised to revolutionize patient care. This article will delve deeper into the recent advancements in bioprinting and its transformative impact on regenerative medicine, highlighting the potential for enhanced therapies, organ transplantation, and disease modeling.

Recent Advancements in Regenerative Medicine

In the early stages of regenerative medicine, basic technologies such as skin grafts played a crucial role in treating patients with severe burns and wounds.[14] Skin grafts involve transplanting healthy skin from one part of the body to another to aid in healing. Additionally, bone marrow transplants emerged as a breakthrough treatment for certain types of cancers, providing patients with an alternative to traditional chemotherapy.[15] Furthermore, the use of engineered cartilage implants has shown promise in repairing joint

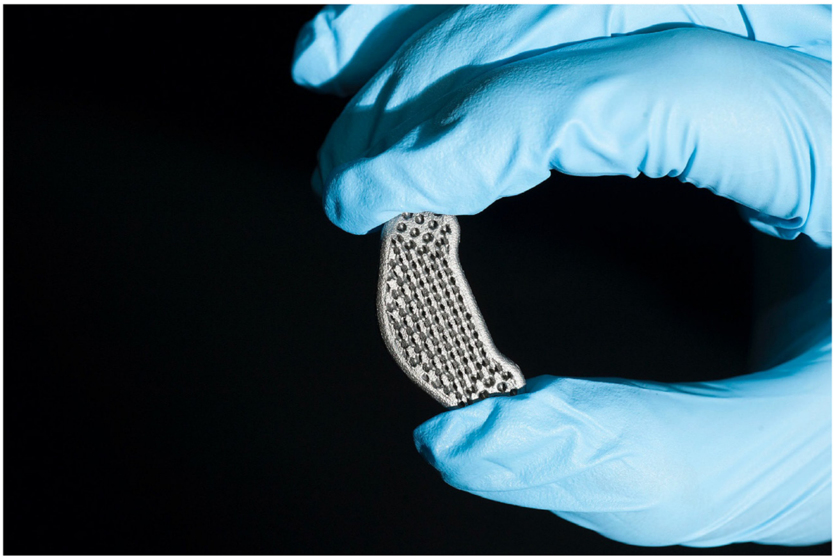

Fig 1 | 3D printed titanium spinal disc

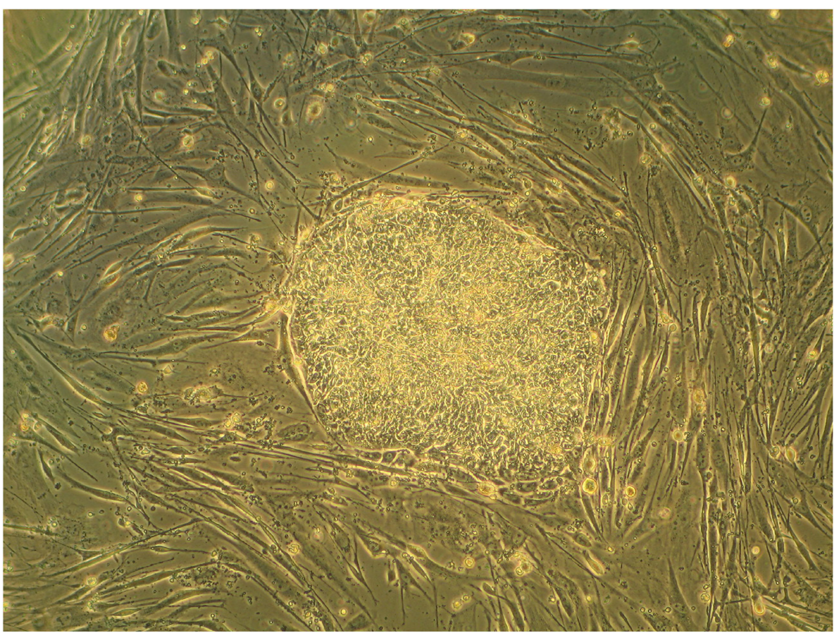

Fig 2 | Colony of human embryonic stem cells

injuries and degenerative conditions, offering patients improved mobility and quality of life.[16]

As regenerative medicine advanced, more complex models and treatments began to emerge, pushing the boundaries of traditional healthcare practices. For instance, researchers developed bioengineered blood vessels using a combination of cells and biomaterials to replace damaged or diseased vessels, presenting a new approach to vascular surgery.[17] Moreover, the establishment of induced pluripotent stem cells opened up avenues for generating patient-specific cells for personalized regenerative therapies, paving the way for tailored treatments in conditions like spinal cord injuries and neurodegenerative diseases:[18] A colony of human embryonic stem cells utilized for regenerative medicine can be found in Figure 2. The use of organoids—miniature organ models grown in the lab from patient cells—allowed for studying disease mechanisms and testing potential treatments in a more accurate and ethical manner.

Despite significant advancements in regenerative medicine, there are still gaps in therapy options that limit the field's progress in both research and clinical applications. Current challenges include the complexity of recreating functional tissues and organs, the lack of suitable cell sources for transplantation, and the inability to manufacture complex structures efficiently.[3] This has led to a growing demand for innovative technologies like bioprinting, which holds the potential to address these limitations by enabling the fabrication of precise, patient-specific tissues and organs.

The Past and Present of Bioprinting

Bioprinting, a revolutionary technology at the intersection of engineering and biology, was first conceptualized in the early 2000s, with contributions from pioneers such as Dr. Gabor Forgacs, Dr. Anthony Atala, and Dr. Thomas Boland. Dr. Thomas Boland, a chemical engineer, was credited with the first successful and viable bioprinter.[11] Dr. Forgacs, a biophysicist, and Dr. Atala, a renowned tissue engineer, played integral roles in developing the foundational principles of bioprinting, which involved the precise deposition of living cells and biomaterials to create complex tissue structures.[12] Their groundbreaking research and innovations laid the groundwork for the emergence of bioprinting as a promising tool in regenerative medicine and tissue engineering.

In its nascent stages, bioprinting relied on simple technologies such as inkjet and extrusion-based printers to deposit bioinks composed of living cells and supportive materials.[11] A picture of a 3D bioprinter can be found in Figure 3. Early applications of bioprinting focused on creating simple tissue constructs like skin and cartilage for research purposes.[12] These rudimentary bioprinting techniques represented the initial steps toward fabricating more intricate and functional tissue models, showcasing the technology's potential for advancing regenerative medicine and personalized healthcare.

Today, bioprinting has evolved significantly, incorporating cutting-edge technologies and advanced materials to enable the fabrication of complex, multi-cellular structures with precise spatial control.[12] Modern bioprinters utilize a variety of printing techniques, including laser-based, extrusion, and droplet-based methods, to create intricate tissue architectures and organ-like structures.[19] The integration of bioactive agents, growth factors, and sophisticated bioinks composed of natural and synthetic materials has further enhanced the capabilities of bioprinting, allowing for the construction of vascularized tissues, organoids, and customized implants.[20] Recent advancements in bioprinting also include the development of 4D bioprinting, which involves printing dynamic structures

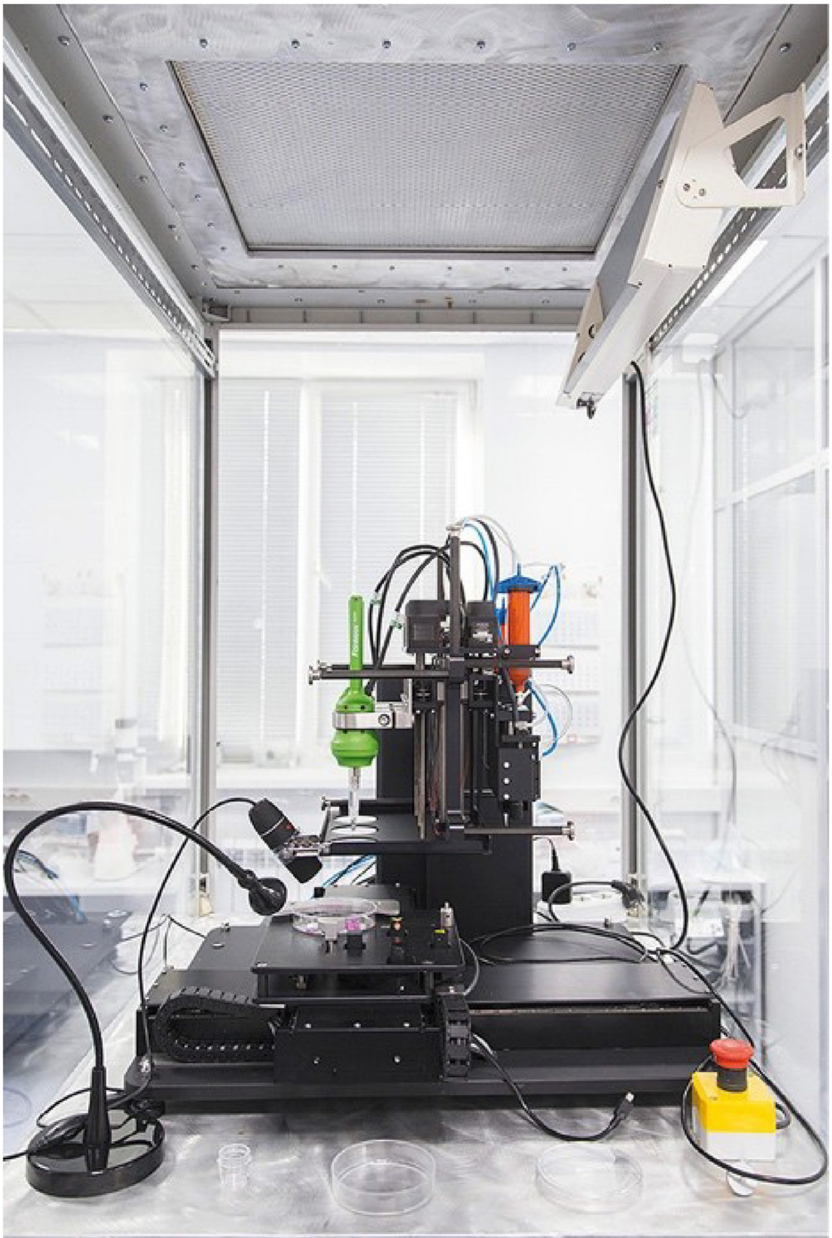

Fig 3 | 3D bioprinter

capable of self-assembly and shape transformation,[12] expanding the possibilities for tissue engineering and regenerative medicine.

Bioprinting Applications

In precision medicine, bioprinting plays a crucial role in personalized healthcare by tailoring treatments to individual patients based on their genetic makeup, lifestyle, and environment. For example, bioprinting has been utilized to create patient-specific tumor models for testing different cancer treatments, leading to more effective and targeted therapies.[21] Additionally, bioprinted skin models are used to test personalized skincare products for individuals with specific skin conditions.[22]

Organ-on-a-chip (OOC) models are microscale systems that mimic the structure and function of human organs, providing a platform for studying diseases and drug responses in a controlled environment. Bioprinting has significantly enhanced OOC technology by enabling the creation of complex biomaterials that closely mimic the extracellular matrix of cells.[23] This advancement has improved the accuracy and reliability of drug testing and disease modeling on OOC platforms, leading to more physiologically relevant results.

In the realm of early drug discovery and research of novel therapy options, bioprinting has enabled the development of pseudo-ex vivo models that closely resemble human tissues and organs. These models can be used to study the efficacy and safety of new drugs before moving on to clinical trials, ultimately speeding up the drug development process. For instance, bioprinted liver models have been instrumental in evaluating the toxicity and metabolism of potential drug candidates.[24]

Bioprinting also holds great promise in the development of personalized drug delivery systems. By creating custom-designed scaffolds and carriers, bioprinting can enhance the efficacy of drugs and facilitate their targeted delivery to specific regions of the body. Examples include bioprinted implants for controlled drug release and 3D-printed microcapsules for sustained drug delivery, minimizing side effects and improving patient outcomes.[25]

In the field of regenerative medicine, bioprinting has shown remarkable potential for tissue engineering and organ transplantation. By precisely depositing bioinks composed of living cells and biomaterials, bioprinting can create functional tissues and organs that closely resemble native structures. This technology has the potential to revolutionize regenerative therapies, offering new solutions for patients with organ failure or tissue damage. Overall, bioprinting's diverse applications in precision medicine, OOC models, drug discovery, drug delivery, and regenerative medicine highlight its transformative impact on the healthcare industry.

Challenges in the Field

Despite the significant progress made in regenerative medicine and bioprinting, there have been challenges hindering Food and Drug Administration (FDA) approval and widespread clinical translation. One key reason for the slow progress in FDA approvals for regenerative medicine is the complex nature of biologics, especially in the context of testing and approval timelines.

Biologics, which include living cells and tissues used in regenerative therapies, present unique challenges in terms of standardization, quality control, and efficacy assessment, making it difficult for regulators to establish clear guidelines for approval.[26] The variability of biologics and the lack of standardized testing protocols further complicate the approval process, contributing to delays in bringing regenerative therapies to the clinic.

While bioprinting has shown great promise in tissue engineering and organ transplantation, several limitations still exist that impede its broader adoption and clinical application. One major limitation is the challenge of vascularization, or the ability to create a functional network of blood vessels within bioprinted tissues and organs.[27]

Without proper vascularization, bioprinted constructs may struggle to survive and integrate with the host tissue. Other limitations include the limited scalability of bioprinting technologies, the need for improved bioinks with appropriate mechanical and biological properties, challenges in achieving cell viability and functionality post-printing, and the lack of long-term data on the safety and efficacy of bioprinted products.[28]

To overcome the obstacles in FDA approval for bioprinting and biologics, several key challenges must be addressed. One crucial aspect is the need for standardized testing protocols and regulatory frameworks that can accommodate the unique characteristics of biologics and bioprinted products. Collaborations between industry, academia, and regulatory agencies can help establish common standards and guidelines for evaluating the safety and efficacy of these innovative technologies. Additionally, the development of predictive preclinical models, such as OOC systems and computational modeling, may offer shortcuts to expedite the translation of bioprinting and biologics into clinical applications. By leveraging these advanced technologies and fostering interdisciplinary collaborations, the path to FDA approval for bioprinting and regenerative therapies can be accelerated, bringing us closer to realizing the full potential of these revolutionary innovations.

The Future of Regenerative Medicine

The future of regenerative medicine holds immense potential, with bioprinting at the forefront of innovative technologies driving this field forward. Bioprinting is continually advancing, and the integration of artificial intelligence (AI) and machine learning is poised to further enhance its capabilities. AI algorithms can optimize the design of bioprinted structures, improve the precision of cell placement, and predict tissue behavior, leading to more efficient and tailored tissue engineering.[29,30] For example, AI-driven bioprinting systems can adjust printing parameters in real time based on environmental conditions and cellular responses, resulting in higher-quality bioprinted constructs with improved functionality.

Recent studies in preclinical settings have showcased the versatility and efficacy of bioprinting across various applications. For instance, researchers have successfully bioprinted cardiac patches using patient-derived cells to repair damaged heart tissue, demonstrating improved cardiac function in preclinical animal models.[31] In another study, bioprinted skin grafts with integrated vasculature have shown accelerated wound healing and enhanced vascularization in preclinical models.[32] Additionally, bioprinted bone scaffolds seeded with stem cells have facilitated bone regeneration and integration in preclinical studies,[33] offering promising solutions for orthopedic applications.

In clinical settings, recent studies have highlighted the potential of bioprinting for personalized patient care and tissue replacement. One groundbreaking study involved the bioprinting of cartilage tissue for reconstructive surgeries, resulting in improved tissue integration and reduced inflammation in clinical trial participants.[34] Another clinical study focused on bioprinting corneal tissue for patients with corneal damage, leading to enhanced visual outcomes and improved overall eye health.[35] Additionally, bioprinted skin substitutes have been successfully used in clinical settings to treat burn patients, demonstrating accelerated wound healing and reduced scarring.[36]

Looking ahead, bioprinting is expected to revolutionize research and therapy options by enabling the creation of functional tissues and organs for transplantation. In the future, bioprinting may be used to replicate organs for individuals in need of organ donation, offering a solution to the shortage of donor organs.[27] With advancements in bioprinting technology, the possibility of manufacturing complex organs like kidneys, livers, and hearts on demand becomes increasingly feasible. This transformative potential of bioprinting in regenerative medicine almost seems like a scene from a science fiction movie, but with recent scientific strides and ongoing research, it is poised to become a new and promising reality that could redefine the future of healthcare.

Conclusion

The convergence of regenerative medicine and bioprinting represents a groundbreaking shift in healthcare innovation. By combining the principles of regenerative medicine with the precision of bioprinting technology, researchers and healthcare professionals are poised to revolutionize patient care. The integration of bioprinting into regenerative medicine has propelled the field forward, enabling the design and fabrication of personalized tissues and organs for transplantation and drug testing, offering new hope for patients with a wide range of conditions. While still in its early stages, the possibilities are grand with this technology, advancing a field that has seen little growth in the past but is about to change dramatically.

Recent advancements in bioprinting have showcased its transformative impact on regenerative medicine, with applications ranging from precision medicine to organ transplantation. The ability of bioprinting to create complex, multi-cellular structures with precise spatial control has revolutionized research and therapy options, paving the way for personalized healthcare and more effective treatments. As bioprinting continues to evolve and integrate with cutting-edge technologies like AI, the future of regenerative medicine holds great promise, with the potential to manufacture complex organs on demand and redefine the landscape of healthcare. The transformative potential of bioprinting in regenerative medicine is on the horizon, offering a new and promising reality that could shape the future of healthcare in profound ways.

References

1 Tatullo M, Zavan B, Piattelli A. Critical overview on regenerative medicine: new insights into the role of stem cells and innovative biomaterials. IJMS. 2023;24(9):7936.
2 Mao AS, Mooney DJ. Regenerative medicine: current therapies and future directions. Proc Natl Acad Sci USA. 2015;112(47):14452–9.
3 Jacques E, Suuronen EJ. The progression of regenerative medicine and its impact on therapy translation. Clin Transl Sci. 2020;13(3):440–50.
4 Kantaros A, Ganetsos T. From static to dynamic: smart materials pioneering additive manufacturing in regenerative medicine. IJMS. 2023;24(21):15748.
5 Matveyenko A, Vella A. Regenerative medicine in diabetes. Mayo Clin Proc. 2015;90(4):546–54.
6 Arjmand B, Abedi M, Arabi M, Alavi-Moghadam S, Rezaei-Tavirani M, Hadavandkhani M, et al. Regenerative medicine for the treatment of ischemic heart disease; status and future perspectives. Front Cell Dev Biol. 2021;9:704903.
7 Rando TA, Jones DL. Regeneration, rejuvenation, and replacement: Turning back the clock on tissue aging. Cold Spring Harb Perspect Biol. 2021;13(9):a040907.
8 Ajmal L, Ajmal S, Ajmal M, Nawaz G. Organ regeneration through stem cells and tissue engineering. Cureus [Internet]. 2023 [cited 2024 Sep 2]; Available from: https://www.cureus.com/articles/134321-organ-regeneration-through-stem- cells-and-tissue-engineering
9 Tripathi S, Mandal SS, Bauri S, Maiti P. 3D bioprinting and its innovative approach for biomedical applications. MedComm. 2023;4(1):e194.
10 Calignano F, Galati M, Iuliano L, Minetola P. Design of additively manufactured structures for biomedical applications: a review of the additive manufacturing processes applied to the biomedical sector. J Healthcare Eng. 2019;2019:1–6.
11 Wilson WC, Boland T. Cell and organ printing 1: protein and cell printers. Anat Rec. 2003;272A(2):491–6.
12 Mendoza-Cerezo L, Rodríguez-Rego J, Macías-García A, Marcos-Romero A, Díaz-Parralejo A. Evolution of bioprinting and current applications. IJB. 2023;9(4):742.
13 Lam EHY, Yu F, Zhu S, Wang Z. 3D bioprinting for next-generation personalized medicine. IJMS. 2023;24(7):6357.
14 Schlottmann F, Bucan V, Vogt PM, Krezdorn N. A short history of skin grafting in burns: From the gold standard of autologous skin grafting to the possibilities of allogeneic skin grafting with immunomodulatory approaches. Medicina. 2021;57(3):225.
15 Granot N, Storb R. History of hematopoietic cell transplantation: Challenges and progress. Haematologica. 2020;105(12):2716–29.
16 Van Osch GJVM, Brittberg M, Dennis JE, Bastiaansen Jenniskens YM, Erben RG, Konttinen YT, et al. Cartilage repair: past and future – lessons for regenerative medicine. J Cellular Mol Med. 2009;13(5):792–810.
17 Pashneh-Tala S, MacNeil S, Claeyssens F. The tissue-engineered vascular graft—past, present, and future. Tissue Eng Part B: Rev. 2016;22(1):68–100.
18 Chang CY, Ting HC, Liu CA, Su HL, Chiou TW, Lin SZ, et al. Induced pluripotent stem cell (iPSC)-based neurodegenerative disease models for phenotype recapitulation and drug screening. Molecules. 2020;25(8):2000.
19 Arumugam P, Kaarthikeyan G, Eswaramoorthy R. Three-dimensional bioprinting: The ultimate pinnacle of tissue engineering. Cureus [Internet]. 2024 [cited 2024 Sep 2]; Available from: https://www.cureus.com/articles/236285-three- dimensional-bioprinting-the-ultimate-pinnacle-of-tissue-engineering
20 Ma Y, Deng B, He R, Huang P. Advancements of 3D bioprinting in regenerative medicine: Exploring cell sources for organ fabrication. Heliyon. 2024;10(3):e24593.
21 Gnatowski P, Piłat E, Kucińska-Lipka J, Saeb MR, Hamblin MR, Mozafari M. Recent advances in 3D bioprinted tumor models for personalized medicine. Transl Oncol. 2023;37:101750.
22 Ahn M, Cho WW, Park W, Lee JS, Choi MJ, Gao Q, et al. 3D biofabrication of diseased human skin models in vitro. Biomater Res. 2023;27(1):80.
23 Chliara MA, Elezoglou S, Zergioti I. Bioprinting on organ-on-chip: Development and applications. Biosensors. 2022;12(12):1135.
24 Ali ASM, Berg J, Roehrs V, Wu D, Hackethal J, Braeuning A, et al. Xeno-free 3D bioprinted liver model for hepatotoxicity assessment. IJMS. 2024;25(3):1811.
25 Li J, Wu M, Chen W, Liu H, Tan D, Shen S, et al. 3D printing of bioinspired compartmentalized capsular structure for controlled drug release. J Zhejiang Univ Sci B. 2021;22(12):1022–33.
26 Seoane-Vazquez E, Rodriguez-Monguio R, Powers JH. Analysis of US Food and Drug Administration new drug and biologic approvals, regulatory pathways, and review times, 1980–2022. Sci Rep. 2024;14(1):3325.
27 Yaneva A, Shopova D, Bakova D, Mihaylova A, Kasnakova P, Hristozova M, et al. The progress in bioprinting and its potential impact on health-related quality of life. Bioengineering. 2023;10(8):910.
28 Liang K. Tissue bioprinting: promise and challenges. Bioengineering. 2023;10(12):1400.
29 Ma L, Yu S, Xu X, Moses Amadi S, Zhang J, Wang Z. Application of artificial intelligence in 3D printing physical organ models. Mater Today Bio. 2023;23:100792.
30 An J, Chua CK, Mironov V. Application of machine learning in 3D bioprinting: focus on development of big data and digital twin. IJB. 2024;7(1):342.
31 Matthews N, Pandolfo B, Moses D, Gentile C. Taking it personally: 3D bioprinting a patient-specific cardiac patch for the treatment of heart failure. Bioengineering. 2022;9(3):93.
32 Baltazar T, Merola J, Catarino C, Xie CB, Kirkiles-Smith NC, Lee V, et al. Three dimensional bioprinting of a vascularized and perfusable skin graft using human keratinocytes, fibroblasts, pericytes, and endothelial cells. Tissue Engineering Part A. 2020;26(5–6):227–38.
33 Yazdanpanah Z, Johnston JD, Cooper DML, Chen X. 3D bioprinted scaffolds for bone tissue engineering: State-of-the-art and emerging technologies. Front Bioeng Biotechnol. 2022;10:824156.
34 Kim M, Kim YJ, Kim YS, Roh TS, Lee EJ, Shim JH, et al. One-year results of ear reconstruction with 3D printed implants. Yonsei Med J. 2024;65(8):456.
35 Jia S, Bu Y, Lau DSA, Lin Z, Sun T, Lu WW, et al. Advances in 3D bioprinting technology for functional corneal reconstruction and regeneration. Front Bioeng Biotechnol. 2023;10:1065460.
36 He P, Zhao J, Zhang J, Li B, Gou Z, Gou M, et al. Bioprinting of skin constructs for wound healing. Burns Trauma [Internet]. 2018 [cited 2024 Sep 3];6. Available from: https://academic.oup.com/burnstrauma/article/doi/10.1186/s41038- 017-0104-x/5680424