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Patent landscape analysis of hydrogel-based bioinks for three-dimensional bioprinting †

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Abstract: There are a variety of hydrogel-based bioinks commonly used in three-dimensional bioprinting. In this study in the form of patent landscape analysis, the state of the art has been reviewed by introducing what has been patented in relation to hydrogel-based bioinks. Furthermore, a detailed analysis of the patentability of the used hydrogels, their preparation methods and their formulations, as well as the 3D bioprinting process using hydrogels, have been provided by determining publication years, jurisdictions, inventors, applicants, owners, and classifications. The classification of patents reveals that most inventions intended for hydrogels used as materials for prostheses or for coating prostheses characterized by their function or properties. Knowledge clusters and expert driving factors indicate that the research based on biomaterials, tissue engineering and biofabrication is concentrated in the most patents.

Keywords: bioinks; hydrogels; 3D bioprinting; intellectual property; patent.

1. Introduction

There are a variety of hydrogels commonly used in three-dimensional (3D) bioprinting which is the process involving the deposition of cell-laden hydrogels (or bioinks) on a substrate (Figure 1). Hydrogels are synthetic matrices made up of a network of hydrophilic polymers that absorb water and/or biological fluids. They can be created from a large number of water-soluble materials including synthetic polymers (e.g., polyethylene glycol, polylactic acid, etc.), proteins (e.g., collagen, gelatin, etc.), and polysaccharides (e.g., alginate, hyaluronic acid, etc.) [1-4].

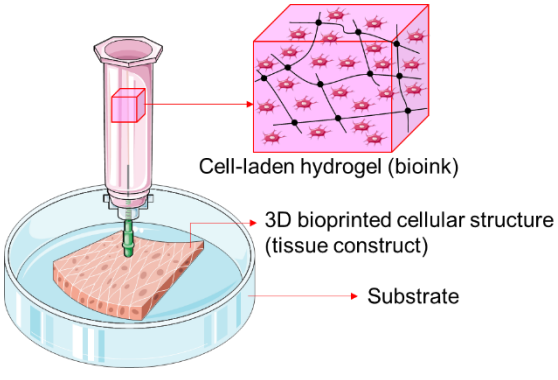

Figure 1. Schema of 3D bioprinting process involving the deposition of cell-laden hydrogels (or bioinks) on a substrate to create 3D cellular structures for tissue engineering applications.

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The 3D structure of these hydrogels is due to crosslinking which forms an insoluble macromolecular network in the environmental fluid (Figure 2). The resemblance to different biological tissues, due to the elasticity and the presence of a large amount of water, allows the use of hydrogels in the regeneration of several types of damaged tissues (e.g., fibrin hydrogel is seeded with neural cells to regenerate brain tissue, keratinocytes are seeded in collagen hydrogel to regenerate skin tissue, etc.) [5,6].

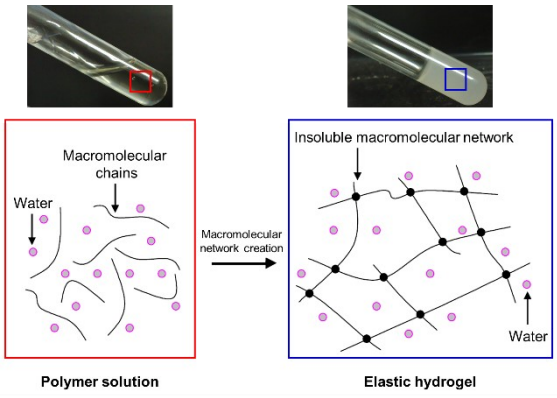

Figure 2. Schema of hydrogel crosslinking which forms an insoluble macromolecular network in the environmental fluid

The first patent application concerning hydrogel-based bioinks was filled in 2005, and then granted in 2012 [7]. Through this patent, Forgacs *et al.* have invented an apparatus comprising among other a cartridge comprising one or more cell aggregates. Inventors have then proved the concept by bioprinting a fused ring structure by using cell aggregates and poly(N-(hydroxypropyl)methacrylamide)-based hydrogel as bioink [7].

To promote the sufficiency of bioinks in 3D bioprinting, several researchers have investigated pathways to enhance bioink properties to meet bioprinting requirements, with several hydrogels developed. Research on hydrogels as bioinks is developing rapidly through the innovation and improvement of raw materials (synthetic and natural polymers), synthesis and methods of preparation, as well as formulations and biofabrication process. Moreover, more than 100 organizations (universities, academic institutes, companies, foundations, government bodies, etc.) around the world are currently involved in the patent activity and filing concerning hydrogel-based bioinks. This trend is justified by the several advantages that hydrogels offer for bioprinting and biomedical applications. This is also evident from the elevation in the number of patent applications filed each year worldwide in research and development of this area. For example, patent applications related to hydrogel-based bioinks have increased from 3 to 103, during the period from 2013 to 2020, respectively [8].

This work in the form of patent landscape analysis, which is a family of techniques for studying the information present within and attached to patents, describes the state of the art by introducing what has been innovated and patented in relation to hydrogel-based bioinks regarding to used hydrogels, their preparation methods and their formulations, as well as the 3D bioprinting process using hydrogels. Furthermore, this work gives a competitive analysis of the past, present and future trends in the hydrogel-based bioinks and leads to various recommendations that could help one to plan and innovate research strategy.

2. Resources and analysis

2.1. Resources and research methods

The supported field codes used in this study was based on the Patentscope search service of the World Intellectual Property Organization (WIPO) [8,9] and The Lens patent

data set [10]. During the search, different keywords and related terms were used and patents were searched according to title, abstract and claims. The search was then filtered to include only documents with the application date until 2020.

2.2. Analysis of the patentability of hydrogel-based bioinks

The search indicates that 119 patent documents have been found. Generally, it encompasses patent applications and granted patents. For relation to hydrogel-based bioinks the found patent documents are classed as: 103 patent applications and 16 granted patents.

Here we will review the state of the art by introducing what has been patented in relation to hydrogel-based bioinks. We provide then a detailed analysis of the patentability of the used hydrogels, their preparation methods and their formulations, as well as the 3D bioprinting process, following these sections:

- Publication year;
- Jurisdiction;
- Inventors;
- Applicants;
- Owners;
- Patent classifications.

3. Results

3.1. Publication year

The date on which a patent document is published, thereby making it part of the state of the art. For hydrogel-based bioinks, 119 patent documents have been found until 2020. The year 2013 knew the registration of 3 patent documents only (exclusively patent applications), however the year 2020 recorded 31 patent documents (24 patent applications and 7 granted patents). The maximum of patent applications (25) was recorded in 2019, however, the maximum of granted patents (7) was recorded in 2020.

3.2. Jurisdiction

An applicant or first mentioned applicant in case of joint applicants can file application for patent at the appropriate Patent Office (e.g., European Patent Office (EPO), United States Patent and Trademark Office (USPTO), Korean Intellectual Property Office (KIPO), China National Intellectual Property Administration (CNIPA), etc.) under whose jurisdiction he normally resides or has his domicile or has a place of business or the place from where the invention actually originated. For hydrogel-based bioinks, the top 10 of jurisdiction of filled patents until 2020 are presented in Table 1.

Table 1. Jurisdiction (top 10) of resulted patents as a function of patent documents and patent contribution (%) of hydrogel-based bioinks.

Jurisdiction	Patent documents	Patent contribution (%)
United States	32	26.89
PCT	26	21.85
China	25	21.01
Republic of Korea	16	13.45
Australia	10	8.40
Europe	6	5.04
Sweden	1	0.84
Russia	1	0.84
Eurasia	1	0.84
Canada	1	0.84

United States through the USPTO encompasses 32 patent documents with a higher patent contribution per total of ~26.9%. On the other hand, the global system for filing patent applications, known as Patent Cooperation Treaty (PCT) and administered by WIPO encompasses 26 patent documents with a patent contribution per total of ~21.8%, as well as China through the CNIPA encompasses 25 patent documents with a patent contribution per total of ~13.4%. Finally, the EPO, through where patent applications filled regionally (Europe), encompasses 6 patent documents with a patent contribution per total of ~5%.

3.3. Inventors

The inventor is a natural person designated for a patent application. In several cases, the inventor can also be the applicant, as well as there may be more than one inventor per patent application [11].

For hydrogel-based bioinks, the top 10 of inventors until 2020 are presented in Table 2. The inventors Murphy Keith and Dorfman Scott from United States are ranked as the co-first inventors which have recorded 18 patent documents each one. In the second place, the inventor Law Richard Jin from United States has recorded 13 patent documents.

All found patent documents of these three above inventors concern the healthcare company Organovo INC (Solana Beach, CA, United States) as applicants and/or owners. It's specialized on the design and development of human tissues for *in vitro* and therapeutic applications, such as preclinical testing and drug discovery research, by utilizing 3D bioprinting technology.

Table 2. Inventors (top 10) of resulted patents as a function of patent documents of hydrogel-based bioinks.

Inventors	Patent documents
Murphy Keith	18
Dorfman Scott	18
Law Richard Jin	13
Martinez Hector	10
Gatenholm Erik	9
Utama Robert Hadinoto	7
Fife Christopher Michael	7
Ribeiro Julio Cesar Caldeira	7
Atapattu Lakmali	7
Le Vivian Anne	7

3.4. Applicants

The applicant is a person (i.e., natural person) or an organization (i.e., legal entity) that has filed a patent application. In several cases, the applicant can also be the inventor, as well as there may be more than one applicant per patent application [11].

For hydrogel-based bioinks, the top 10 of applicants until 2020 are presented in Table 3. Regarding to this top 10, all applicants are considered as organizations: companies, foundations, academic institutions, or universities.

The company Organovo INC (Solana Beach, CA, United States), as a legal entity, is ranked as the first applicant which has recorded 19 patent documents. In the second place, the company Cellink AB (Gothenburg, Sweden), as a legal entity, has recorded 10 patent documents. Thirdly, the company Inventia Life Science PTY LTD (Alexandria, Australia), as a legal entity, has recorded 7 patent documents.

Table 3. Applicants (top 10) of resulted patents as a function of patent documents of hydrogel-based bioinks.

Applicants	Patent documents
Organovo INC	19
Cellink AB	10
Inventia Life Science PTY LTD	7
POSTECH Academy-Industry Foundation	5
Advanced Solutions Life Sciences LLC	5
Korea Institute of Science and Technology	5
Hangzhou Meizhuo Biotechnology CO LTD	3
Ulsan National Institute of Science and Technology	3
Texas A&M University System	3
Revotek CO LTD	2

3.5. Owners

Assignee or patent owner is a person (i.e., natural person) or an organization (i.e., legal entity) to whom the inventor or applicant assigned the right to a patent. The patent owner has the right, for a period limited to the duration of the patent term to protect his brainchild. The patent system stops others from making, using or selling the invention without his permission or requires others to use the invention under agreed terms with the inventor [12].

For hydrogel-based bioinks, the top 10 of owners until 2020 are presented in Table 4. Regarding to this top 10, all owners are considered as organizations: companies, universities, foundations, or government bodies).

The company Organovo INC (Solana Beach, CA, United States), as a legal entity, is ranked as the first owner which has recorded 8 patent documents. In the second place, the company Cellink AB (Gothenburg, Sweden), as a legal entity, has recorded 3 patent documents. As for the podium of the third place it is shared between eight legal entities that are: Inventia Life Science PTY LTD (Alexandria, Australia), Medical University of South Carolina (Charleston, SC, United States), Advanced Solutions Life Sciences LLC (Louisville, KY, United States), Texas A&M University System (College Station, TX, United States), MUSC Foundation for Research Development (Charleston, SC, United States), Revotek CO LTD (Lewes, DE, United States), Board of Regents the University of Texas System (Austin, TX, United States), and Curators of the University of Missouri (Columbia, MO, United States), with 2 patent documents each one.

Table 4. Owners (top 10) of resulted patents as a function of patent documents of hydrogel-based bioinks.

Owners	Patent documents
Organovo INC	8
Cellink AB	3
Inventia Life Science PTY LTD	2
Medical University of South Carolina	2
Advanced Solutions Life Sciences LLC	2
Texas A&M University System	2
MUSC Foundation for Research Development	2
Revotek CO LTD	2
Board of Regents the University of Texas System	2
Curators of the University of Missouri	2

3.6. Patent classifications

The International Patent Classification (IPC) is a hierarchical system in the form of codes, which divides all technology areas into a range of sections, classes, subclasses, groups and subgroups. It is an international classification system that provides standard information to categorize inventions and to evaluate their technological uniqueness [13,14].

For hydrogel-based bioinks, the top 10 of IPC codes until 2020 are presented in Table 5. The most IPC code corresponds to A61K9/52 which is a subgroup of materials for prostheses or for coating prostheses characterized by their function or physical properties, more specifically, it concerns hydrogels or hydrocolloids. This subgroup recorded it alone 38 patent documents. The second IPC code corresponds to A61L27/38 which is a subgroup of materials for prostheses or for coating prostheses containing ingredients of undetermined constitution or reaction products thereof, such as animal cells, has recorded 34 patent documents.

Table 5. IPC codes (top 10) of resulted patents concerning hydrogel-based bioinks as a function of patent documents with the meaning of each IPC code [13].

IPC	Description	Patent documents
A61L27/52	Materials for prostheses or for coating prostheses characterized by their function or physical properties: hydrogels or hydrocolloids.	38
A61L27/38	Materials for prostheses or for coating prostheses containing ingredients of undetermined constitution or reaction products thereof: animal cells.	34
B33Y80/00	Products made by additive manufacturing.	32
B33Y10/00	Processes of additive manufacturing.	30
B33Y70/00	Materials specially adapted for additive manufacturing.	26
A61L27/20	Materials for prostheses or for coating prostheses in the form of macromolecular materials: polysaccharides.	20
C12M1/00	Apparatus for enzymology or microbiology.	18
C12N5/00	Undifferentiated human, animal or plant cells (e.g., cell lines; tissues; cultivation or maintenance thereof; culture media therefor).	18
B33Y30/00	Apparatus for additive manufacturing; details thereof or accessories therefor.	18
C12M3/00	Tissue, human, animal or plant cell, or virus culture apparatus.	17

4. Conclusions

This study in the form of patent landscape analysis concerned only the innovation and improvement of hydrogel-based bioinks until 2020. A detailed analysis of the patentability of the used hydrogels, their preparation methods and their formulations, as well as the 3D bioprinting process using hydrogels, have been provided. During search, we found 119 patent documents (103 patent applications and 16 granted patents) have been found. The United States was ranked first with 32 patent documents and 2020 was the year with the maximum number of patent documents (31).

The innovation and improvement of hydrogel-based bioinks concerned especially raw materials (synthetic and natural polymers), synthesis and methods of preparation, as well as formulations and fabrication process. Based on the patent classification, all filled patents and the most inventions intended for materials for prostheses or for coating prostheses, characterized firstly by their function or physical properties such as hydrogels or hydrocolloids, and containing secondly ingredients of undetermined constitution or reaction products thereof such as animal cells. Knowledge clusters and expert driving factors indicate that the research based on products made by additive manufacturing, processes of additive manufacturing, and materials specially adapted for additive manufacturing, is concentrated in the most patents.

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References

1. Zhang, S.; Huang, D.; Lin, H.; Xiao, Y.; Zhang, X. Cellulose Nanocrystal Reinforced Collagen-Based Nanocomposite Hydrogel with Self-Healing and Stress-Relaxation Properties for Cell Delivery. *Biomacromolecules* **2020**, 21, 2400-2408, doi:10.1021/acs.biomac.0c00345.
2. Roehm, K.D.; Madihally, S.V. Bioprinted chitosan-gelatin thermosensitive hydrogels using an inexpensive 3D printer. *Biofabrication* **2017**, 10, 015002, doi:10.1088/1758-5090/aa96dd.
3. Narayanan, L.K.; Huebner, P.; Fisher, M.B.; Spang, J.T.; Starly, B.; Shirwaiker, R.A. 3D-Bioprinting of Polylactic Acid (PLA) Nanofiber–Alginate Hydrogel Bioink Containing Human Adipose-Derived Stem Cells. *ACS Biomaterials Science & Engineering* **2016**, 2, 1732-1742, doi:10.1021/acsbiomaterials.6b00196.
4. Skardal, A.; Zhang, J.; Prestwich, G.D. Bioprinting vessel-like constructs using hyaluronan hydrogels crosslinked with tetrahedral polyethylene glycol tetracrylates. *Biomaterials* **2010**, 31, 6173-6181, doi:10.1016/j.biomaterials.2010.04.045.
5. Lee, C.; Abelseth, E.; de la Vega, L.; Willerth, S.M. Bioprinting a novel glioblastoma tumor model using a fibrin-based bioink for drug screening. *Materials Today Chemistry* **2019**, 12, 78-84, doi:10.1016/j.mtchem.2018.12.005.
6. Lee, V.; Singh, G.; Trasatti, J.P.; Bjornsson, C.; Xu, X.; Tran, T.N.; Yoo, S.-S.; Dai, G.; Karande, P. Design and Fabrication of Human Skin by Three-Dimensional Bioprinting. *Tissue Engineering Part C: Methods* **2013**, 20, 473-484, doi:10.1089/ten.tec.2013.0335.
7. Forgacs, G.; Jakab, K.; Neagu, A.; Mironov, V. Self-assembling cell aggregates and methods of making engineered tissue using the same. Granted Patent: US 8241905 B2; Published: Aug 14, 2012; Filed: Feb 24, 2005, United States, 2012.
8. World Intellectual Property Organization. Patentscope. Available online: https://patentscope.wipo.int (accessed on September 2, 2021).
9. World Intellectual Property Organization. Patentscope fields definition. Available online: https://patentscope.wipo.int/search/en/help/fieldsHelp.jsf (accessed on September 2, 2021).
10. Cambia Institute. The Lens Patent Data Set. Available online: https://www.lens.org, Version 8.0.14 (accessed on September 2, 2021).
11. European Patent Office. Espacenet Glossary. Available online: https://worldwide.espacenet.com/patent, Version 1.24.1 (accessed on September 2, 2021).
12. World Intellectual Property Organization. What is Intellectual Property? Frequently Asked Questions: Patents. Available online: https://www.wipo.int/patents/en/faq_patents.html (accessed on September 2, 2021).
13. World Intellectual Property Organization. IPC Publication. Available online: https://www.wipo.int/classifications/ipc/ipcpub, IPCPUB v8.5 (accessed on September 2, 2021).
14. World Intellectual Property Organization. Guide to the International Patent Classification (IPC). Available online: https://www.wipo.int/edocs/pubdocs/en/wipo_guide_ipc_2020.pdf (accessed on September 2, 2021).