Recent Progress in Hydrogel-Based Bioinks for 3D Bioprinting: A Patent Landscape Analysis and Technology Updates

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Abstract: Hydrogel-based bioinks have emerged as a critical component in the field of three-dimensional (3D) bioprinting, with numerous polymers being explored and utilized for this purpose. The high volume of patent applications reflects a competitive and dynamic research environment, where various entities are actively developing new formulations and applications for hydrogel-based bioinks. As this field continues to evolve, tracking these trends is essential for understanding the future direction of the technology and identifying key innovations and players in the industry. This study reveals substantial growth in the patent landscape for hydrogel-based bioinks in 3D bioprinting, with 173 patent documents published between 2013 and 2024. The marked increase in patent filings, particularly from 2018 onwards, underscores the growing recognition of the technologys potential in diverse applications, including tissue engineering and regenerative medicine. Although patent applications have outpaced granted patents, the steady rise in granted patents indicates the fields maturation and the transition of innovations from concept to legally protected technologies. The leading patent applicants in this domain include both industry leaders and academic institutions. Companies such as Organovo INC and Cellink AB are driving innovation through extensive patent activity, while academic institutions and foundations also make significant contributions, highlighting a robust ecosystem where industrial and academic research propel the technology forward. The global distribution of intellectual property filings in this field is broad, with significant activity in the United States, Europe, and Asia. This diversity in patenting jurisdictions reflects the global interest in advancing bioprinting technologies, particularly for healthcare applications. Patent classifications for hydrogel-based bioinks in 3D bioprinting illustrate the convergence of materials science, biotechnology, and advanced manufacturing. These classifications highlight the diverse applications of bioinks, ranging from tissue regeneration and stem cell therapy to the development of medical devices and multifunctional bioactive materials based on polymers.

Keywords: Polymers, hydrogels, biomaterials, bioink, 3D bioprinting, biofabrication, innovation, patent.

1. INTRODUCTION

Three-dimensional (3D) bioprinting is an advanced manufacturing technique that utilizes 3D printing principles to create living tissue-like structures by combining cells, growth factors, and biomaterials [1]. This innovative process allows the fabrication of complex, functional structures that can mimic the architecture and functionality of natural tissues [2]. The significance of 3D bioprinting in tissue engineering is profound, as it enables the reconstruction of various tissues, offering potential solutions for organ transplantation and regenerative medicine [2]. By creating patient-specific tissue models, 3D bioprinting can be used for drug testing and disease modeling, thereby reducing the reliance on animal models [3]. This capability is crucial for developing functional organs that require specific cellular arrangements and interactions.

Additionally, 3D bioprinting allows for the precise placement of multiple cell types and biomaterials, facilitating the creation of heterogeneous tissues that closely resemble natural structures. The technology can produce scaffolds that support cell growth and tissue development, designed to degrade over time, allowing the newly formed tissue to take over and function independently [4]. In the realm of regenerative medicine, 3D bioprinting holds promise for treating various medical conditions, including injuries and degenerative diseases [5]. The potential to print tissues such as skin [6-8], cartilage [9-14], bone [15-17], and

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even organs like the heart [18] and liver [19] represents a significant advancement in medical science.

Hydrogels are a critical component of bioinks used in 3D bioprinting, playing a vital role in the fabrication of living tissue-like structures [1]. These materials are hydrophilic polymeric networks capable of absorbing large amounts of water, which allows them to closely mimic the natural extracellular matrix (ECM) found in biological tissues. Among the diverse biomaterials suitable for the formulation of bioinks, numerous polymers have been explored and utilized as hydrogel-based bioinks for 3D bioprinting. These include synthetic hydrogels based on synthetic polymers [20-23]. On the other hand, natural hydrogels comprise two main categories: hydrogels based on proteins [12,17,24-29], and hydrogels based on polysaccharides [10,13,14,30-36]. Their unique properties, such as biocompatibility, tunable mechanical characteristics, and ability to support cell adhesion, proliferation, and differentiation, make hydrogels particularly suitable for applications in tissue engineering and regenerative medicine [37]. In the context of 3D bioprinting, hydrogels serve as bioinks or as biomaterial inks that facilitate the precise positioning of cells and biomaterials, enabling researchers to create complex, multi-cellular structures that replicate the architecture and functionality of native tissues (Figure **1**).

The ideal hydrogel bioink would not only provide structural support but also create an environment conducive to cell survival and function, closely resembling the conditions found in living organisms [38]. The development of hydrogel-based bioinks has evolved significantly, with both natural and synthetic hydrogels being utilized. Natural hydrogels, derived from biological sources, often exhibit inherent bioactivity and biocompatibility, while synthetic hydrogels can be chemically engineered to achieve desired mechanical properties and degradation rates [1]. Hybrid hydrogels, which combine the advantages of both types, are also being explored to enhance the performance of bioinks in 3D bioprinting applications [18,20,39].

To provide a more comprehensive understanding of the subject matter according to hydrogel bioinks and 3D bioprinting, detailed background is proposed in the following sections (cf., Sections 2 and 3).

The purpose of this article is to analyze recent patents and technological advancements in hydrogel-based bioinks for 3D bioprinting. By exploring the current patent landscape and highlighting recent innovations, this article aims to provide insights into the ongoing developments in hydrogel technology, the challenges faced in the field, and the future directions for research and application in tissue engineering. Understanding these advancements is crucial for researchers, industry professionals, and stakeholders looking to leverage hydrogel-based bioinks in the quest for creating functional tissues and organs.

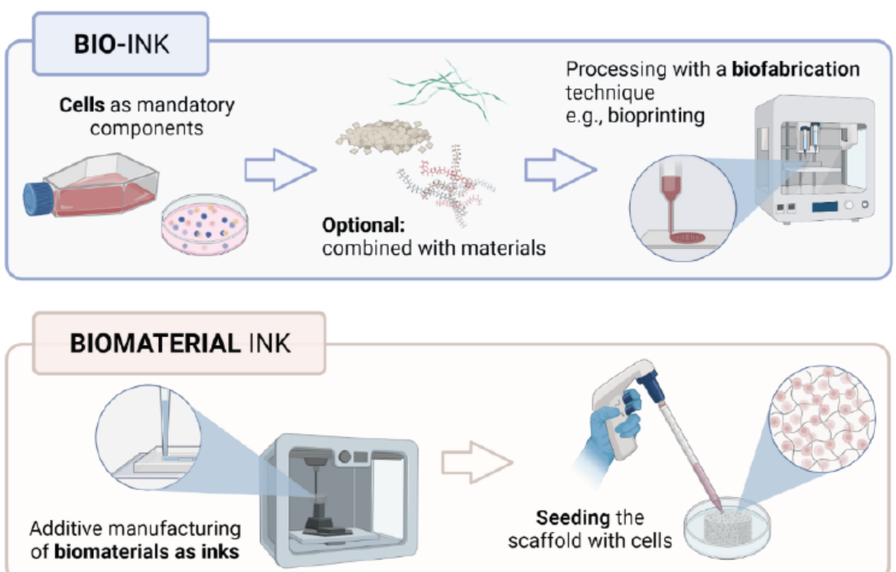

Figure 1: Schematic illustration Distinction between bioinks (i.e., cell-laden scaffold) and biomaterial inks (i.e., cell-free scaffold). In bioinks (upper image), cells are intrinsic components of the printing formulation (e.g., seeded onto micro-carriers, embedded in microgels, formulated in a physical hydrogel or formulated with hydrogel precursors). In biomaterial inks (bottom image), cells are introduced within the 3D bioprinted biomaterial scaffold, reducing the biological constraints on the inks (Reproduced from Fatimi *et al*., 2022 [1]. Copyright © 2022 MDPI under the terms of the Creative Commons Attribution 4.0 International License).

2. OVERVIEW OF HYDROGEL-BASED BIOINKS

2.1. Definition and Composition

Hydrogels are 3D networks of hydrophilic polymers that can swell in water and retain significant amounts of water while maintaining their structural integrity [40]. By definition, a hydrogel must contain at least 10% water by weight or volume, which is crucial for its ability to mimic the physical properties of biological tissues. The hydrophilic nature of hydrogels arises from the presence of functional groups such as hydroxyl groups –OH (e.g., cellulose, polyvinyl alcohol (PVA), agarose, etc.), carboxyl groups –COOH (e.g., alginate, polyacrylic acid (PAA), hyaluronic acid, etc.), and amino groups $–NH_2$ (e.g., chitosan, gelatin, poly-L-lysine (PLL), etc.) attached to the polymer chains, allowing them to absorb and hold large volumes of water [41]. This unique property not only contributes to their flexibility but also facilitates interactions with biological tissues, making hydrogels particularly suitable for biomedical applications, including tissue engineering and drug delivery systems [42].

Hydrogels can be categorized into two main types: natural and synthetic. Natural hydrogels are derived from biological sources and include polysaccharides (such as lignin, cellulose, alginate, chitosan, and hyaluronic acid) [10,13,14,30-36,43-47] and proteins (such as collagen and gelatin) [12,17,24-29]. These materials are often biocompatible and biodegradable, making them ideal for applications where cell interaction is essential. However, natural hydrogels can sometimes exhibit limitations in mechanical strength and stability. In contrast, synthetic hydrogels, such as polyethylene glycol (PEG), polyurethane, polyester, and PVA, are chemically engineered to achieve specific properties, including enhanced mechanical strength and controlled degradation rates [20-23]. The ability to tailor synthetic hydrogels allows for greater versatility in designing bioinks that meet the specific requirements of various bioprinting applications [41,48].

2.2. Hydrogel-Based Bioink Characteristics

Hydrogel-based bioinks are extensively studied in scientific literature due to their potential in 3D bioprinting for tissue engineering and regenerative medicine. The selection of hydrogel-based bioinks is influenced by several key characteristics (Table **1**). These characteristics are continuously being optimized

Table 1: Selection of Hydrogel-Based Bioink Characteristics

Characteristic	Description	Ref.
Biocompatibility	Ensures that the bioink is non-toxic and supports cell survival, proliferation, and differentiation. Hydrogels like alginate, gelatin, and collagen are favored for their natural origin and compatibility with various cell types.	[30] [49] [50]
Printability	Refers to the ability of the bioink to be extruded smoothly and maintain shape fidelity during and after printing. The rheological properties of the bioink, including viscosity and shear-thinning behavior, are critical. For example, gelatin-methacrylate (GelMA) and PEG derivatives are often optimized for printability.	[39] [51]
Mechanical properties	The stiffness and elasticity of the hydrogel must match the requirements of the target tissue. For instance, softer hydrogels are used for neural tissue engineering, while stiffer hydrogels are suitable for cartilage or bone. Synthetic hydrogels like PVA allow for tunable mechanical properties.	[52]
Gelation kinetics	The rate of gelation affects the stability and shape retention of the printed structure. Thermoresponsive hydrogels like Pluronic F127 and photo-crosslinkable hydrogels like GelMA are tailored for controlled gelation.	[53] [54]
Degradation rate	The bioink should degrade at a rate that matches tissue formation and integration. Hydrogels like hyaluronic acid and chitosan are known for their controlled biodegradability.	[43] [33]
Cell adhesion	Certain hydrogels promote better cell attachment and spreading, crucial for tissue formation. Protein-based hydrogels like collagen and fibronectin-enhanced formulations are particularly effective.	[55] [56]
Swelling behavior	The ability of the hydrogel to absorb water without dissolving is important for maintaining tissue integrity and nutrient diffusion. Alginate and agarose are examples of hydrogels with favorable swelling properties.	[30] [52]
Bioactivity	Incorporation of bioactive molecules (e.g., growth factors, peptides, etc.) can enhance the bioinks functionality. Hydrogels like fibrin can be loaded with growth factors to promote angiogenesis.	[57]
Transparency	For applications in ocular or neural tissues, the transparency of the hydrogel is critical. Hydrogels like agarose and PEG are preferred in such cases due to their optical clarity.	[58] [59]
Cost and Scalability	The economic feasibility and ease of production are also considered, especially for clinical translation. Synthetic hydrogels can be cost-effective and scalable, while natural hydrogels might require more complex processing.	[60]

in divers studies to develop bioinks that are tailored for specific applications in tissue engineering and regenerative medicine using 3D bioprinting [1]. Furthermore, the unique properties of hydrogels, including their biocompatibility, water retention capability, and tunable mechanical characteristics, make them indispensable components of bioinks in 3D bioprinting [47]. Their ability to mimic the ECM and support cellular functions is critical for advancing tissue engineering applications, paving the way for the development of functional tissues and organs for regenerative medicine.

2.3. Importance in 3D Bioprinting

Hydrogels play a crucial role in 3D bioprinting by serving as bioinks that closely mimic the ECM found in natural tissues. The ECM provides structural and biochemical support to surrounding cells and is essential for maintaining tissue integrity and function. By replicating the ECMs properties, hydrogel bioinks facilitate cell adhesion, proliferation, and differentiation, which are critical for creating functional tissue constructs [61]. The ability of hydrogels to maintain a high water content also contributes to a favorable microenvironment for cells, promoting their viability during and after the printing process [41].

The mechanical properties of hydrogels significantly affect cell viability and functionality in bioprinted tissues [62]. Ideal hydrogel bioinks should exhibit appropriate stiffness and elasticity to support the mechanical demands of the specific tissue being engineered. For instance, hydrogels used for soft tissues, such as ocular tissue, require lower stiffness to allow for flexibility, while those intended for load-bearing applications, such as bone, need to possess higher mechanical strength [63]. The cross-linking density of the hydrogel, which determines its mechanical behavior, can be adjusted to optimize these properties [37]. Additionally, the viscoelastic nature of hydrogels enables them to withstand deformation and recover their shape, which is essential for maintaining structural integrity in dynamic biological environments [4,48].

3. RECENT TECHNOLOGICAL ADVANCEMENTS

3.1. Innovations in Hydrogel Formulations

Recent advancements in hydrogel formulations have focused on enhancing their mechanical strength and printability, crucial for their application in 3D bioprinting. Innovations in synthetic and modified hydrogels have led to the development of materials that not only exhibit improved mechanical properties but also maintain the necessary biocompatibility for biological applications. For instance, the introduction of double-network (DN) hydrogels has significantly improved toughness and mechanical strength. These hydrogels consist of two interpenetrating networks that allow for greater energy dissipation and resilience under stress, making them suitable for applications where flexibility and strength are paramount, such as in soft tissue engineering and wound healing [62,64].

Additionally, the incorporation of nanocomposites into hydrogel formulations has emerged as a promising strategy to enhance their properties. Nanocomposite hydrogels, which integrate nanoparticles or nanofibers, exhibit improved mechanical strength, elasticity, and thermal stability. These enhancements are attributed to the unique interactions between the polymer matrix and the nanofillers, which can reinforce the hydrogel structure and provide additional functionalities, such as electrical conductivity or antibacterial properties [30]. For example, recent studies have demonstrated that the addition of graphene oxide or carbon nanotubes to hydrogels can significantly enhance their tensile strength and stretchability, broadening their application scope in flexible electronics and biomedical devices [30,64,65].

Moreover, the functionalization of hydrogels with bioactive molecules has gained attention for its potential to promote cell behavior and tissue regeneration. By incorporating growth factors, peptides, or other signaling molecules, researchers can create hydrogels that not only serve as structural scaffolds but also actively participate in biological processes, such as angiogenesis and cell differentiation. This approach allows for the design of smart hydrogels tailored to specific therapeutic needs, enhancing their effectiveness in tissue engineering applications [41,65].

3.2. Bioprinting Techniques

The performance of hydrogel bioinks in 3D bioprinting is significantly influenced by the bioprinting techniques employed [1,66,67]. Various methods, including extrusion-based bioprinting, inkjet-based bioprinting, and laser-assisted bioprinting, have been developed to optimize the deposition of hydrogel bioinks (Figure **2**).

Extrusion-based bioprinting is one of the most widely used techniques, where bioinks are extruded

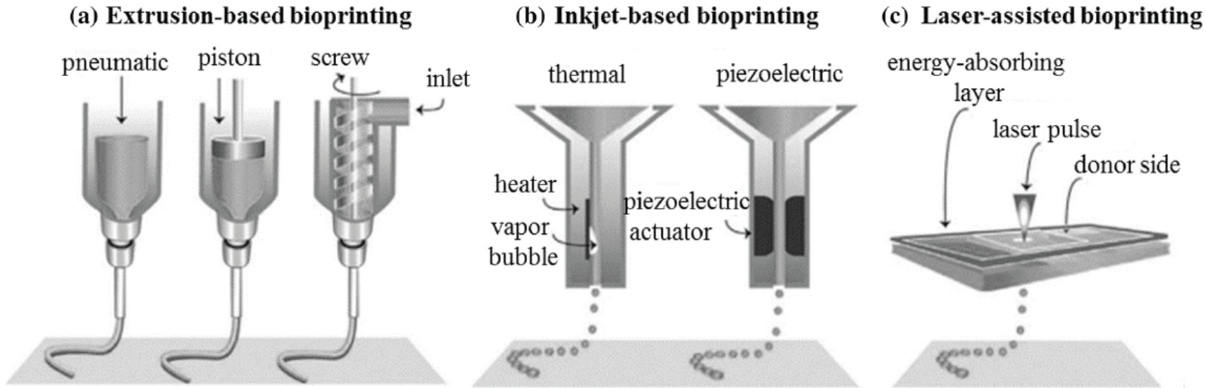

Figure 2: Selection of the most used scaffold-based 3D bioprinting: (**a**) extrusion-based, (**b**) inkjet-based, and (**c**) laser-assisted bioprinting (Adapted from Malda *et al.*, 2013 [67], with the permission of John Wiley & Sons Inc., Published under license. Copyright © 2013 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim).

through a nozzle to create continuous filaments. This method allows for precise control of the printing process and is particularly effective for hydrogels with high viscosity. The ability to layer multiple materials and cell types enables the creation of complex tissue architectures that closely mimic natural tissues. This technique, including three different printing processes (i.e., pneumatic, piston, and screw), is advantageous for producing larger constructs and can accommodate a variety of hydrogel formulations, making it versatile for different applications in tissue engineering [66-69].

Inkjet-based bioprinting, on the other hand, utilizes thermal or piezoelectric mechanisms to eject small droplets of bioink onto the substrate. This technique is advantageous for creating fine structures and patterns but may be limited by the viscosity of the hydrogel. To address this challenge, researchers are developing low-viscosity hydrogel formulations that maintain cell viability while allowing for efficient droplet ejection. The choice of bioprinting technique can also affect the mechanical properties of the printed constructs, as the shear forces experienced during printing can influence the cross-linking and gelation processes of the hydrogels [66,67,69,70].

Laser-assisted bioprinting is another innovative technique that has gained traction in the field of 3D bioprinting. This nozzle-free technique utilizes focused laser beams to initiate polymerization or cross-linking of bioinks at specific locations, allowing for high precision and resolution in the fabrication of intricate structures. Laser-assisted printing can produce features at the microscale, making it particularly suitable for applications requiring fine detail, such as vascular networks or cellular arrangements. Additionally, this technique minimizes shear stress on cells, which can enhance cell viability and functionality within the printed constructs [66,67,69,71,72].

Overall, the advancements in hydrogel formulations and bioprinting techniques are paving the way for the development of more effective and functional tissue-engineered products. By optimizing the mechanical properties and printability of hydrogel bioinks, researchers are enhancing their potential for creating complex, viable tissues that can be used in regenerative medicine and other biomedical applications. The ongoing exploration of new materials and printing methods will continue to drive innovation in the field of 3D bioprinting, ultimately contributing to improved patient outcomes in tissue repair and regeneration [73,74].

4. PATENT LANDSCAPE ANALYSIS

4.1. Resources, Methods, and Data Collection

Patent analysis for hydrogel bioinks used in 3D bioprinting from 2013 to the present was carried out. Data was collected using different patent databases, such as the United States Patent and Trademark Offices (USPTO) PatFT/AppFT databases [75], the World Intellectual Property Organizations (WIPO) Patentscope search service [76], the European Patent Offices (EPO) Espacenet patent search [77], and the Cambia Institutes Lens patent data set [78]. Based on the list of supported field codes in patent databases, different codes have been used as search strategies. The field codes used for this study concern “boolean operators”, “field of search”, “fuzzy searches”, “proximity searches”, and “wildcard operators” [60]. During the search, different keywords and related terms were used, and patent documents were searched according to title, abstract, and claims.

Finally, the search was then filtered to include only patent applications and granted patents with publication dates until 31 August 2024.

4.2. Publication Year

The patent landscape for hydrogel-based bioinks has shown dynamic growth over the past decade. A total of 173 patent documents have been published, including 147 patent applications and 26 granted patents, reflecting the increasing interest and advancements in this emerging technology (Figure **3**).

During the initial phase from 2013 to 2017, patent activity was modest, with a total of 19 patent documents published (17 patent applications and 2 granted patents). In 2013, the landscape began with only three patent applications and no granted patents, signifying the early exploratory stage of hydrogel-based bioinks in 3D bioprinting. The number of patent applications gradually increased, reaching a peak of 7 in 2018. However, granted patents remained low during this period, with only a few appearing in 2016. This indicates that most of the innovations were still in their developmental phase and had not yet progressed to the stage of being granted full patent protection.

The years 2018 to 2020 marked a significant shift, with a total of 47 patent documents published (41 patent applications and 6 granted patents). In 2018, patent filings saw a modest increase with 7 applications but no granted patents, indicating ongoing research and development. By 2019, there was a notable surge in patent activity, with 20 applications and the emergence of 2 granted patents. This sharp increase reflects a growing recognition of the potential applications of hydrogel-based bioinks in various biomedical fields. The trend continued into 2020, with 14 applications and 4 granted patents, further underscoring the acceleration in innovation and the beginning of more frequent legal protections being granted.

In 2021, patent activity continued its upward trajectory with 23 patent documents (18 applications and 5 granted patents), demonstrating sustained innovation. The year 2022 saw the highest number of patent documents published during this period, with a total of 26 (22 applications and 4 granted patents). This reflects a significant phase of technological advancement, where numerous innovations were both filed and granted patent protection. The increase in granted patents during these years indicates that the research had matured enough for several innovations to meet the stringent criteria required for patent protection.

The period from 2023 to 2024 marks the peak of patent activity within this domain, with a total of 58 patent documents published (49 applications and 9 granted patents). The year 2023 saw an unprecedented spike, with 34 patent documents (31 applications and 3 granted patents). This peak suggests a period of intense innovation, likely driven by advancements in 3D bioprinting technology and a broader exploration of hydrogel-based bioinks. The trend remained strong in 2024, with 24 patent

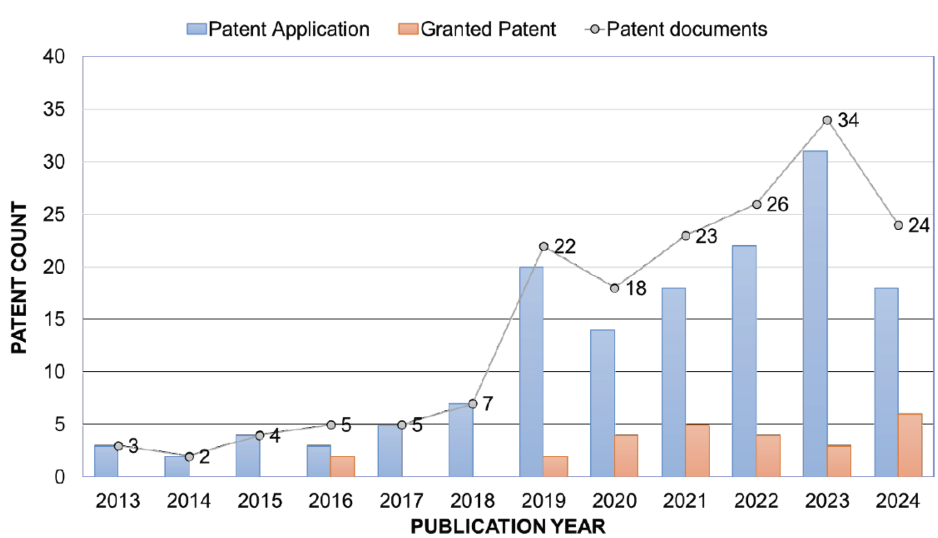

Figure 3: Distribution of patents related to hydrogel-based bioinks for 3D bioprinting as a function of publication year. The bar chart presents document types, which are categorized by patent applications, granted patents, and patent documents (sum of patent applications, granted patents).

documents (18 applications and 6 granted patents), indicating sustained innovation and a steady pace of patent filings.

4.3. Patent Applicants

The analysis of top patent applicants in the field of hydrogel-based bioinks for 3D bioprinting reveals a diverse array of organizations, ranging from companies to academic institutions, actively contributing to the innovation landscape (Figure **4**).

Organovo INC (Solana Beach, CA, United States) stands out as the leading patent applicant, with a total of 16 patent documents. As a company known for its pioneering work in 3D bioprinting, Organovos significant number of filings highlights its strategic focus on advancing hydrogel-based bioinks. Their extensive patent portfolio reflects ongoing efforts to innovate and secure intellectual property in this competitive field. Cellink AB (Gothenburg, Sweden), with 14 patent documents, is another major player in the industry. As a leader in the development of bioinks and bioprinting technologies, Cellinks strong presence in the patent landscape underscores its role as a key innovator in this domain. TDBT IP INC (New York, NY, United States) and Advanced Solutions Life Sciences LLC (Louisville, KY, United States) also demonstrate considerable patent activity, with 5 and 4 patent documents, respectively. These companies are actively exploring the potential of hydrogel-based bioinks, contributing to the expansion of intellectual property in this sector. Lung Biotechnology PBC (Silver Spring, MD, United States) is another notable company with 4 patent documents, indicating its interest in utilizing hydrogel-based bioinks for applications likely related to pulmonary and respiratory treatments.

Korea Institute of Science and Technology (Seoul, Republic of Korea), with 4 patent documents, represents the significant contribution of academic research to the development of hydrogel-based bioinks. As an academic institution, its involvement indicates a focus on foundational research and the exploration of new scientific frontiers in 3D bioprinting.

Universities such as the National University of Singapore (Queenstown, Singapore), North Carolina State University (Raleigh, NC, United States), and the University of Sydney (Sydney, New South Wales, Australia), each have 4 patent documents. These universities are playing a crucial role in advancing the knowledge base and developing novel applications for hydrogel-based bioinks, likely through collaboration with industry partners and through independent research initiatives. On the other hand, the University of Tampere Foundation (Tampere, Finland) and the University of Virginia Patent Foundation (Charlottesville, VA, United States), with 4 patent documents, exemplify the role of foundations in fostering innovation. As organizations dedicated to supporting academic research and innovation, these foundations involvement in patenting highlights their contribution to the translation of academic research into practical applications.

4.4. Patenting Jurisdictions

The global patent landscape for hydrogel-based bioinks in 3D bioprinting reveals significant patenting

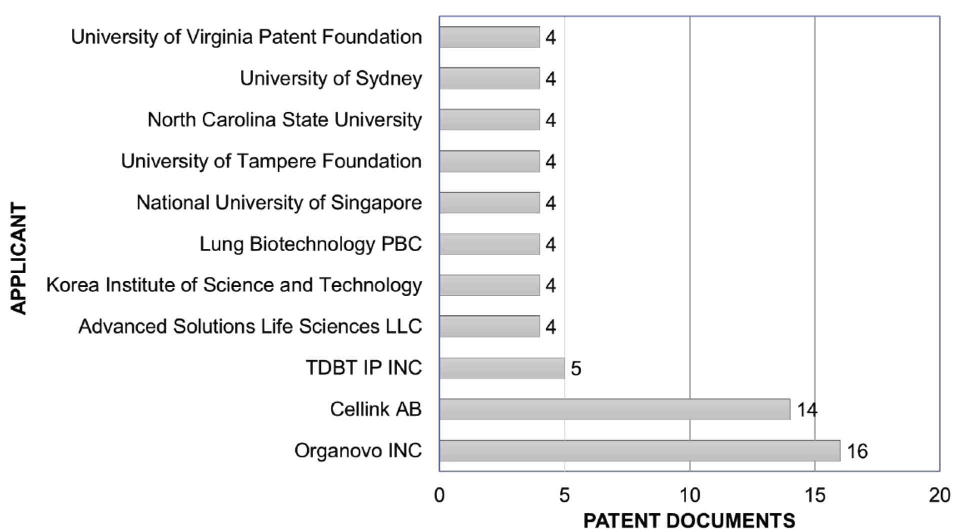

Figure 4: Distribution of patent documents as a function of patent applicants related to patenting activities in the area of hydrogel-based bioinks for 3D bioprinting.

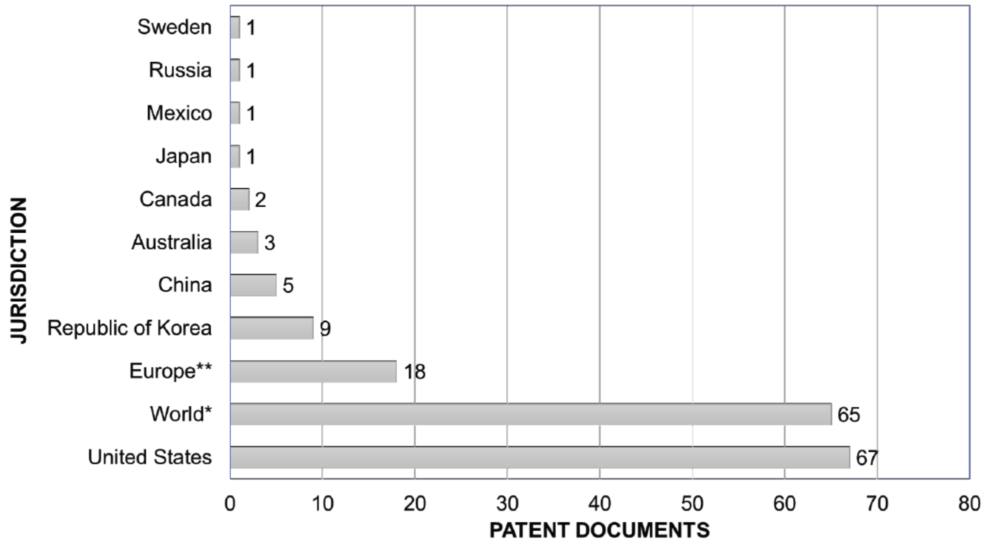

Figure 5: Distribution of patent documents across various jurisdictions related to patenting activities in the area of hydrogel-based bioinks for 3D bioprinting. *This refers to patent applications submitted under the Patent Cooperation Treaty (PCT), administered by WIPO. It allows an inventor to seek patent protection in multiple countries simultaneously by filing a single "international" patent application [79]. **This refers to the process of filing a patent application directly with the EPO. The EPO grants patents that are effective across multiple European countries, based on the European Patent Convention (EPC) [80].

activity across several key jurisdictions. This distribution of patent filings reflects the geographical hotspots of innovation as well as the regions actively pursuing intellectual property rights in this emerging field. Understanding these jurisdictional trends is crucial for stakeholders in academia, industry, and policy to identify competitive markets and regions of technological advancement. Figure **5** presents the distribution of patent documents across various jurisdictions related to patenting activities in the area of hydrogel-based bioinks for 3D bioprinting.

The United States emerges as a leading jurisdiction in the patenting of hydrogel-based bioinks, with 67 patent documents filed. This dominant position is reflective of the countrys strong infrastructure for innovation in biotechnology, advanced materials, and bioprinting technologies. US research institutions, startups, and established corporations are heavily involved in pushing the boundaries of 3D bioprinting, particularly in the biomedical field where hydrogel-based bioinks play a crucial role. The US patenting landscape is characterized by a combination of both established industry players and emerging firms focused on novel biomaterials for regenerative medicine and tissue engineering applications.

Following closely behind the United States, 65 patent documents have been filed through the WIPO. The strong presence of WIPO filings suggests a significant interest in international patent protection, indicating that innovators in the field recognize the global potential of hydrogel-based bioinks. WIPO applications allow inventors to seek protection across multiple countries, reflecting a strategy aimed at penetrating diverse markets and securing intellectual property rights on a global scale.

The EPO also shows considerable activity, with 18 patents filed. Europe has been at the forefront of research and development in the fields of advanced materials and biotechnology, which is reflected in the patent filings for hydrogel-based bioinks. European institutions and companies have been active in exploring innovative bioink formulations and bioprinting techniques, particularly in healthcare applications. The regions strong regulatory framework and focus on ethical and sustainable innovation further contribute to its position as a key player in this technological space.

Asia, particularly South Korea and China, also demonstrates notable patenting activity in hydrogel-based bioinks. South Korea has filed 9 patent documents, while China follows with 5. Both countries have made significant strides in advanced manufacturing technologies, including 3D bioprinting. South Koreas strong emphasis on biomedical innovation and Chinas rapidly growing biotechnology sector highlight these countries as important jurisdictions for the development and commercialization of hydrogel-based bioinks.

A smaller number of patent documents have been filed in other regions, including Australia (3 patents), Canada (2 patents), Japan (1 patent), Mexico (1 patent), Russia (1 patent), and Sweden (1 patent). These jurisdictions, while having fewer filings, represent emerging or specialized innovation centers within the broader field of hydrogel-based bioinks. Australia and Canada, for example, are known for their strong research ecosystems in life sciences, while Japans focus on precision manufacturing and materials science makes it a noteworthy player. The patent filings in Mexico, Russia, and Sweden suggest the beginning of activity in these regions, possibly driven by local academic research or niche commercial applications.

4.5. IPC Codes and Classification

In analyzing the patent landscape for hydrogel-based bioinks in 3D bioprinting, it is essential to examine the International Patent Classification (IPC) codes most frequently associated with these technologies. IPC codes categorize inventions by their technical features, and identifying the top IPC codes provides insight into the core technological domains where innovation is concentrated. Figure **6** presents the top 10 IPC codes related to hydrogel-based bioinks in 3D bioprinting. For more details, a synthesis of these codes related to hydrogel-based bioinks in 3D bioprinting based on their domains and applications is displayed in Table **2**.

The IPC code A61L27/38 pertains to materials specifically designed for tissue regeneration. Hydrogel-based bioinks fall within this classification due to their biocompatibility and ability to support cell growth in tissue engineering applications. The high number of patent filings underscores the significant research focus on developing bioinks that can serve as scaffolds for tissue repair and regeneration, which is critical in regenerative medicine and organ bioprinting.

A61L27/52 represents biocompatible hydrogels, a foundational component of many bioinks used in 3D bioprinting. These hydrogels are crucial for creating bioactive environments that can support cell viability and differentiation. The large number of patents in this category highlights the ongoing innovation in optimizing hydrogel formulations for various biomedical applications, including wound healing, drug delivery, and tissue scaffolding.

This IPC code, B33Y10/00, relates to additive manufacturing processes, specifically the printing of biological materials. As a core technology in bioprinting, this category covers the methods and apparatuses used for 3D printing cells and tissues. The significant patent activity in this area reflects the rapid advancements in bioprinting technologies, which are essential for producing complex tissue structures with high precision.

The B33Y80/00 code focuses on hybrid additive manufacturing, which integrates multiple technologies and materials, including biological and synthetic components. This classification is important for the development of multifunctional bioinks that can combine various properties, such as mechanical strength and biological activity, to meet the complex requirements of tissue engineering and organ fabrication.

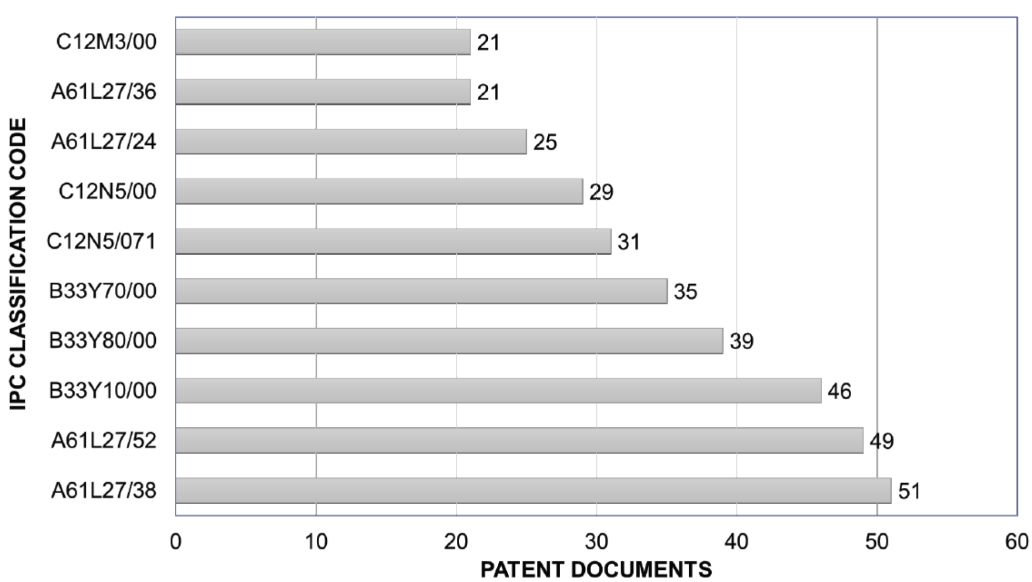

Figure 6: Top 10 IPC codes related to hydrogel-based bioinks in 3D bioprinting.

Table 2: Synthesis of IPC Codes Related to Hydrogel-Based Bioinks in 3D Bioprinting

Subclass	IPC code	Domain	Applications
A61L (Medical devices and biomaterials)	A61L27/38	Biomaterials for medical use	Compositions used for coatings, fillers, or adhesives that are biocompatible, often used in surgical implants or prosthetics. These materials may include hydrogels or other polymers suitable for interaction with biological tissues.
	A61L27/52	Materials for medical use	Bioactive materials that promote tissue regeneration, including those used in 3D-printed scaffolds. It includes substances that encourage cell attachment and growth, making them ideal for tissue engineering.
	A61L27/24	Coatings for medical devices	Surface modifications of implants or prosthetics, specifically coatings that are designed to be biocompatible and may include drug-eluting coatings or anti-microbial surfaces.
	A61L27/36	Artificial organs and tissues	Materials and methods for creating artificial tissues and organs, including 3D-printed constructs that mimic the ECM of natural tissues.
B33Y (3D Bioprinting and additive manufacturing)	B33Y10/00	Additive manufacturing, particularly 3D printing	Methods and apparatuses used in 3D printing, especially in the context of bioprinting. This code includes techniques for layering materials to create complex structures, which are particularly relevant in the manufacturing of medical devices and tissues.
	B33Y80/00	Materials used in additive manufacturing	Various materials used in 3D printing, including bioinks, polymers, and other substances suitable for creating biological tissues or implants.
	B33Y70/00	Product-specific applications of additive manufacturing	Specific products made via 3D printing technologies, including medical implants, prosthetics, and possibly custom-fitted devices for individual patients.
C12N (Biotechnology)	C12N5/071	Culturing of cells, including stem cells	Methods for culturing human or animal cells, particularly stem cells, and can include the use of these cells in bioprinting applications for regenerative medicine or tissue engineering.
	C12N5/00	General biotechnology related to cells	Manipulation and use of animal or human cells for various biotechnological applications, including but not limited to genetic engineering, therapeutic uses, and cell-based assays.
C12M (Biotechnology equipment)	C12M3/00	Apparatus for enzymology or microbiology	Devices and apparatus specifically designed for cultivating, maintaining, or manipulating microorganisms or cells, including those used in bioreactors or other systems for cell culture. This is relevant to bioprinting as it involves the equipment necessary for preparing and handling cells and bioinks before and during the printing process.

B33Y70/00 covers the post-processing of products created through additive manufacturing. In the context of hydrogel-based bioinks, post-processing may involve curing, cross-linking, or further modification of printed structures to enhance their mechanical properties or biological performance. The patents under this code reflect the importance of refining printed tissues or scaffolds after the initial printing process to achieve the desired functionality.

C12N5/071 pertains to culture media used for stem cells, which are a critical component in many bioinks for tissue engineering. The use of hydrogel-based bioinks to encapsulate and support stem cells is a significant area of research, particularly for applications in regenerative medicine and therapeutic treatments. This IPC code indicates ongoing innovation in creating optimal environments for stem cell proliferation and differentiation within bioprinted structures.

C12N5/00 relates to undifferentiated cells, including stem cells. Bioinks that incorporate undifferentiated cells are essential for creating tissues that can develop and mature into functional organs or structures after bioprinting. The patents in this classification highlight the focus on leveraging the pluripotent or multipotent nature of stem cells within bioprinted constructs for medical applications.

A61L27/24 covers coatings used on implants or prostheses, particularly biocompatible coatings. In 3D bioprinting, hydrogel-based bioinks are often used to coat or encapsulate printed structures to improve biocompatibility and integrate with the host tissue. This classification underscores the intersection between bioinks and medical devices, where bioinks are used to enhance the performance of implants or tissue scaffolds.

A61L27/36 is associated with bioactive materials that can elicit specific biological responses, such as promoting cell adhesion, proliferation, or differentiation. Hydrogel-based bioinks that incorporate bioactive components are designed to interact with the biological environment and facilitate tissue regeneration or repair. The patents in this category reflect the importance of developing bioinks with functional properties that go beyond simple structural support.

C12M3/00 involves devices for enzymatic or microbiological treatment, which can be relevant for bioinks designed for bioreactor environments or other applications where biological processes play a key role. The inclusion of this IPC code in the top 10 indicates that some hydrogel-based bioinks are being developed for specialized applications where microbial or enzymatic activity is integral to the overall functionality of the bioprinted constructs.

5. CHALLENGES AND PERSPECTIVES

5.1. Current Limitations and Challenges

In the domain of biomaterials for medical use (A61L27/38), current limitations include the challenge of ensuring long-term stability in biological environments, which remains a key obstacle. Achieving the necessary mechanical properties for different applications is another critical hurdle, as many biomaterials fail to replicate the strength and flexibility needed. Additionally, these materials may provoke immune rejection or inflammation, which further limits their clinical effectiveness [81].

For materials used in medical applications (A61L27/52), controlling the release kinetics of bioactive agents is particularly difficult, making it challenging to deliver consistent therapeutic effects over time. The materials also struggle to replicate the intricate structures of natural tissues, which is essential for advanced medical interventions. Moreover, scaling up production for clinical use presents significant technical and logistical challenges, further impeding widespread adoption [82].

In the realm of coatings for medical devices (A61L27/24), the application methods often require complex procedures that may not ensure uniform coating thickness or consistent properties across the device. This inconsistency can affect the performance and reliability of the coated medical devices in clinical environments [83].

Artificial organs and tissues (A61L27/36) face substantial challenges in achieving high-resolution precision during the fabrication process, particularly for complex tissue structures. Functional vascularization, which is essential for tissue survival and integration, remains difficult to achieve, limiting the success of artificial organ development [84].

Additive manufacturing, particularly 3D printing (B33Y10/00), also encounters several limitations. One of the most pressing issues is the limited resolution available for fine tissue structures, which hinders the creation of intricate designs. Slow printing speeds, especially for large or complex constructs, further reduce the feasibility of using 3D printing for many medical applications. Additionally, maintaining cell viability during lengthy printing processes is difficult, as cells may be damaged or lose functionality over time [85].

When it comes to materials used in additive manufacturing (B33Y80/00), maintaining material properties after printing is a significant challenge, especially when dealing with biopolymers or novel composites. Creating multi-material constructs with distinct properties is also difficult, limiting the ability to produce complex devices with tailored characteristics. Moreover, the availability of suitable materials for specific additive manufacturing processes can be a barrier, particularly for advanced medical applications [86].

Product-specific applications of additive manufacturing (B33Y70/00) face regulatory challenges, especially when it comes to custom medical devices that require individual approval. The high costs associated with personalized manufacturing make it difficult to scale these solutions for broader use. Additionally, there is a lack of long-term clinical data on 3D-printed implants, which hinders their widespread acceptance in medical practice [1].

For cell culturing, including stem cells (C12N5/071), maintaining stem cell pluripotency over time is difficult, which limits their therapeutic potential. Directing differentiation toward specific cell types presents additional challenges, and the risk of genetic instability in long-term cultures raises concerns about the safety and effectiveness of stem cell therapies [87].

General biotechnology related to cells (C12N5/00) is also constrained by ethical and regulatory concerns surrounding certain types of cell manipulations, particularly when it comes to genetic editing or cloning. Scaling up these technologies for industrial applications is difficult, as cell behavior can vary widely between *in vitro* and *in vivo* environments, making reproducibility a challenge [1].

Lastly, apparatus for enzymology or microbiology (C12M3/00) often face difficulties in maintaining sterility within complex systems, which is critical for ensuring reliable results. The high cost of specialized equipment required for these processes adds further strain. Additionally, the devices can inadvertently cause cell damage and uneven nutrient distribution, which may affect cell health and compromise experimental outcomes [88].

5.2. Potential Solutions and Future Perspectives

As the field of hydrogel bioinks continues to evolve, several emerging trends point to promising future directions for development. One key area of focus is the introduction of DN hydrogels, which consist of two interpenetrating networks that allow for greater energy dissipation and resilience under stress, making hydrogels suitable for applications where flexibility and strength are paramount, such as in soft tissue engineering and wound healing [62,64]. Another key area of focus is the incorporation of advanced materials, such as nanocomposites, to enhance the functionality and performance of hydrogels [30,64,65]. Additionally, the development of stimuli-responsive hydrogels that can undergo dynamic changes in response to environmental cues, such as temperature or pH, is expected to enable more sophisticated control over cell behavior and tissue regeneration [73].

Functionalization of hydrogels with bioactive molecules and/or incorporating growth factors, peptides, or other signaling molecules could also be considered as potential solutions. They will promote cell behavior and tissue regeneration as well as actively participate in biological processes, such as angiogenesis and cell differentiation. This approach allows for the design of smart hydrogels tailored to specific therapeutic needs, enhancing their effectiveness in tissue engineering applications [41,65].

Another promising solution is the use of interdisciplinary approaches to advance hydrogel bioink technology. By combining expertise from fields like materials science, engineering, biology, and medicine, researchers can create more effective and innovative solutions for tissue engineering challenges [73,89]. For instance, the integration of computational modeling and high-throughput screening techniques can accelerate the development and optimization of hydrogel formulations, while collaborations between academia and industry can facilitate the translation of research into clinical applications.

6. OVERVIEW OF RECENT PATENTS AND IMPLICATIONS OF PATENT TRENDS

The patent landscape for hydrogel bioinks used in 3D bioprinting has seen significant developments in recent years, reflecting the growing interest and innovation in this field [90]. To demonstrate the innovation trends in hydrogel bioinks, a selection of recent patent documents is proposed hereinafter. Table **3** presents a selection of the latest innovations and improvements in hydrogel-based bioinks used in 3D bioprinting and biofabrication that are demonstrated by inventions and patents.

The types of innovations covered by these patents range from novel hydrogel formulations to tissue and organ replacements via advanced bioprinting techniques. Many patents focus on the functional properties of hydrogels, such as their mechanical strength, biocompatibility, and degradation rates, which are critical for their application in tissue engineering. Additionally, there is a growing trend toward the incorporation of bioactive molecules and nanocomposites into hydrogel formulations, enhancing their performance and enabling new functionalities. This diversification in patent filings indicates a shift towards more sophisticated bioink formulations that can better meet the demands of complex tissue engineering applications [68,73].

The trends observed in patent activity for hydrogel bioinks provide valuable insights into industry priorities and innovation areas. The increase in patent filings suggests a heightened focus on developing advanced materials and techniques that can overcome existing limitations in hydrogel performance, such as mechanical strength and printability. This reflects a broader industry trend towards creating more functional and versatile bioinks capable of supporting the intricate structures required for effective tissue regeneration. The emphasis on hybrid hydrogels and nanocomposites in recent patents indicates a strategic move towards enhancing the mechanical properties

Table 3: Selection of Top 10 Recent Patents Related to Hydrogel Bioinks used in 3D Bioprinting

Patent N°	Publication date	Title	Patent document	Ref.
WO 2024166113A1	August 15, 2024	Reinforced engineered cellularized-tissue	Patent Application	[91]
US20240261475A1	August 8, 2024	3D Bioprinting of cell-laden-collagen gellan gum interpenetrating network hydrogel	Patent Application	[92]
KR20240114492A	July 24, 2024	Bioink composition for preparing immunopolarized exosome laden 3D bioprinted hydrogel and use of the same	Patent Application	[93]
EP3755305B1	July 17, 2024	Morphogenic compound-releasing microspheres and use in bioink	Granted Patent	[94]
US12029832B2	July 9, 2024	Three-dimensional bioprinting of cardiac patch with anisotropic and perfusable architecture	Granted Patent	[95]
EP3946483B1	July 3, 2024	Methods of making tissue and organ replacements	Granted Patent	[96]
US20240200026A1	June 20, 2024	Compositions, systems, and methods related to plant bioprinting	Patent Application	[97]
US20240189482A1	June 13, 2024	Human nasal turbinate-derived mesenchymal stem cell-based, 3d bioprinted construct, and use thereof	Patent Application:,	[98]
US20240182883A1	June 6, 2024	Interpenetrating network microbial hydrogel with natural polysaccharide and protein and preparation method thereof	Patent Application	[99]
WO2024118942A1	June 6, 2024	3D printing of high cell density vascularized tissue	Patent Application	[100]

and biological functionalities of these materials, aligning with the growing demand for high-performance bioinks in clinical applications.

However, the competitive nature of the patent landscape also presents potential barriers to entry for new players in the field. The concentration of patent ownership among a few key companies and institutions may limit opportunities for smaller entities or startups to innovate without infringing on existing patents. Additionally, the rapid pace of technological advancements in hydrogel formulations and bioprinting techniques necessitates continuous research and development efforts to stay relevant in the market. Despite these challenges, the evolving patent landscape also presents opportunities for collaboration and partnerships between academia and industry, fostering innovation and accelerating the translation of hydrogel bioinks from research to clinical practice [73,90].

7. CONCLUSIONS

The analysis of hydrogel-based bioinks for 3D bioprinting highlights their critical role in advancing tissue engineering and regenerative medicine. Hydrogels, with their unique properties such as high water content, biocompatibility, and tunable mechanical characteristics, serve as essential materials that mimic the extracellular matrix. Recent technological advancements have led to the development of innovative hydrogel formulations, including nanocomposites and bioactive molecules, which enhance mechanical strength and functionality. Furthermore, various bioprinting techniques, such as extrusion-based and inkjet printing, have been explored to optimize the performance of hydrogel bioinks, enabling the creation of complex, viable tissue constructs.

The patent landscape analysis in this study reveals significant activity in the field, indicating a growing interest and investment in hydrogel bioinks. However, challenges remain, including achieving ideal mechanical properties, ensuring long-term cell viability, and navigating the regulatory landscape for commercialization. Addressing these challenges will be crucial for the successful translation of hydrogel technologies from the laboratory to clinical applications.

Looking to the future, continued research and innovation in hydrogel-based bioinks are essential for advancing 3D bioprinting technologies. Emerging trends, such as the incorporation of advanced materials and interdisciplinary approaches, promise to enhance the capabilities of hydrogel bioinks and expand their applications in regenerative medicine. By fostering collaboration between academia and industry, the potential for developing effective and functional tissue-engineered products can be realized, ultimately improving patient outcomes and transforming the field of medicine. As the landscape of hydrogel research evolves, it will be important to remain vigilant in addressing the challenges while capitalizing on the opportunities that arise, ensuring that hydrogel bioinks continue to play a pivotal role in the future of 3D bioprinting.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study is available within this articles content.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare that this articles content has no conflict of interest. The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in this article.

ACKNOWLEDGEMENTS

The authors acknowledge the WIPO for the Patentscope search service, the EPO for the Espacenet patent search, the USPTO for the PatFT/AppFT databases, and the Cambia Institute for the Lens patent data set used in this study. Ms. Raja Saadan gratefully acknowledges the CNRST (Centre National pour la Recherche Scientifique et Technique) in Morocco for the PhD-Associate Scholarship (PASS 2024-2027). Additionally, she acknowledges the French Embassy in Morocco and the CNRST. for the grant obtained through the “Doctoral Mobility Program 2024”. On the other hand, Ms. Chaymaa Hachimi Alaoui gratefully acknowledges the CNRST in Morocco for the PhD scholarship (PBER 2022). She also acknowledges Campus France and the CNRST for the grant obtained (PHC TBK/23/175 48607YF) through the “Partenariat Hubert Curien TOUBKAL 2023”. Furthermore, she is a beneficiary of the “Short-Term Support Program for Doctoral Mobility 2023” and the “Doctoral Research Stay in France Program 2024”, both funded by the Cultural Cooperation and Action Service of the French Embassy in Morocco.

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Received on 07-08-2024 Accepted on 03-09-2024 Published on 27-09-2024

https://doi.org/10.6000/1929-5995.2024.13.14