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Review

# Transforming Neurological Disease Modeling and Therapy with 3D Bioprinting

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## Abstract

Three-dimensional (3D) bioprinting is transforming neuroscience, tissue engineering, and regenerative medicine by enabling the precise fabrication of complex, functional biological structures. This review provides a comprehensive overview of the latest advances in 3D bioprinting for neural applications, including brain tumor modeling, neurodegenerative disease research, peripheral nervous system (PNS) repair, and cancer drug delivery. We discuss the principles and techniques of major bioprinting methods including extrusion-based, inkjet, laser-assisted, multimaterial, and coaxial bioprinting. The unique advantages are highlighted for engineering neural tissues and disease models. Special attention is given to the development of patient-specific brain tumor organoids, innovative scaffolds for neurodegenerative disease modeling, and bioprinted nerve guidance conduits for PNS regeneration. The review also addresses the challenges of vascularization, cell viability, and clinical translation, and explores future directions integrating 3D bioprinting with tissue engineering and digital technologies for personalized medicine. By bridging critical gaps in disease modeling and neural repair, 3D bioprinting holds the promise to revolutionize research and therapy for neurological and oncological disorders.

## Keywords

3D Bioprinting, Neural Tissue Engineering, Brain Tumor Models, Peripheral Nerve Repair, Regenerative Medicine

## 1. Introduction

Research and studies show that about 45,000 brain tumor deaths occur annually in Europe, around 19,000 in North America, and about 75,000 in Asia. These tumors typically go through conventional methods of removal such as surgery, radiation therapy, and chemotherapy. These approaches often face significant challenges such as inability to reach tumor's location or invasiveness or high doses to penetrate the blood-brain barrier (BBB)—a selective, protective boundary that separates the brain from the bloodstream. Administering such high doses also poses the risk of systemic toxicity. The resulting neurotoxic side effects can include cognitive impairment, inflammation, and, in severe cases, permanent brain damage [1].

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Emerging nanomedicine approaches, particularly the use of engineered nanocarriers, are beginning to overcome longstanding barriers to effective brain tumor treatment by enabling targeted drug delivery and reducing systemic side effects [2]. Nanocarriers are the nano sized particles (1 nanometer to 100 nanometers) used as a mode of transport for drugs or substances, which enhances drug delivery during the process. The concept of nanoparticles was first brought into light by Paul Ehrlich in 1954. After the theory was proposed, the initial study was done by Ursula Scheffel and Professor Peter Speiser in the late 1960s and the early 1970s [3]. The first liposome - a type of nanocarrier - was first discovered in 1965 by Bangham. Work on PEGylated liposomes (liposomes containing polyethylene glycol) began, paving way for further exploration in this field of medicine. Later, in the 21st century, nanocarriers became more popular and are being considered as a better alternative to many other conventional methods such as chemotherapy and surgical exploration in many aspects of medicine. Presently, nanocarriers mainly focus on drug delivery, diagnostics, etc.

The blood-brain barrier (BBB) poses a formidable obstacle to most therapeutics, often rendering conventional chemotherapy ineffective and increasing the risk of neurotoxicity. The selectivity is due to the tight junctions between brain capillary endothelial cells as shown in Figure 1. This mechanism prevents antibiotics and neuropeptides that aid the patient to fight against the tumor and make it past the BBB in very limited quantities. To deliver therapeutic agents across the BBB, the process typically involves either invasive or non-invasive strategies. Invasive methods aim to temporarily disrupt the BBB using chemical, biological, or physical stimuli. However, these approaches are costly, carry significant risks, and can be uncomfortable or dangerous for patients. Non-invasive techniques—particularly those involving nanocarriers—have shown greater promise and efficiency. These nanoparticles, due to their extremely small size, can interact with the BBB to induce subtle chemical changes that allow them to cross into the brain. Importantly, these disruptions are associated with minimal toxicity, targeting tumors more effectively while reducing harm to healthy brain tissue compared to traditional chemotherapy [4]. Due to their extremely small size, nanoparticles can induce subtle chemical disruptions in the BBB, enabling them to cross into the brain. These disruptions are typically associated with low toxicity, allowing the nanoparticles to deliver therapeutic agents more effectively to the tumor with minimal damage to healthy brain tissue—an advantage over conventional treatments like chemotherapy [5]. This review goes over neuro-engineering progresses in the disease modelling leveraging 3D-bioprinting practices.

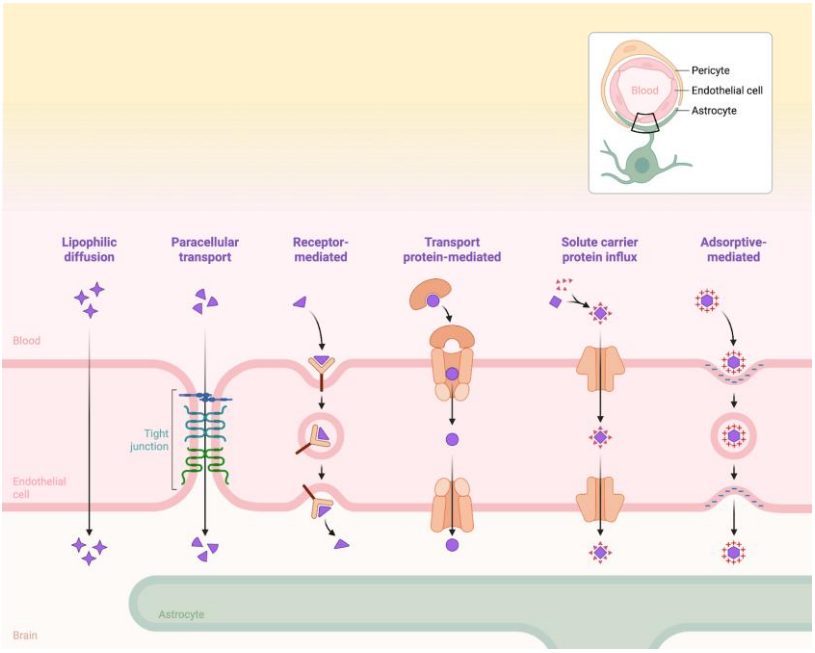


*Figure 1. Created in BioRender. Verma, S. (2025) https://BioRender.com/97u9y1c.*

## 2. Advances in 3D Bioprinting for Neural Applications

### 2.1. Bioprinting Brain Tissue: Techniques and Biomaterials

Recent breakthroughs in 3D bioprinting have enabled researchers to engineer functional brain tissue models with unprecedented precision and complexity. These advances are overcoming longstanding barriers in neuroscience, such as the inability to replicate the brain's intricate architecture and limited regenerative capacity, and are opening new avenues for disease modeling, drug testing, and regenerative therapies. 3D Bioprinting is the process in which bioinks are used to create viable cells or tissues that are functionally useful once implanted in the human body, provided a few conditions are met.

The 3D bioprinting workflow typically begins with high-resolution imaging and digital modeling, followed by the formulation of specialized bioinks containing living cells and supportive biomaterials. Advanced printing platforms—such as extrusion, inkjet, laser-assisted, and multimaterial systems—enable precise spatial placement of these bioinks, resulting in constructs that can be further matured and validated for biological function. These technical innovations are rapidly expanding the possibilities for neural tissue engineering

The biomaterials used in the bioinks of tissue construction provide mechanical support, and provide a flexible, 3D space. They also increase the rate of cell adhesion and cell growth by replacing the extracellular matrix. Axonal growth is the process by which axons extend from the neuron and reach their target cell. The architecture of Advanced Biomaterials guide axonal growth towards their target, allowing for faster and a more efficient way of connecting damaged tissue and healthy tissue, allowing for faster and better regeneration of the tissue. These biomaterials, when combined with living cells, create a viable bioink, ready to be used in the bioprinter to engineer tissues. These implants are usually molded or self assembled. Even though those two processes are preferred to create tissues, the process that provides more control is Light Based 3D Printing [6].

Table 1 summarizes the key features, applications, and advantages of the five principal bioprinting techniques discussed in this section: extrusion-based, inkjet, laser-assisted, multimaterial, and coaxial bioprinting. This comparison highlights the rationale for their selection and relevance to neural tissue engineering. Having established the importance of 3D bioprinting in neural tissue engineering, it is essential to understand the specific techniques that enable the fabrication of complex, functional constructs. The following section provides an overview of five principal bioprinting methods—extrusion-based, inkjet, laser-assisted, multimaterial, and coaxial bioprinting—each offering unique advantages and applications for brain and nerve tissue modeling. The extrusion based bioprinting technique combines both a fluid dispensing system and an automated robotic system for extrusion and printing respectively. Extrusion based bioprinting is mainly used for its high quality and resolution of the cell structure. They are also used because of their ability to print a wider range of biomaterials with varying viscosity. Biomaterials with a higher viscosity in this technique often provide structural support for the constructed print and the biomaterials with a lower viscosity provide a suitable environment for the cells constructed. Their application in the research of brain tissues is also pronounced as their high cell resolution aids in the creation of neural tissue scaffolds, tumoroids, etc. This usage of multiple types of viscosities makes extrusion based bioprinting popular in the field of biotechnology. Inkjet Bioprinting was the first bioprinting technique to be mentioned in 2003. The Inkjet Bioprinters deliver a controlled amount of bioink to the desired surface. The constructs which are the product of Inkjet Bioprinting have a relatively high cell viability rate (greater than 90%). This technique is an extremely cost effective technique as well, allowing for a higher level of exploration on this technique. This technique also allows us to deposit multiple cells or proteins onto a targeted spatial position, allowing for the fabrication of complex multicellular constructs. In the field of neurosciences, Inkjet Bioprinting is used for creating in-vitro models of the brain, and models neural diseases and makes them easier to study. The delivery of biological substances to the targeted area, along with its high cell viability, makes Inkjet Bioprinting a popular bioprinting technique. Laser Assisted Bioprinting (LaBP) is a modified version of a technique which was developed to transfer biological materials. During the process of printing, there is no direct contact between the bioink and the dispenser, which prevents cell stress and leads to a cell viability range that is greater than 95% which is one of the main reasons why LaBP is used by researchers [7]. In brain tissue research, this technique creates complex 3D models of the brain, mimicking the intricate structures and functions of the brain. The high cell viability makes LaBP a widely popular technique in biotechnology. Multi-material bioprinting is also a relatively useful technique due to its suitability for the fabrication of constructs that mimic the heterocellular structures of native tissues, enabling incorporation of graded composition or environmental adaptations. Multi-material bioprinting consists of 4 main subtechniques: Extrusion bioprinting, Inkjet Bioprinting, LIFT Bioprinting and Vat Polymerisation bioprinting. Multi Material bioprinting is also useful in brain tissue research as it creates complex neural tissue models and

mimics neural circuits. Co-Axial bioprinting is mostly used for printing vascular structures, tumor models, etc [8]. Its applications in brain tissue research are quite helpful as products mimic native neural tissue structures and create micro environments. Its ability to fabricate complicated configurations makes coaxial bioprinting a popular technique among researchers.

| Reference | Bioprinting technique | Features | Applications | Advantages |
|---|---|---|---|---|
| [7] | Extrusion-Based Bioprinting | Uses pneumatic or mechanical force to extrude bioink through a nozzle | Neural tissue scaffolds, tumoroids | High cell density, cost-effective |
| [7] | Inkjet Bioprinting | Delivers a controlled amount of bioink by forcing the content to flow continuously or drop out from the nozzle | Creating In-vitro models of the brain, studying neural diseases | High resolution, inexpensiveness, reproducibility, relatively high cell viability |
| [7] | Laser-Assisted Bioprinting | Consists of: a pulsed laser beam, a focusing system, a ribbon structure layer containing an energy absorbing layer that responds to laser stimulation, a layer of liquid bioink solution, a receiving substrate for patterning and crosslinking bioink | Creates complex 3D models of the brain, mimics the intricate structures and functions of the brain | Prevents cell stress, high viability, compatible with different types of bioinks, wide range of viscosities |
| [8] | Multimaterial Bioprinting | Extrusion of different bioinks through one single nozzle, flow of bioinks through one or every nozzle. | Creates complex neural tissue models, mimics neural circuits, developing novel therapies | Induce less cell stress, more complex features and larger build volumes fabricated at a faster pace |
| [8] | Co-Axial Bioprinting | Fabricates hollow structures with compositional and geometrical complexities | Mimics native neural tissue structures, creates micro environments, implants 3D constructs | Fabricates more complicated configurations, aids in multimaterial bioprinting |

***Table 1.*** *Overview of 3D bioprinting techniques and their applications in brain tissue research..*

## 2.2. 3D Bioprinting in Brain Tumor Modelings

Studying brain tumors—especially aggressive types like glioblastoma—remains a major challenge due to the complexity of the brain's microenvironment and the risks of direct experimentation in patients. Traditional models, including animal studies and 2D cell cultures, fail to capture the true architecture and invasive behavior of brain tumors, limiting our understanding of disease progression and drug response. Recent advances in 3D bioprinting now allow researchers to fabricate highly realistic, patient-specific brain tumor models that closely mimic the tumor microenvironment, cellular diversity, and vascular networks found in vivo. These models enable dynamic investigation of tumor growth, invasion, and therapeutic response, providing a powerful platform for drug screening and personalized medicine.

3D bioprinting enables the creation of patient-specific tumor models by combining multiple cell types, precisely tuning biomaterial properties, and engineering structurally complex microenvironments. These models replicate critical aspects of tumor biology, such as heterogeneity and invasive behavior, providing researchers with versatile platforms to identify therapeutic vulnerabilities and test targeted interventions. Organoids or tumoroids are 3D printed tumors or tumor cells which contain the direct tumor cells from the patient themselves. This type of approach helps doctors provide medication or slow down tumor growth by using a specific type of approach that is of better help to the patient. Assembloids on the other hand, display a greater level of complexity, as multiple cell types are used in constructing the tumor, and the diverse multitude of tissues used provide for a better understanding of the tumor's structure, how it functions, what potential weaknesses it has, etc [9]. The above types of

creation of tumors provide a better understanding on how to use 3D Bioprinting to study brain tumors.

### 2.3. Bioprinting Approaches for Neurodegenerative Disease Research

Neurodegenerative Diseases are disorders of the central nervous system characterized by the gradual and irreversible loss of neurons, leading to worsening neurological functions over time. A few of the diseases that fall under the category of neurodegenerative disease are Alzheimer's, Parkinson's disease, Huntington's Disease, sclerosis, etc. To combat this issue, there is a special field of medicine known as the field of regenerative medicine. However, obtaining an innovative scaffold that aims at improving new methods used for stem cell therapy is a challenge for this new field of medicine. 3D Bioprinting is being implemented in the field of regenerative medicine in order to engineer or fabricate precise 3D scaffolds. The design of the scaffolds must be specific in every aspect of the tissue needed to be constructed. As the brain is complex, sensitive, and susceptible to damage, it is hard to properly study and understand neurodegenerative diseases. By using newly implemented technology, it is now possible to create the tissues that mimic the complex structure and function of the human brain. Precisely, 3D cell culture systems aim to mimic the tissues in the brain and provide an environment similar to that of the region in or around the brain. Decellularized scaffolds and hydrogel based biomaterials are two innovative approaches useful for modelling neurodegenerative diseases. The above models help in the creation of tissue scaffolds with utmost precision, and can also mimic the environment the tissue is usually present in. This helps researchers understand better, what the disease does exactly, and what can be done to prevent or reduce the effects it causes on the nervous system as they can work freely and explore many possibilities on how to combat neurodegenerative diseases [10].

### 2.4. Bioprinting Strategies for Peripheral Nervous System Repair

Peripheral nerve injuries remain a major clinical challenge, often resulting in significant loss of sensory and motor function. Traditional treatments such as autografts and nerve grafts are limited by donor tissue availability, risk of immune rejection, and imperfect anatomical matching. Recent advances in 3D bioprinting are transforming the field by enabling the rapid fabrication of personalized nerve guidance conduits (NGCs) that closely mimic the structure, function, and microenvironment of native peripheral nerves. These bioprinted conduits can be precisely tailored using patient imaging data and a combination of natural and synthetic biomaterials, supporting axonal regeneration and functional recovery in ways that were previously unattainable with conventional approaches. As an alternative, 3D bioprinting offers another possible, effective way of treating PNS injuries. 3D bioprinted nerve scaffolds offer quick creation of peripheral nerve conduits. Bioprinting also allows the medical workers to replace the injured nerve tissues with lab cultured, bioprinted nerve tissues. The peripheral nerve conduits are hollow tubes that are used to repair peripheral nervous system injuries. These nerve conduits mainly focus on promoting healing of damaged nerves or tissues. Bioprinting uses the cells as scaffolds and manufactures the conduits in such a way that they mimic the biological and physical attributes of the nerve it will be repairing [11]. This new and emerging method of using bioprinting to create nerve guide conduits will reduce the likeliness of permanent damage and a much more efficient method of healing nervous tissues in the peripheral nervous system.

### 2.5. 3D Bioprinting in Cancer Research and Drug Delivery

Cancer cells evolve in a complex and heterogeneous environment and have the ability to grow uncontrollably, spreading and ignoring the immune system's orders to self-destruct when their basic cell function has been compromised. To study tumor or cancer cells, surgical exploration is very complex. The conventional method is to take out cancer cells and examine their 2D cultures is possible, however, this method is very limited in terms of their ability to mimic the cancer cell environment. As the conventional methods are proving to be very limited in giving us information about the cancer cells, a new technique that is proving to be very helpful in cancer modelling is 3D Bioprinting. Using live scaffolds, 3D bioprinting has made it possible to create various models of cancer cells in recent years. As 3D Bioprinting produces complex and reproducible constructs, many researchers around the globe prefer 3D Bioprinting to mimic the tumor microenvironment. These models are incredibly helpful as the 3D cancer models are used for drug screening as well before moving on to preclinical trials. 3D bioprinting is not only used for drug testing alongside experimental research, it is also used as a drug delivery agent. Specifically, drug delivery hydrogels used in the bioink are used for delivering drugs to various cancer sites [12]. 3D Bioprinting is a new and effective way of modelling cancer cells and has a lot of uses in oncology.

### 2.6. Innovations in Tissue Regeneration via Bioprinting

Tissue regeneration, as the name implies, is the repairment or regeneration of tissues, following damage caused to the tissue, and is a natural process. In some cases, the complete restoration of tissues is not done naturally in tissues with extensive damage. To overcome this problem, a technology known as tissue engineering comes into the field. Tissue engineering is a field that uses cells and biomaterials to develop artificial tissue substitutes. It provides a platform for regenerating functional tissues when they can't be repaired naturally. Granted that tissue engineering is an advanced method, there are limitations such as shortage of tissues and insufficient tissue regeneration.

3D Bioprinting is a new and emerging technology that is looking to solve the problems faced by tissue engineering. This additive manufacturing technique shows a lot of promise for creating complex tissue scaffolds through precise placement of living cells and biomaterials. The artificially 3D printed scaffolds serve as templates that support cells to attach, proliferate and differentiate. These newly printed cells also secrete an extracellular matrix (ECM), eventually leading to the generation of mature cell grafts. With progress being made on how the applications of 3D Bioprinting can be used in Tissue Engineering, bioprinting aims to revolutionize the field of tissue engineering [7].

## 3. Challenges and Future Directions

Tissue Engineering has progressed tremendously over the past few decades as it fabricates functional tissue substitutes for regenerative medicine. Tissue Engineering also helps in carrying out pharmaceutical research. These two main applications have made tissue engineering grow in popularity over the past few decades [7]. Another distinctive feature of this aspect is that it aims to regenerate the patient's own tissues, which makes poor biocompatibility, low biofunctionality, and the rejection of the grafts or tissues by the immune system have the least or no concern at all by the researchers [13].

Although all of the above qualities of tissue engineering look very promising, there are only a few reported applications of tissue engineering [13]. Even this aspect of biotechnology has its limitations and challenges as well. There is a continuous shortage of tissues that are to be used for transplantation, or insufficient tissue regeneration. Other limitations are vascularization challenges, cell survival, requirements of viable cell components, etc. Cell Survival, in fact, is one of the primary challenges in tissue engineering as the high volume to surface ratio severely limits the longevity of the cell [14]. With precision medicine advancements in the fields of microfluidics, single cell sequencing and next gen sequencing, tissue engineering has potential to integrate for improved accuracy and results [15] [16] [17]. Another limitation of tissue engineering is that despite it being really helpful for pharmacological drugs research, there is still a lack of tissue models with complex architecture and tissue to tissue interface for drug testing [18] [19] [20].

Challenges faced by tissue engineering such as cell survival can be answered by the prefabrication of a vascular supply. This is a process in which it aids tissue engineering in constructing a 3D scaffold that directs the growth of the vascular tree that will support the metabolic demands of the engineered tissue. However, how promising this may seem, it is yet to be studied in a wounded environment where the tissue needs repairing and regeneration [21]. There is also improvement needed as in some cases, tissue regeneration does not occur fully in the engineered tissue.

To address all of the limitations and challenges faced by tissue engineering at once, a new and emerging aspect known as 3D Bioprinting is brought to light to revolutionize the field of tissue engineering. This process is able to create complex 3D tissue constructs via precise placement of cells using various methods within bioprinting. The ability of the bioprinter to deposit biomaterial with pinpoint precision in a cell or tissue friendly environment gives bioprinting an advantage over conventional scaffold based tissue engineering. This is because printing constructs with such precision enables control over scaffold fabrication and cell distribution [22]. The functional vascular networks mentioned earlier can also be printed via bioprinting, offering more advantages over traditional fabrication of vascular networks. These advantages that 3D Bioprinting has when implemented with tissue engineering and e-health technologies make it a popular referral that is often referred to by researchers when conventional tissue engineering does not deliver the appropriate results [23] [24] [25].

Table 2 below details the challenges faced by the various drugs or pharmacological agents to cross the Blood Brain Barrier. The selective permeability of the BBB allows particular particles to pass through based on the brain’s physiological needs. By default, this quality of the BBB might prevent key drugs and agents that aid in curing or prevention of neurological diseases. To progress and develop technologies or particles that would aid in crossing the BBB,

3D bioprinting plays a key role as it models the BBB, allowing for a much more free environment to conduct research on the BBB. High System toxicity refers to the consequences that would occur should a disruption or breakdown in the BBB occur. The normal neurological function of the BBB relies on the delicate chemical balance between neurons and their synapses [26]. General pharmaceutical drugs, if used in higher concentrations, could potentially cause harm or disrupt the chemical balance in the BBB. 3D Bioprinting is a viable option for improving the progress being made on the challenge high system toxicity presents. The lack of standardized models of the BBB is a big challenge as well because it only allows limited studies to be conducted on the BBB as direct trials cannot be conducted on live subjects. Standardized models allow the researchers to freely explore, navigate and study the BBB closely and carefully, allowing for many more studies to give informative results. 3D Bioprinting is a new and emerging technique which can be used for producing standardized models of the BBB [27].

| Reference | Challenges | Description | Impact on Drug Delivery | Role of 3D-Bioprinting |
|---|---|---|---|---|
| [26] | Selective Permeability | The BBB restricts entry of large molecules, drugs, and therapeutic agents | Limits efficacy of systemic therapies | Bioprinted BBB models enable testing nanocarriers and drug delivery systems under physiological conditions. |
| [26] | High Systemic Toxicity | Consequences that would occur should the BBB have a breakdown | Limits drug dosage as an increase in dosage leads to high system toxicity. | 3D Bioprinted models of the BBB which mimic its intricate structure and function, allow studies on how nanoparticles can be delivered past the BBB without causing high system toxicity. |
| [27] | Lack of Standardized Models | Difficulty replicating the complex structure and function of the BBB in vitro | Hinders reproducibility in preclinical studies | Standardized 3D Bioprinted models of the BBB aid researchers to conduct studies on the accurately printed models |

***Table 2.*** *Challenges in crossing the BBB and role of 3D bioprinting.*

## 3. Conclusion

3D bioprinting has emerged as a transformative technology in tissue engineering and regenerative medicine, offering unprecedented precision in fabricating complex, functional tissues for neural repair, disease modeling, and drug testing. By overcoming many of the limitations associated with traditional tissue engineering—such as donor scarcity, poor anatomical matching, and limited physiological relevance—bioprinting enables the creation of patient-specific scaffolds, organoids, and nerve conduits that closely mimic native tissue architecture and function [28]. These innovations are already advancing our understanding of brain tumors, neurodegenerative diseases, and peripheral nerve injuries, while also accelerating the development of targeted therapies and personalized medicine.

Despite these advances, significant challenges remain. Achieving reliable vascularization, improving bioink formulations, and ensuring the scalability and reproducibility of bioprinted constructs are critical hurdles that must be addressed before widespread clinical adoption. Ethical, regulatory, and manufacturing considerations will also shape the future trajectory of the field. Integration with artificial intelligence and other digital technologies holds promise for optimizing scaffold design, predicting biological outcomes, and personalizing treatments even further [29] [30]. Looking ahead, continued interdisciplinary collaboration and innovation will be essential to unlock the full therapeutic potential of 3D bioprinting. As the technology matures, it is poised to revolutionize not only tissue engineering but also the broader landscape of regenerative medicine, offering hope for more effective, patient-specific solutions to some of the most challenging neurological and oncological diseases.

## Author Contributions

V.K., S.V., literature review, writing – original draft and writing; S.V. conceptualization, writing - review & editing.

## Conflicts of Interest

The authors declare no competing financial interests or conflicts of interest.

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