



TRAILBLAZING THE FUTURE WITH EMERGING BIOMATERIALS

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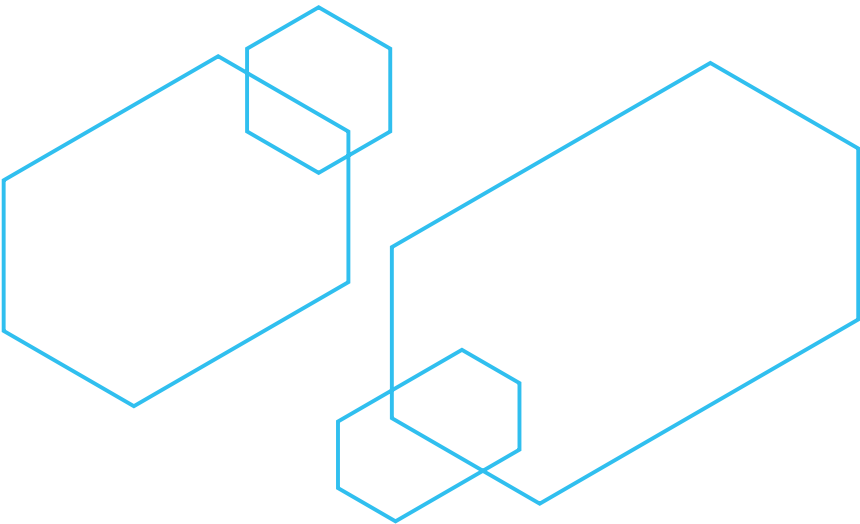
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Synopsis

Health stands as the bedrock of human existence and the linchpin for a high-quality life, therefore research in this area represents a vital global aspiration for a healthier future. Yet, the evolving societal landscape and environmental shifts have ushered in diverse health challenges. Issues such as the rapid transmission of infectious diseases like COVID-19 and environmental pollution pose significant threats to human well-being. Modern lifestyles further elevate the risks of chronic diseases and mental health concerns. Confronting these shared health challenges has become an urgent global imperative.

Materials silently influence our quality of life, continually enhancing human health, from commonplace consumer goods to intricate medical devices and surgical materials. Materials science, through its involvement in cutting-edge medical equipment, improved drug delivery systems, innovative diagnostic tools, and the development of intelligent monitoring and sustainable materials, emerges as a key element in improving human health. Strides in material science have become pivotal in propelling advancements in healthcare, and the future augmentation of human health will increasingly hinge on progress in materials science. Ongoing fundamental research and the application of novel materials are not only steering the future trajectory of the health industry but also shaping the industries of the future, catalyzing the formation of transformative productive forces.

This report is a collaborative effort between Westlake University and CAS, a division of the American Chemical Society. Together, teams from these two organizations delved into the dynamic landscape of the future development of materials used in biomedical applications. Westlake University focuses on cutting-edge scientific research, dedicates itself to breakthroughs in advanced technology, emphasizes interdisciplinary collaboration, and consistently places the promotion of human health and well-being as one of its core missions. CAS, with its diverse reservoir of expert scientific knowledge, extensive collection of indexed content, and state-of-the-art data analytics capabilities, stands as a singular hub uniquely positioned to generate panoramic insights into scientific trends. These two organizations have collaborated to explore the role of materials to address the challenges confronting human health, with the goals of unraveling future trends in materials development to provide foresight for pertinent scientific research and industrial advancement, and to spark profound discussions and facilitate extensive exchanges within the scientific, industrial, and investment community, contributing to build a healthy future together.



I. Introduction

Over the past two decades, the realm of biomaterials has undergone a surge in research and development. These materials, which are designed to interact with the human body to perform therapeutic and diagnostic functions, hold the promise of revolutionizing the landscape of healthcare. In this report, you will find materials that allow antitumor drugs to target tumor cells, then release drug payloads; materials that can heal themselves autonomously after being cut or sheared; implantable devices that are safely absorbed by the body over time; and conductive, soft, stretchable composite materials that are used to make two-way electrical interfaces bridging dynamic human tissue and precision electronics.

This report's unprecedented level of detail and expansive scope is made possible through a dynamic fusion of interdisciplinary expertise at Westlake University and CAS, coupled with the CAS Content Collection™, the largest human-curated collection of scientific data in the world.

This database, housing nearly 60 million journal and patent records across chemistry, biomedicine, materials science, and more, has been analyzed by specialists to unveil the substances, chemical reactions, and scientific concepts discussed in each.

The eight emerging research areas in this report were identified using the approach described in the Methods section as a representation of the most active and fast-growing fields of biomaterials research (where a field is often signified by its most prominent feature, where the feature may be a specific material type, application, or function). The selection of these fields was the result of a seamlessly integrated research process among data scientists and biomaterial scientists. This process involved utilizing cutting-edge natural language processing methods, with iterative adjustment and refinement by biomaterial scientists, to identify emerging research areas. The report has also undergone multiple peer review cycles, ensuring that each revelation within it stands as a pinnacle of scientific rigor.

In this report, each research area has its own chapter and begins by recent publication trends, with information including:

- Comparison of the growth of journal and patent publications as an indicator of research, development, and commercialization interest in the field.
- Leading research institutions for journal publications.
- Leading patent assignees and their geographical distribution.
- Time trends in patent publications broken down by geography.
- Chronological flow of filing initial patent applications within patent families, leading eventually to individual patent publications in national patent offices.

Next, the materials used in each of the topic areas and their key applications are presented and discussed. Throughout this discussion, examples from literature are provided to illustrate prominent trends. Most chapters also include additional data to address topics that were found to be especially relevant for that chapter. (The chapter on self-healing materials, for example, contains a breakdown of the chemical mechanisms used to provide self-healing properties.)

To highlight recent examples of innovative biomaterials research, each chapter includes tables of notable journal articles and patent publications from 2018-2023. These examples represent the range of materials identified through data analysis, and were selected based on journal impact factor, number of citations, and the assignee (for patents). Finally, the most difficult challenges facing each topic are identified.

The report has yielded a series of fascinating insights, exploring the ongoing innovation and evolution in the field of biomaterials. Some of the topic areas, for example protein-based materials, have been well known to science for more than 20 years, but have shown continued research interest in recent years. Others, like bioinks, are relatively new fields of research that have undergone rapid expansion, with the majority of research having been published in the past 5 years. In at least two areas, lipid-based materials and sustainable biomaterials, research interest has increased significantly due to the use of these materials in the response to the COVID-19 pandemic.^{1, 2}

The diversification in biomaterial research encompasses both applications and the substances used in them. A representative list of substances that appear in this report includes naturally-derived polymers, such as silk, chitosan, and DNA, chemically modified naturally-derived polymers, stem cells, synthetic polymers including PEDOT:PSS, metals, alloys, and nanoscale materials such as carbon nanotubes. In addition, a strong trend in many of the topic areas is combining individual substances to make highly engineered composites or hybrid materials that can perform complex functions, while maintaining biocompatibility.

Notable applications that appear throughout the eight chapters include drug delivery, wound healing, tissue engineering, implantable devices, and sensors, among others. A significant fraction of the research efforts in biomaterials today involves combining or modifying existing materials, or discovering new materials, to achieve improved performance for these applications, with the goal of developing them to the point of clinical use.

The materials used in these applications can have several synergistic properties. For example, drug delivery materials can possess both the ability to self-heal, preserving their physical form after placement inside the body, combined with a stimulus-response profile that triggers the release of a drug payload at a specific location, such as tumor or infection sites.³ Multi-functional biomaterials can also cross between application areas, such as self-healing antimicrobial materials developed for wound healing.^{4,5}

Overall, this report aims to provide a thorough overview of the rapidly advancing field of biomaterials research, including insightful guidance on the expected future research trajectories in this field. Additionally, we aspire for the information contained herein to serve as a valuable resource for professionals involved in the development and commercialization of emerging biomaterial technologies. By offering data-supported insights into anticipated growth areas, challenges, and opportunities for new materials and applications, we aim to facilitate informed decision-making within this dynamic industry.

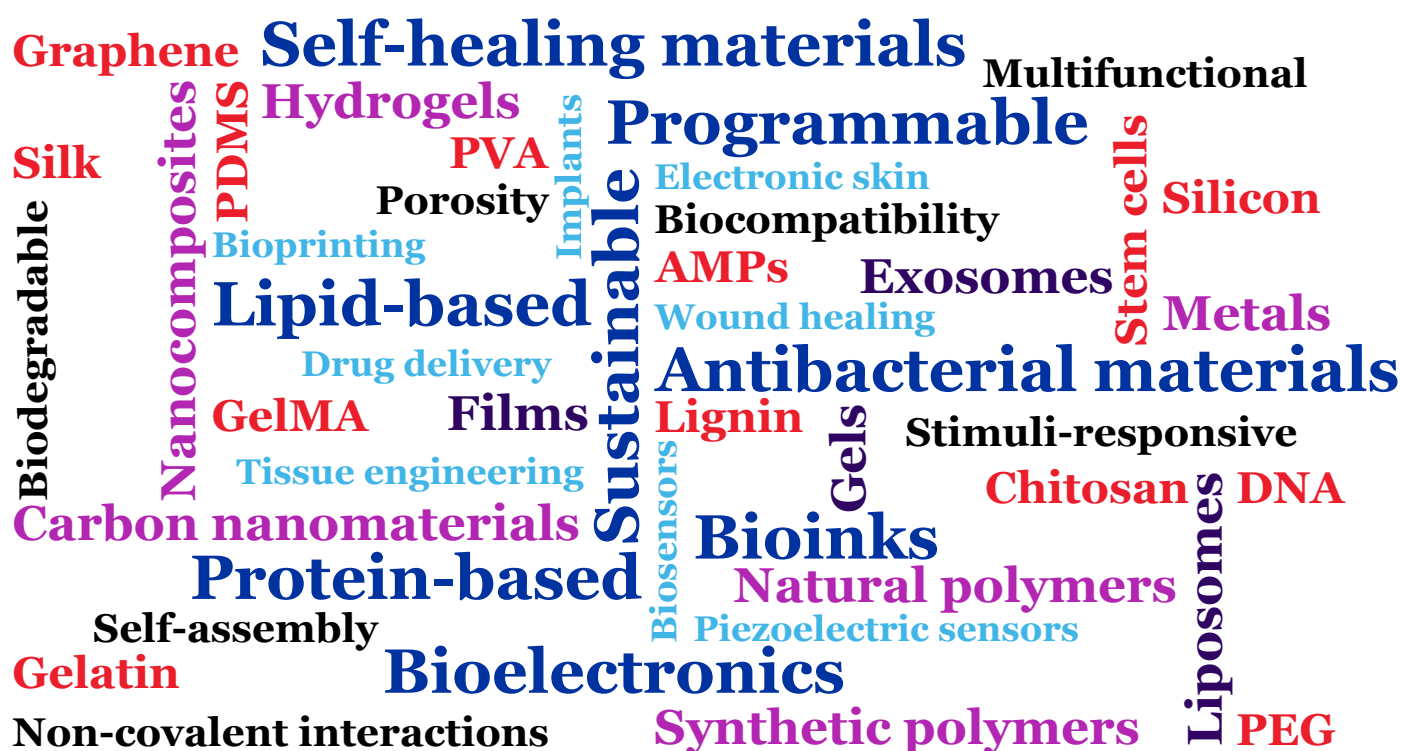
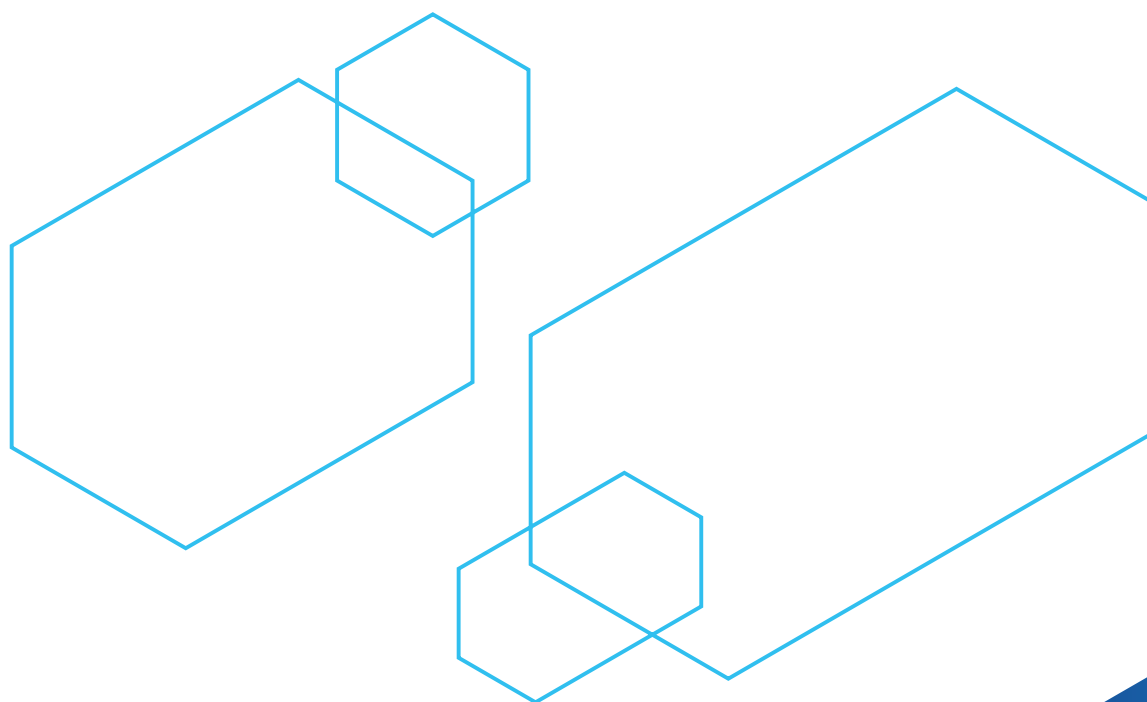


Figure 1. Word cloud representing key concepts in this report. (blue: 8 chapters in the report, light blue: applications, purple: broad material categories, red: specific materials, dark purple: forms, black: properties). Terms were chosen to be representative of the content of this report and are purely illustrative.

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II. Antibacterial Materials

Introduction

Antibacterials are a class of antimicrobials that target bacteria. Depending on their effect on bacterial cells, antibacterials can be classified either as bactericidal, which kill the bacterium, or bacteriostatic, if they arrest the bacterial growth.¹ Since the discovery of Penicillin G in the 1940s, various classes of antibiotics have been developed. Lack of regulation and overuse of antibiotics in both humans as well as animals has led to various bacteria becoming unresponsive to numerous classes of existing antibiotics and this phenomenon is referred as multidrug resistance (MDR).²⁻⁴ The development of resistance towards existing drugs is an urgent problem crippling the world with the World Health Organization (WHO) declaring antimicrobial resistance as one of the top 10 global health threats.⁵ According to data presented by the Centers for Disease Control and Prevention (CDC), more than 2.8M antimicrobial-resistant (AMR) bacterial infections occur each year leading to 35K+ deaths per year.⁶ Amongst resistant bacteria, ESKAPEE pathogens (an acronym for a group of Gram-positive and Gram-negative bacteria such as *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter species*, and *E.coli*) are responsible for the largest fraction of hospital-acquired infections (HAIs).⁷⁻⁹

To create awareness about the diverse and prevalent resistant bacterial species, the CDC has published a list of microbes and classified them as either urgent antimicrobial resistance threats, serious AMR threats, or AMR watchlist (microbes that could become serious threats in the future due to their propensity to become multidrug resistant) in 2019.^{10, 11} The serious AMR threat category comprises of drug-resistant *Acinetobacter*, *Neisseria gonorrhoeae*, *Clostridioides difficile*, and

Enterobacterales. Resistant variants of bacteria such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Enterococcus*, *Mycobacterium tuberculosis*, *Salmonella*, *Shigella*, *Campylobacter*, and *Streptococcus pneumoniae* are featured in the CDC's serious AMR threat list. Drug-resistant *Mycoplasma genitalium* and *Bordetella pertussis* are included in the CDC's watch list as they have the potential to become multidrug-resistant in the near future. To counter the problem of increasing drug resistance, traditional small molecule-based antibiotics continue to be developed. However, development has been slow, and novel classes remain elusive. A continued necessity for newer antibiotics and a lack of newer classes of small-molecule antibiotics have led researchers to explore other avenues. In addition to traditional antibiotics, biomaterials with antibiotic functions, such as antimicrobial polymers, antimicrobial peptides (AMPs), antimicrobial enzymes, nanomaterials, bacteriophages can reduce (not replace) antibiotics usage and biomaterials which are biocompatible as scaffolds for antibiotics, such as glass, ceramics, polymers, can help more effective drug delivery and act, in a way reducing the load of drugs.¹²⁻¹⁷ This interest is exemplified by the increase in journal publications in the field of antibacterial biomaterials over the last two decades (**Figure 1**). Growth in patent publications appears to be more modest indicating a gap between research and commercialization of antibacterial biomaterials (**Figure 1**).

In this chapter, we showcase our findings with regards to publication trends from extensive analysis of more than 90,000 documents (journals and patents) from the CAS Content Collection, spanning two decades of research (2003-2023) in the field of antibacterial biomaterials. In addition to a publication trend overview, we also identified emerging materials in the field, their forms, and applications.

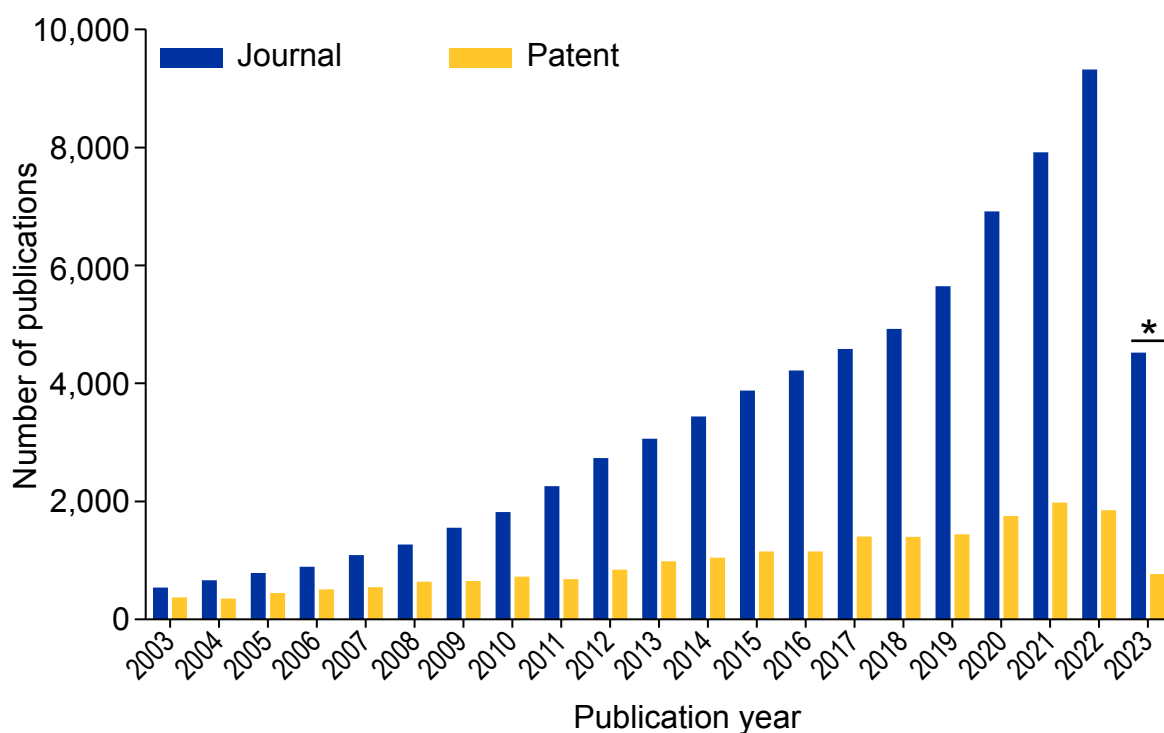


Figure 1. Number of journal and patent publications per year in the field of antibacterial materials (shown as blue and yellow bars, respectively) for the last two decades (2003-2023). * The data for 2023 only include months from Jan to Aug.

Journal and patent publication trends

Ranking research institutions firstly by the volume of journal publications followed by the average number of citations per publication allowed identification of the leading organizations in antibiotic research. The top 15 organizations show a diverse spread across different countries or regions (**Figure 2**). The United States of America (USA) and China (CHN) led by a small margin, each contributing 3 organizations to the top 15, respectively. This was closely followed by the Republic of Korea (KOR) and Singapore (SGP), each contributing 2 organizations. While the University of British Columbia ranked relatively low in terms of the actual number of journal publications (little more than 60), the average number of citations per publication was >90 indicating the scientific impact of those publications. An example of a journal publication from the University of British Columbia with a high number of citations is "Anti-adhesive antimicrobial peptide coating prevents catheter-associated infection in a mouse urinary infection model".¹⁸

The geographical distribution of commercial and non-commercial entities in terms of patent

documents published shows overlapping members (**Figure 3**). China (CHN) leads by a wide margin for both commercial and non-commercial organizations accounting for >50% of patents published. The United States of America (USA) accounts for a much smaller fraction as compared to its contribution to patent publications for other biomaterials discussed in this report. This may indicate low interest in antibiotic development because of the high costs associated with antibiotic discovery and development and limitations on the use of new antibiotics which reduce their market size and thus potential earnings. Additionally, bacterial infections, especially of the multi-drug resistant variety, are perceived to be more prevalent in and therefore a bigger problem in developing or low- and middle-income countries as compared to developed or high-income countries.¹⁹ However, this perception might be flawed as due to extensive globalization the world has become extremely interconnected and increasingly diseases affecting human beings can no longer be contained in any given geographical area, perhaps best exemplified by the COVID-19 pandemic. Other key countries or regions in the

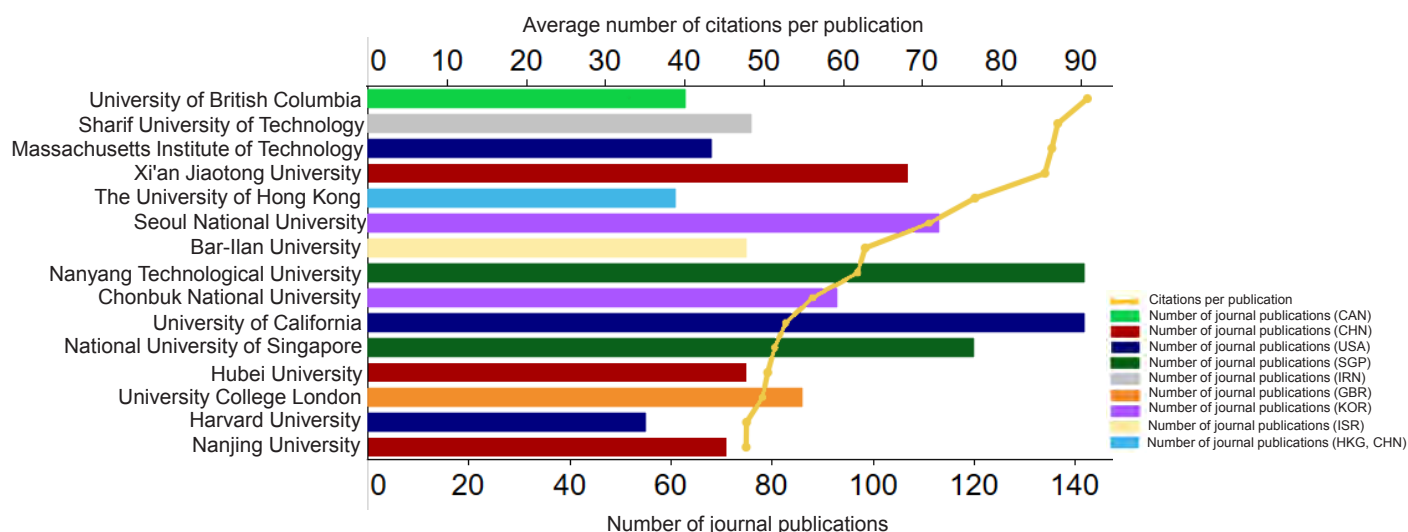


Figure 2. Leading research organizations in the field of antibacterial biomaterials over the last two decades (2003–2023) from the CAS Content Collection. Bar graphs have been color coded by country/region with standard three letter codes used to represent countries/regions.

commercial and non-commercial sectors include: Japan (JPN), Republic of Korea (KOR), Germany (DEU), Russia (RUS), India (IND), Italy (ITA), United Kingdom (GBR) and France (FRA). Japan in particular appears to have a more favorable contribution in patent publications by commercial organizations as compared to non-commercial organizations (**Figure 3**). Among the commercial patent assignees, Chinese companies led the way accounting for 60% of the top 15. This was followed by Japan with 25% and the United States which made up the remainder. The Japanese companies Lion Corporation and Kao Corporation appear to have been more active in the early part of the 2010s with patent publications related to the use of antibiotics in oral hygiene including incorporating antibacterial agents in dentifrices (JP2010150155A²⁰ and JP2011136956A²¹). Similarly, Colgate-Palmolive, a US-based company, also has patents mostly focused on antibacterial agents in oral care (US20190185490A1²²). The Chinese company Guangdong Taibao Medical Technology Co., Ltd. applied for patents starting in 2013 for the use and incorporation of biomaterials such as chitosan and alginate among others in medical dressings aimed at wound healing (CN103356692A²³ and CN106267309A²⁴). Other Chinese commercial organizations part of the top 15 such as Suzhou BEC Biology Technology

Co., Ltd. as well as Guangzhou Rainhome Pharm & Tech Co., Ltd. also appeared to have similar commercial pursuits i.e. use of chitosan and other biomaterials in wound healing (CN105617451A²⁵ and CN107970488A²⁶). In terms of non-commercial organizations, the leading entities all originate from China with Sichuan University, South China University of Technology, and Zhejiang University leading of the rest by a modest margin (**Figure 3**). Sichuan University appears to have been more prolific after 2010 with patents revolving around diverse areas including iron oxide nanoparticles for targeted delivery of antibacterial agents (CN115040662A²⁷) and use of a polymer, polyurethane, in antibacterial coatings (CN103214646A²⁸).

The overall growth of patent publications shows a distinct upward trend for the Republic of Korea and Japan post-2020 and India post-2018 (**Figure 4A**). Germany and the United Kingdom also show modest increases in the number of patents published. While the US showed an increase in patent publications in the early 2000s (between 2003 and 2008), this was followed by a decrease in 2009–2010 with a more or less flat trajectory until the present year. Among the leading countries or regions, China is the only one that shows a sharp and dramatic increase in patent publications,

almost doubling between 2012 and 2016. This growth appears to have continued beyond 2016 to the present year at a fast rate. In terms of the sheer volume of patent publications, China clearly dominates having 16 times as many patent publications in 2021-2022 as USA. An analysis of patent family activity data in **Figure 4B** shows the flow from the patent assignee country (left) to the patent office where the first application in a given family is filed (center) and finally to the destination patent office for individual patent publications within the family. For China, the country leading

in terms of sheer volume of patent publications, an overwhelming majority of patent applications appear to have been filed and granted at their home office. The US and UK had a greater number of patent filings at the World Intellectual Patent Office (WIPO) than at their respective home offices. On the other hand, Japan, Republic of Korea, and India showed a distinct preference for their respective home offices both for the initial and destination patent filings. Germany and Italy appear to only show preference for their respective home offices for the initial patent filing

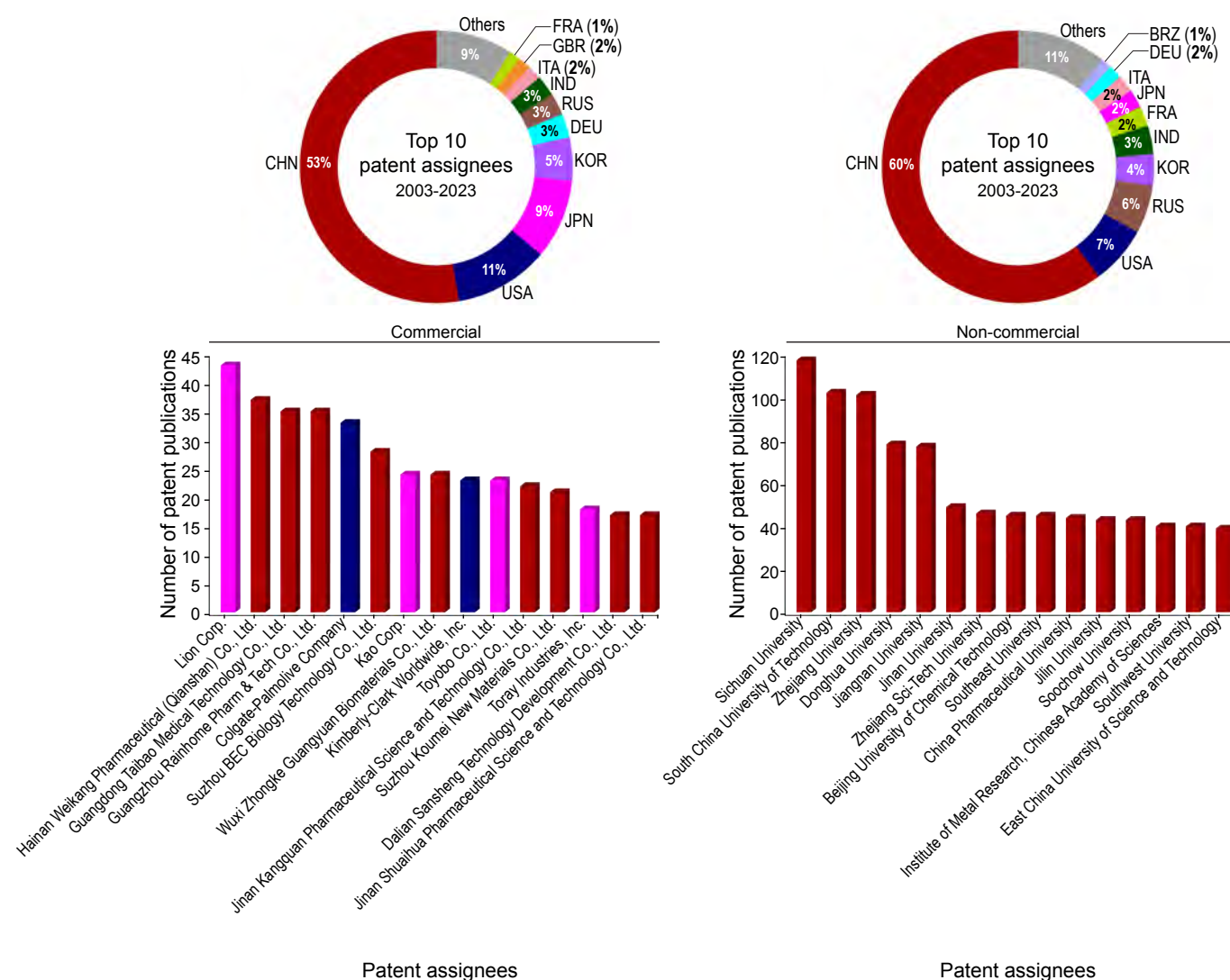


Figure 3. Leading patent assignees in the field of antibacterial biomaterials over the last two decades (2003-2023) as reflected in the CAS Content Collection. Patent assignees have been separated in to two groups: commercial and non-commercial. Bar graphs have been color coded by country/region to match color scheme used in donut charts. Standard three letter codes used to represent countries/regions.

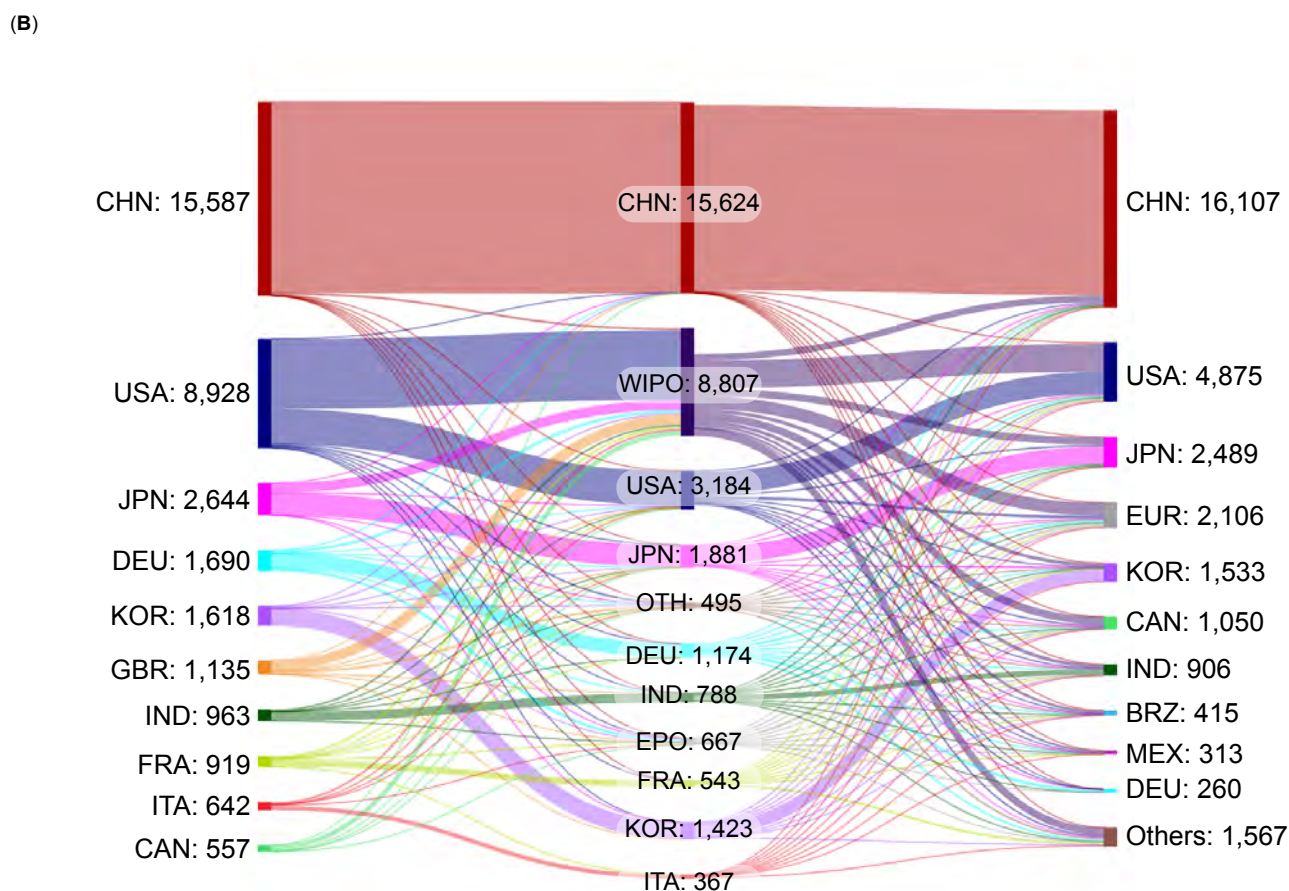
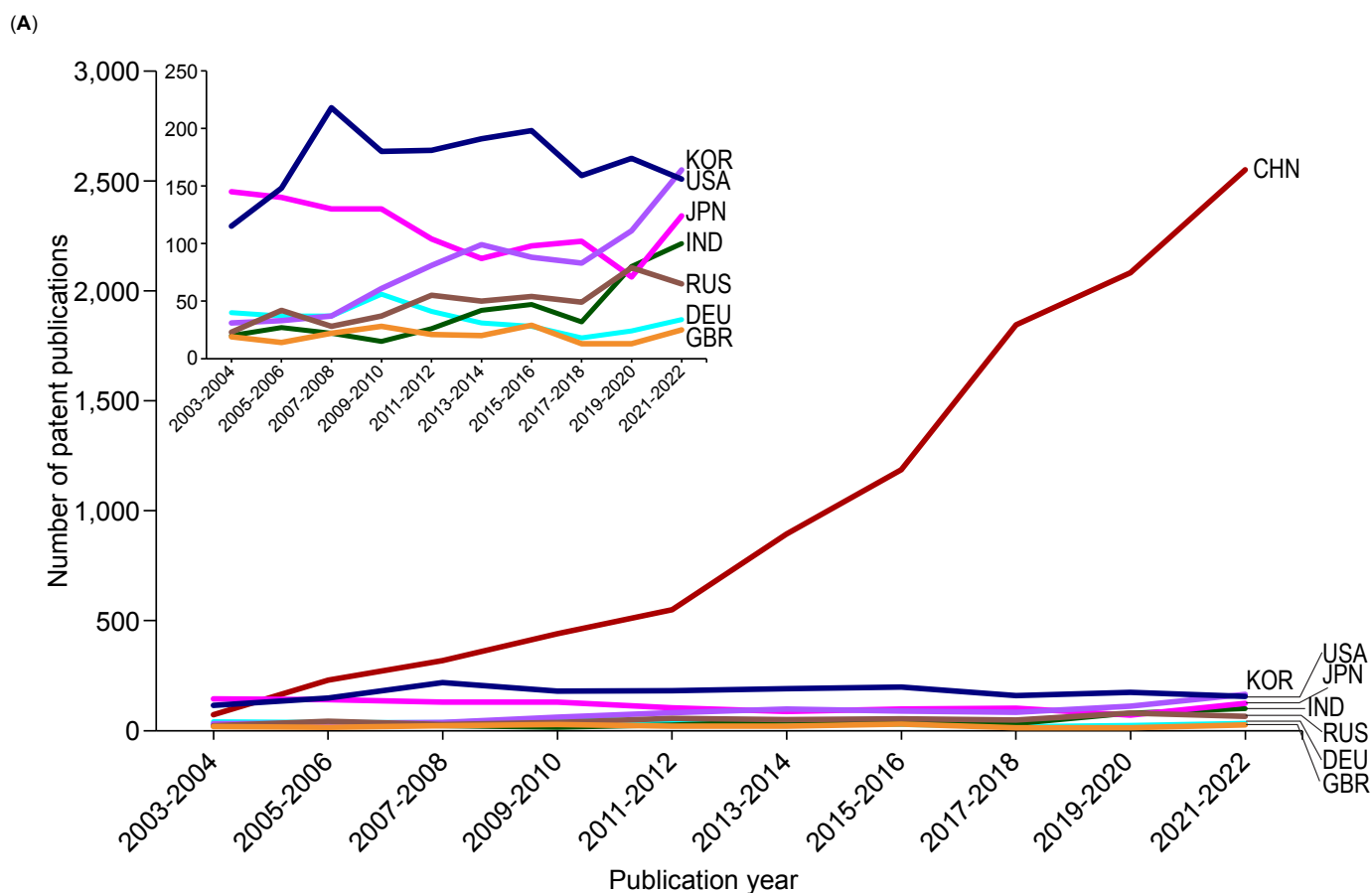


Figure 4. (A) Growth in patent publications in the field of antibacterial biomaterials for the leading countries or regions over the last two decades (2003-2022) from the CAS Content Collection. **(B)** Sankey graph depicting flow of patent families in the antibacterial biomaterials field between assignee countries or regions (left), office where the first application in a family is filed (center) and the office where individual patent publication activities take place (right).

with a more or less even spread across various patent offices worldwide in terms of the final destination.

We analyzed both journal and patent publications in our dataset exhaustively in an effort to identify the research interest distribution across different bacterial species (Figure 5A). The two genera, *Staphylococcus* and *Escherichia* account for half of all publications associated with bacterial species. Other key bacterial species that appear to be of interest in the field of antibacterial biomaterials include *Pseudomonas*, *Bacillus*, *Klebsiella*, *Salmonella*, *Streptococcus*,

Enterococcus, *Acinetobacter*, and *Proteus* (Figure 5A). Drug-resistant strains for several of these species have been identified and classified as threats by authorities such as the WHO and CDC. Publications associated with the ESKAPEE pathogens show steady and consistent growth for the last two decades (Figure 5B). Similarly, publications associated with bacterial species classified as “Urgent” threats by the CDC also show steady growth (Figure 5C). Overall, these trends are indicative of the interest in developing antibacterial biomaterials to combat the very real and growing threat of multidrug-resistant bacteria.

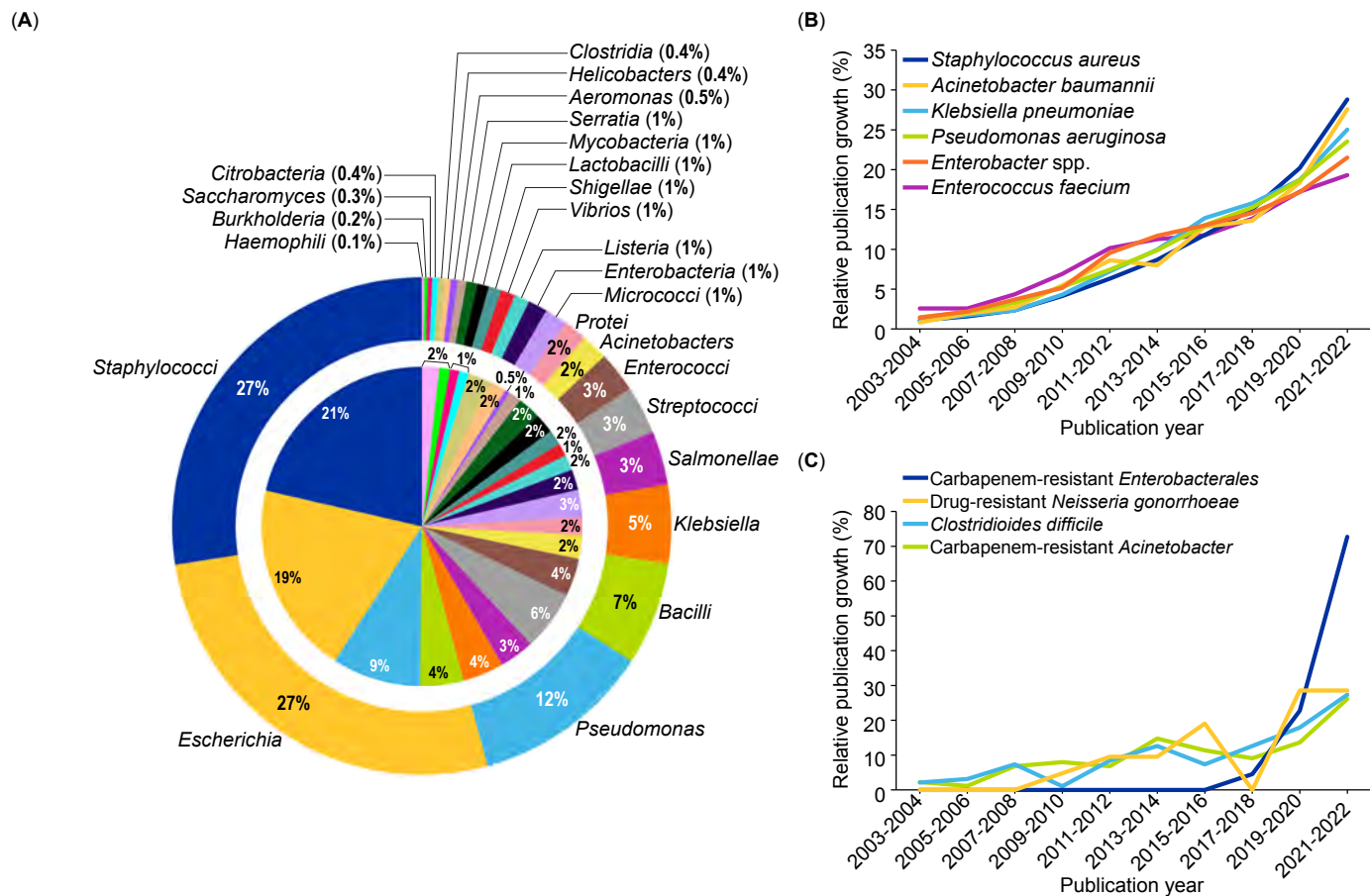


Figure 5. (A) Distribution of publications (journals and patents) in the field of antibacterial biomaterials across various bacterial species. Growth in publications (journals and patents) associated with **(B)** ESKAPEE pathogens and bacteria classified as **(C)** “urgent” threats by the CDC in the field of antibacterial biomaterials. Data includes both journal and patent publications from the CAS Content Collection for the last two decades (2003-2022) in the field of antibacterial biomaterials.

Key materials, properties/forms and applications

Data mined from the CAS Content Collection allowed the identification and classification of biomaterials occurring/used frequently in the field of antibacterial biomaterials into the following broad categories:

- Polymers
- Organic molecules
- Metals and metal oxides
- Carbon-based materials
- Protein-based materials
- Others

The quantitative distribution of identified materials and their breakdown across various categories are shown in **Figure 6**. Three of the bigger categories have been further sub-divided to give a more nuanced/granular view of emerging materials – polymers into synthetic, natural, and conductive, organic molecules into antibiotics, and others (consisting of substances such as steroids, quaternary ammonium compounds, zinc chloride, silver chloride, etc.) and metal into noble and transition metals.

Relative growth in publications of a few shortlisted materials identified as emerging across the last two decades are shown in **Figure 7A**. Graphene shows a sharp and continued increase in publications post-2014. The use of graphene oxide²⁹ and graphene-based hybrid nanocomposites in the form of hydrogels for antibacterial effect has been reported.^{30, 31} Other emerging materials include polycaprolactone (PCL) and chitosan – a synthetic and a natural polymer, respectively; metals such as zinc, copper, and silver known for their antibacterial properties; antimicrobial peptides (AMP) and quaternary ammonium-containing compounds. Chitosan is among the few biomaterials that possess inherent antimicrobial activity.³² This along with other favorable properties such as biocompatibility, biodegradability, and abundance along with reduced propensity of development of resistance by bacterial species means that chitosan has been explored in novel ways including as a carrier for drug delivery,³³ in combination with other materials³⁴ and incorporated into hydrogels along with other polymers and loaded with antibiotics

for drug delivery and wound healing.³⁵ Recently, a light-responsive chitosan nano-assembly³⁶ and a synthetic analog of chitosan with improved antimicrobial efficacy have been developed.³⁷ Chitosan and its derivatives continue to be of high interest in the field of antibacterial biomaterials. The synthetic biodegradable polymer, polycaprolactone, is often used in conjunction with other biomaterials such as gelatin,³⁸ silica,³⁹ and others⁴⁰ fashioned into nanostructures,⁴¹⁻⁴³ hydrogels, etc. for applications such as targeted drug delivery⁴⁴ and wound healing.⁴¹ Despite the antimicrobial effect/activity of metals such as silver,^{45, 46} copper,^{47, 48} and zinc⁴⁹ being well-known, interest in these materials has sustained over the years with efforts being made to use these metals in combination with other biomaterials in novel ways. Silver in particular continues to be utilized along with other biomaterials in combating multi-drug resistant strains^{50, 51} including for the disruption of biofilms.⁵² In addition, dead bacteria with accumulated silver appear to retain the ability to kill other living bacteria in its vicinity,^{53, 54} an effect that can be exploited for increased/greater antimicrobial effect.

AMPs are small peptides of variable length composed of natural amino acids⁵⁵ which are classified by their structures, sources, activities, and other properties.⁵⁶ Interest in AMPs has been consistent with several AMP candidates currently in clinical trials.⁵⁷ A large majority of the protein-based materials identified in our dataset result from AMPs. In terms of growth in publications, we see a steady growth over the last two decades. This is in agreement with the overall sustained interest in AMPs as alternatives to traditional antibiotics. A few examples of AMPs in the context of biomaterials include the use of AMPs as anti-biofilm agents for medical implants and devices⁵⁸⁻⁶⁰ as well as incorporation of AMPs in hydrogels⁶¹ and AMP-polymer conjugates.⁶²⁻⁶⁴ Ceramics loaded with antibiotics have been used for local/targeted delivery of antibiotics for prolonged periods of time (up to several days), especially in bone-related applications.^{65, 66} Biomaterials such as bamboo, which are naturally antibacterial, are being explored in their natural or composite forms for biomedical applications such as designing medical gauze and wound dressing for accelerated wound healing.⁶⁷⁻⁶⁹

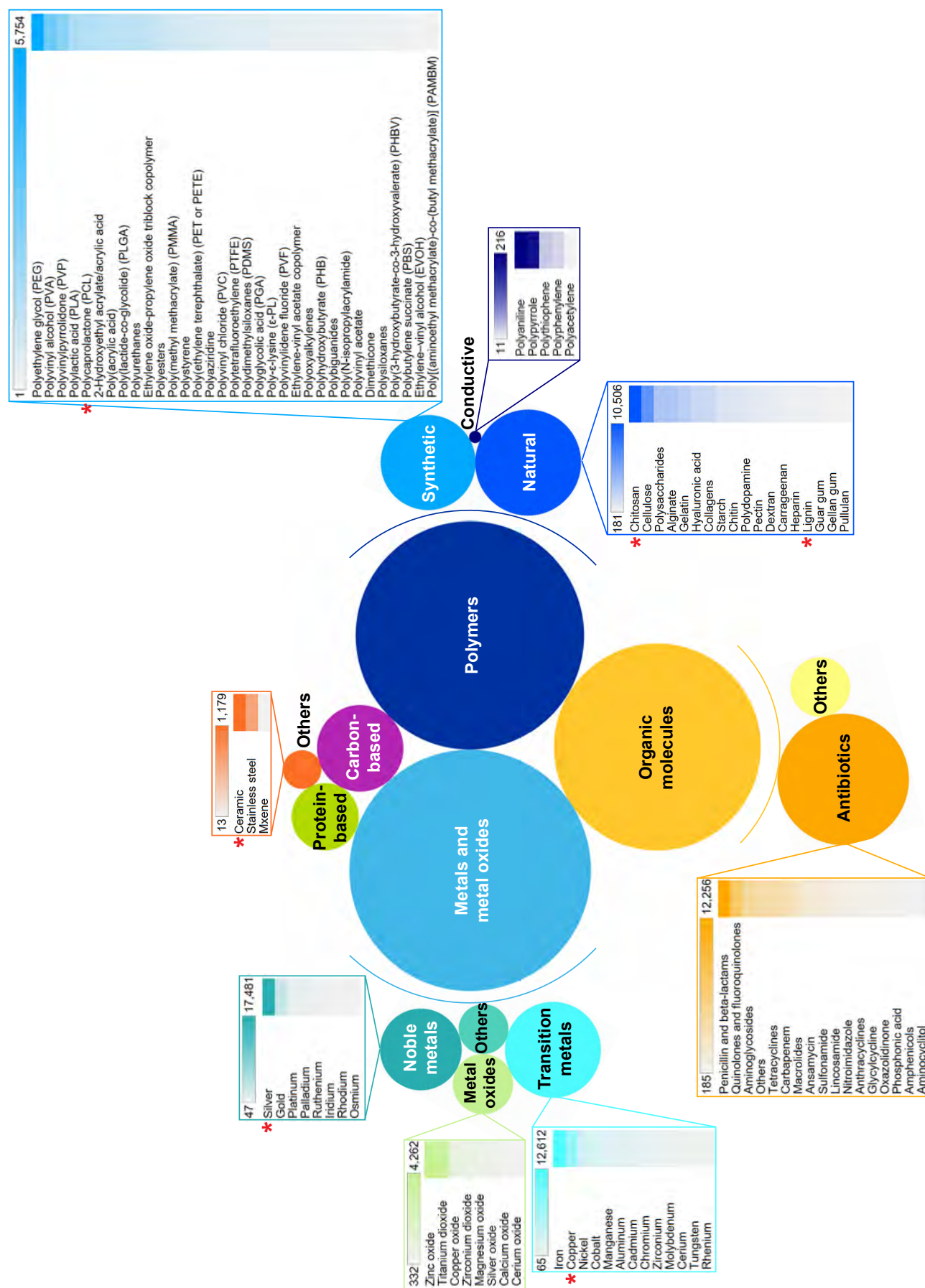


Figure 6. Distribution of materials in the field of antibacterial biomaterials over the last two decades (2003-2022) from the CAS Content Collection. Size of the circle corresponds to number of publications (journals and patents). Growth of materials marked with an asterisk are shown in Figure 7.

Established classes of antibiotics such as tetracyclines, macrolides, and others have reportedly been used in conjunction with biomaterials often to aid in their delivery and to boost their antibacterial effectiveness in applications such as tissue engineering and wound healing.⁷⁰⁻⁷³ Among the various classes of antibiotics, we identified a few that appear to be most prolific and show a steady rate of increase in publications (**Figure 7B**). These classes of antibiotics are most often formulated/ incorporated into either hydrogel, nano-based systems such as nanoparticles, nanofibers, nanosheets, etc., or liposomes. Among the various forms listed, nano-based systems appear to dominate (**Figure 8A**). All the forms show steady growth more so over the last decade. Hydrogels and quantum dots in particular show a sharp growth in publications post-2016 (**Figure 8B**). Liposomes, a subtype of nanocarriers was originally focused on packaging and delivery of anticancer drugs, but is increasingly being explored for effective delivery of antibiotics.⁷⁴⁻⁷⁶ For instance, a hydrogel comprising lignin and silver nanoparticles has shown antibiotic activity against *S. aureus*, a Gram-positive bacterium, and *E. coli*, a Gram-negative bacterium indicating

its applicability and versatility.⁷⁷ In another recent example, a self-assembled peptide hydrogel made from naphthyl anthranilamide capped, short cationic peptides that showed promising antibacterial activity against *S. aureus* and *E. coli*.⁷⁸ The high surface area to volume ratio of nanoparticles allows them to deliver antibacterial drugs effectively.^{79, 80} Nanoparticles made using silver, gold, selenium, calcium oxide, copper, titanium dioxide, iron oxide, poly (lactic-co-glycolic acid) (PLGA), chitosan, etc. are widely used in the field of antibacterials.⁸¹⁻⁸⁶

To understand the preference for a particular form, we searched for various classes of antibiotics and forms and generated a Sankey graph to visually represent these co-occurrences (**Figure 9**). Among the different classes of antibiotics, a majority had a higher number of co-occurrences with nano-based systems as compared to other forms, the exceptions being oxazolidinones, glycylicyclines, phosphonic acids, amphenicols, and aminocyclitol which showed co-occurred more or less evenly across hydrogels, nano-based systems, and liposomes (**Figure 9**). We generated a heat map to effectively showcase co-occurrences between specific bacterial species and the classes

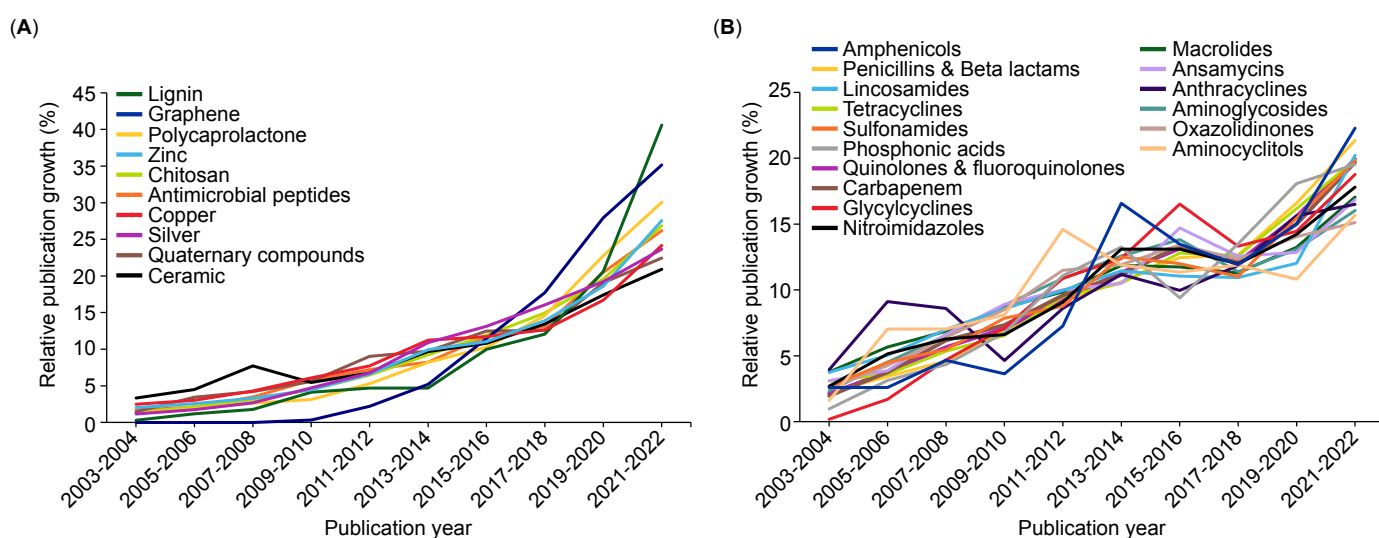


Figure 7. Growth in publications for (A) emerging materials and (B) major classes of antibiotic drugs in the field of antibacterial biomaterials from the CAS Content Collection for 2003-2022. Data includes both journal and patent publications.

of antibiotics deployed against them (**Figure 10**). The bacterial species we chose to focus on were based on our findings described earlier i.e., the most prevalent bacterial species in the current dataset of antibacterial materials (**Figure 5A**). Discussed below are a few observations from the heat map:

1. The bacterial species that co-occurred most frequently across the different classes of antibiotics are *Staphylococcus*, *Escherichia*, *Pseudomonas*, and *Klebsiella*. This is unsurprising since drug-resistant strains of *Staphylococcus*, *Pseudomonas*, and *Klebsiella* have long been identified.
2. Certain classes of antibiotics are more effective against Gram-negative bacteria while some have a preferential effect against Gram-positive bacterial species. For instance, carbapenems (including *imipenem*, *doripenem*, and *meropenem*) are mostly effective against Gram-negative bacteria belonging to genera such as *Acinetobacter*, *Escherichia*, *Klebsiella*, *Pseudomonas*, *Enterobacter* etc.^{87, 88}

3. Certain broad-spectrum antibiotics such as tetracycline and their derivatives like glycylcycline are effective against both Gram-positive (*Staphylococcus*) and Gram-negative bacteria (*Escherichia*) which also correlates well with literature.^{89, 90}

The distribution of applications that antibacterial biomaterials can be utilized for is shown in **Figure 11A**. One of the biggest applications is the use of biomaterials to effectively target and deliver antibiotics accounting for nearly 12K publications in the last two decades (2003-2023). Biomaterials such as antimicrobial peptides, enzymes, and biopolymers are being used effectively in the field of antibiotics.¹² Another major application involves the use of antibacterial biomaterials in the design and fabrication of medical apparatuses, devices, and implants to reduce the risk of infections. Various polycationic polymers (including quaternary ammonium salt-containing polymers), zwitterions, polyethylene glycol (PEG), and antibacterial peptides are used to design antimicrobial coatings for preventing bacterial infections.⁹¹⁻⁹³ Besides these, other notable

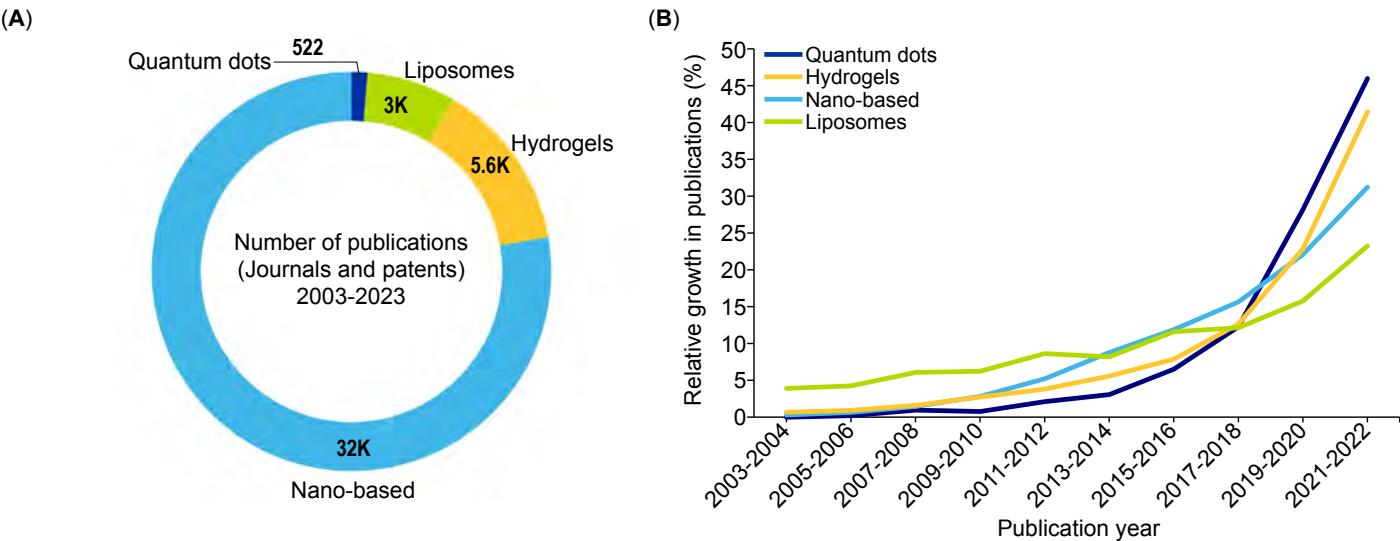


Figure 8. (A) Distribution of various forms in the field of antibacterial biomaterials and **(B)** relative growth in publications related to chosen forms in the field of antibacterial biomaterials over the last two decades from the CAS Content Collection.

applications of antibacterial biomaterials appear to be in the food industry and as antifouling agents. PEG-based materials, zwitterions, hydrogels, cationic, and fluoropolymers are some commonly used antifouling agents^{94, 95} used to coat surfaces in order to prevent bacterial infections. In the food industry, antibacterial biomaterials are

used to increase the shelf-life of perishable food products by preventing bacterial infections. Phenolic compounds, enzymes such as lysozyme, and antimicrobial peptides are a few examples of biomaterials being actively utilized to design more effective and safer food preservatives.⁹⁵⁻⁹⁷

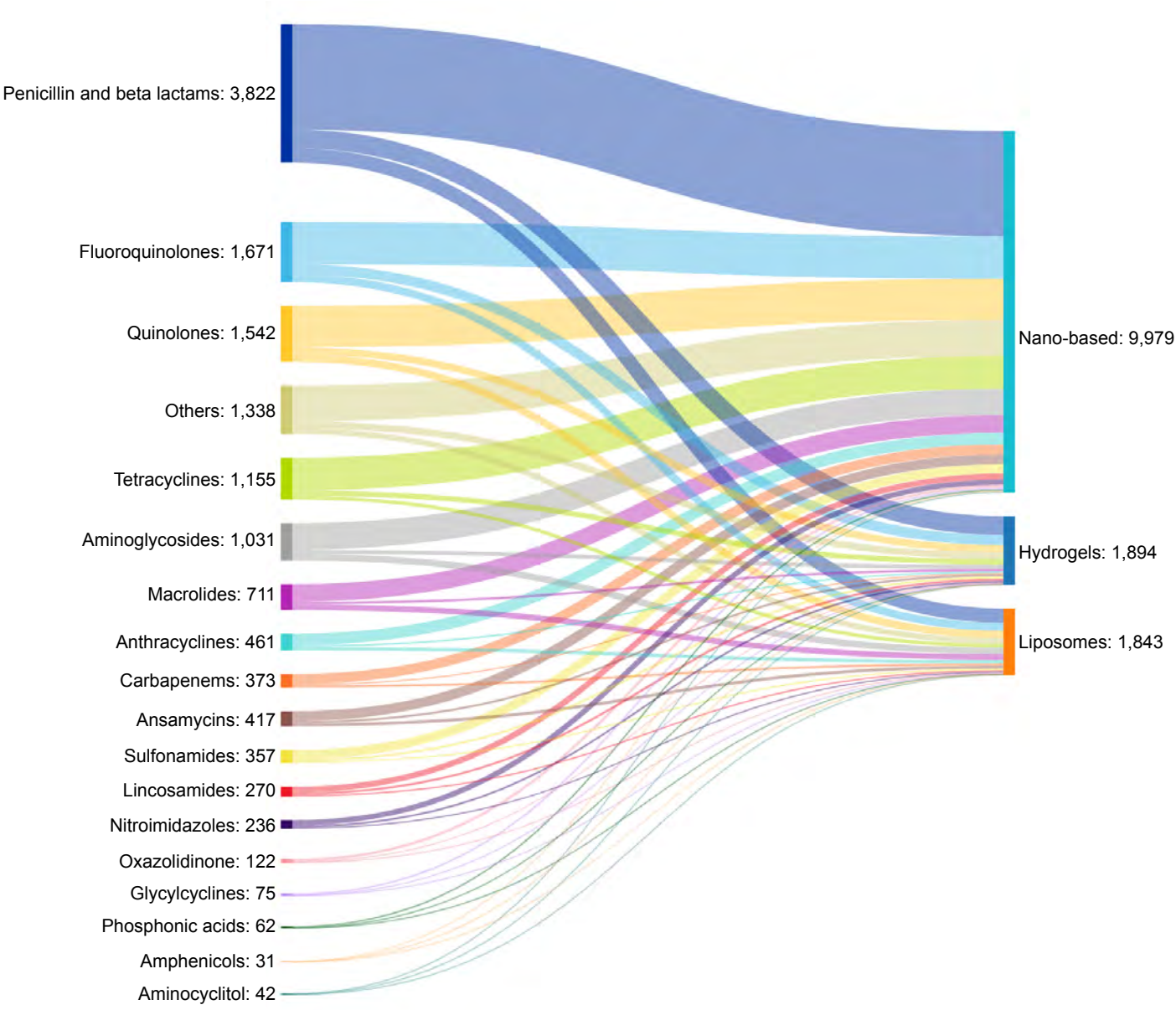


Figure 9. Sankey graph showing co-occurrences between various classes of antibiotics and the forms such as nano-based, hydrogels and liposomes. Data is for publications (journals and patents) in the field of antibacterial biomaterials from the CAS Content Collection for the period 2003-2023.

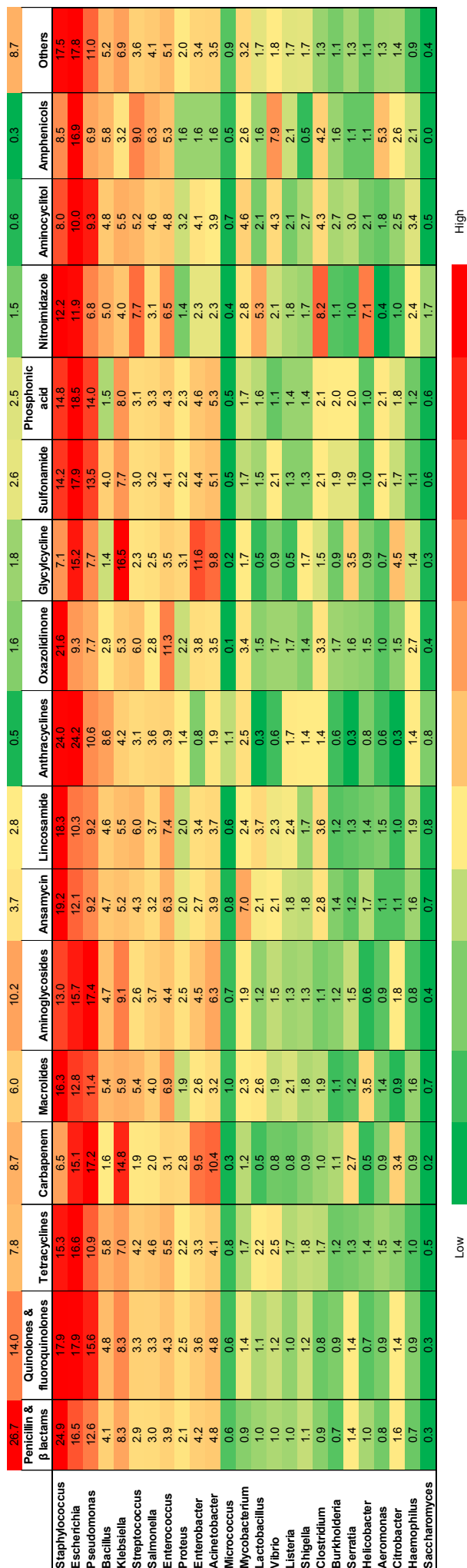


Figure 10. Heat map showing co-occurrences between major antibiotic classes and bacterial species. Data is for publications (journals and patents) in the field of antibacterial biomaterials from the CAS Content Collection for the period 2003-2023. Values shown are in percentages.

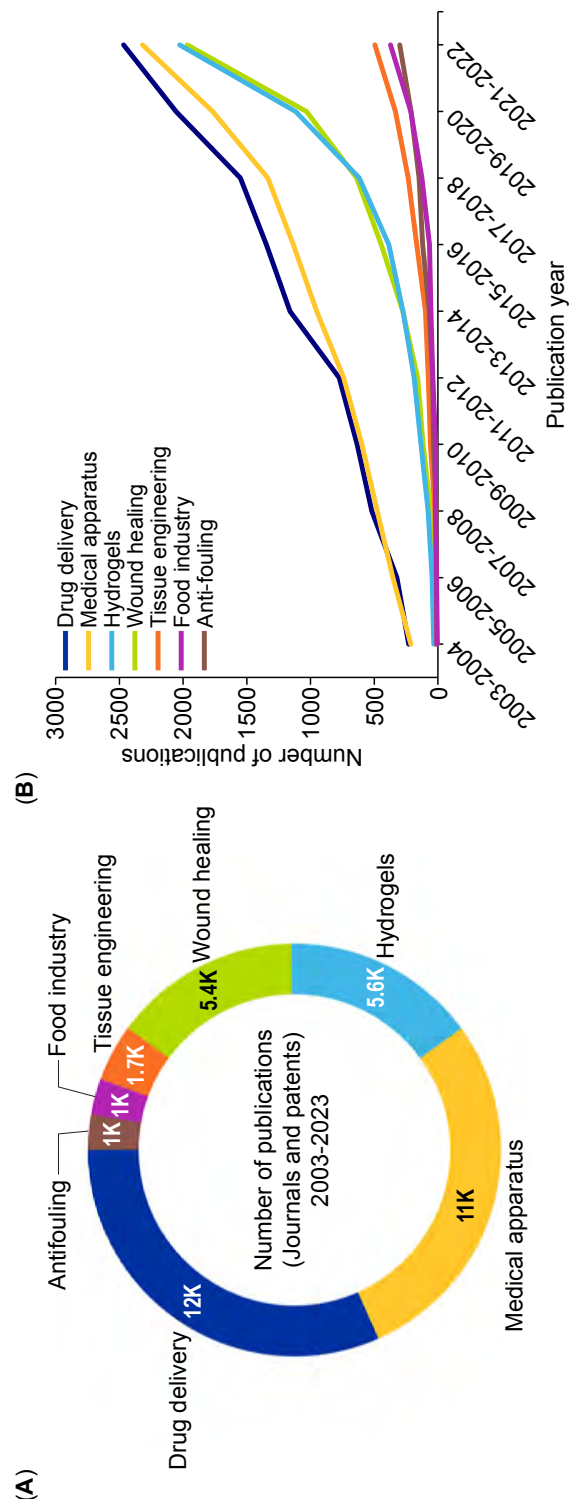


Figure 11. (A) Distribution of applications in the field of antibacterial biomaterials and (B) and growth in publications related to chosen applications in the field of antibacterial biomaterials over the last two decades from the CAS Content Collection.

Notable journal articles and patents

Table 1 consists of a set of research articles published from 2020-2023 that are representative of emerging trends in this field. Articles were selected on the basis of collective factors such as journal impact factor, citations, and type of study and describe the usage of different antibacterial materials for various bacterial species. Notable examples from **Table 1** include an article titled "Graphdiyne-modified TiO₂ nanofibers with osteoinductive and enhanced photocatalytic antibacterial activities to prevent implant infection" published in 2020 in *Nature Communications*. The article describes the use of a stable carbon allotrope-based nanomaterial (GDY), that forms a composite with titanium oxide (TiO₂) nanofibers to improve the antibacterial properties of titanium oxide. TiO₂/GDY nanofibers have enhanced photocatalytic and ROS production activity.⁹⁸

Another example includes a recent publication titled "Injectable wound dressing based on carboxymethyl chitosan triple-network hydrogel for effective wound antibacterial and hemostasis" which describes the synthesis of a hydrogel comprising carboxymethyl chitosan (CMCS), oxidized dextran ((OD), and poly-γ-glutamic acid (γ-PGA). Components of CMCS-OD-γ-PGA (COP) hydrogel such as CMCS and OD are responsible for antibacterial action while γ-PGA is responsible for wound healing and maintaining homeostasis at the wound site.

Furthermore, researchers at Westlake University have developed chitin and cellulose nanofibril-based adhesive tape which can be incorporated with antibiotics. In this article, nanofibril-stabilized latex (poly-2-ethylhexyl acrylate-co-polymethyl

acrylate) was infused with the antifungal drug miconazole nitrate. The resultant antibiotic-loaded tape was used to effectively inhibit the growth of *Staphylococcus aureus*.⁹⁹

Table 2 shows notable patents in the field of antibacterial biomaterials published from 2018 to 2023. Patents were selected based on relevance, novelty, applicability, and field of study. Most of these involve different forms of biomaterials and their diverse applications. For instance, US10662203B2 by Hoffmann La Roche Inc. describes the synthesis of heterocyclic compounds that can be used as DNA gyrase/topoisomerase inhibitors thereby eliminating bacterial infections.¹⁰⁰

In another example, US11234997B2 describes the topical formulation that comprises varying ratios of galactooligosaccharide and xylitol (ranging from 1:10 to 10:1). These formulations selectively inhibited the formation of biofilm by *Staphylococcus aureus* and helped to reduce atopic dermatitis without causing skin inflammation and irritation.¹⁰¹

In a recent example, CN113277563B describes a composite powder made using molybdenum-doped cesium tungsten bronze/montmorillonite where montmorillonite acts as a carrier for molybdenum doped cesium tungsten bronze which is loaded on to the surface of the film. These composites were used to inhibit the growth of *E. coli*.¹⁰²

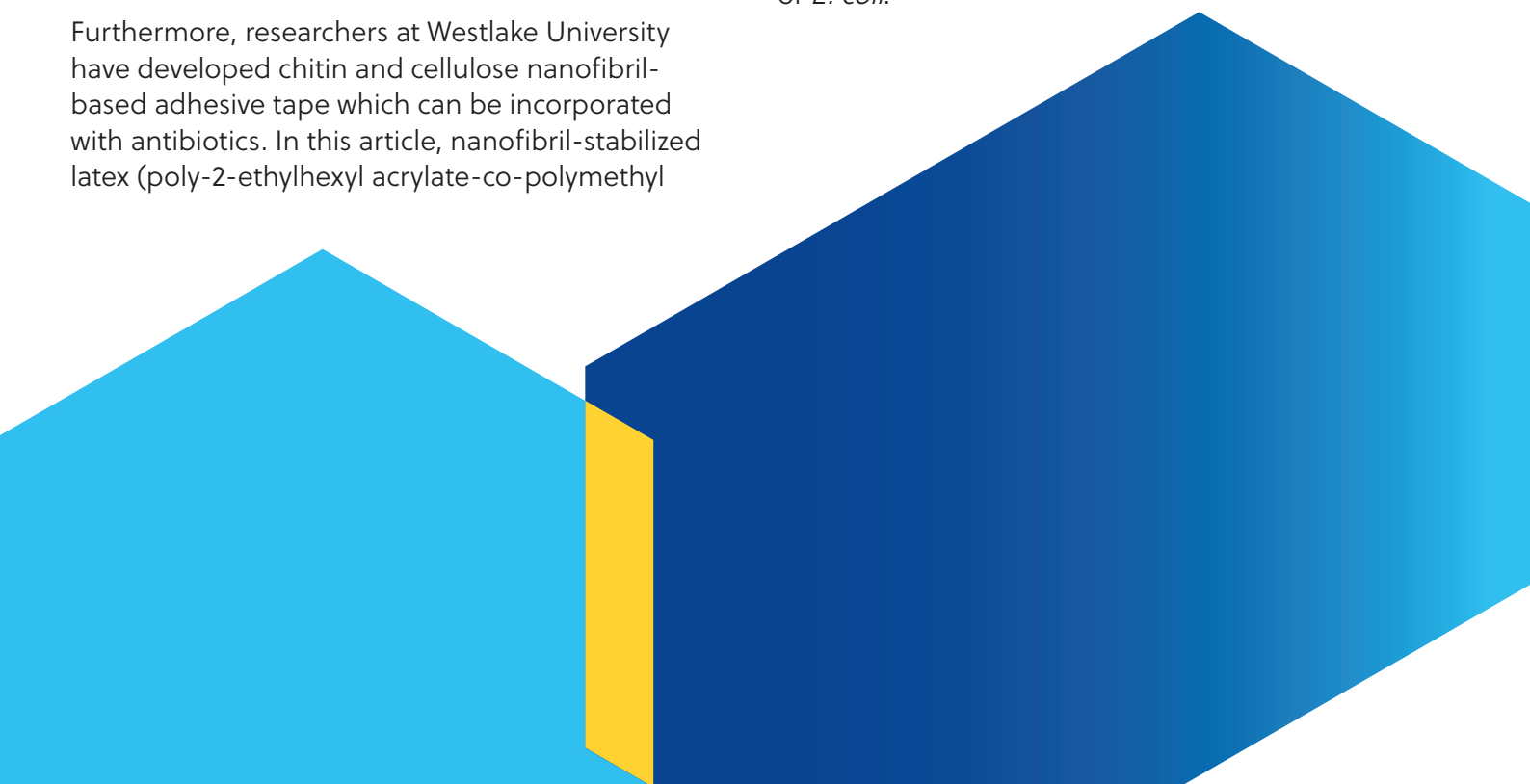


Table 1. Notable journal articles in the field of antibacterial biomaterials in recent years.

Year	Title	Journal	Research Institute	Application
2020	Designing a 0D/2D S-scheme heterojunction over polymeric carbon nitride for visible-light photocatalytic inactivation of bacteria ¹⁰³	Angewandte Chemie	Wuhan University	Antibacterial coating effective against <i>S. aureus</i> .
2020	Graphdiyne-modified TiO ₂ nanofibers with osteoinductive and enhanced photocatalytic antibacterial activities to prevent implant infection ⁹⁸	Nature Communications	Guangzhou Laboratory and Wuhan University	Graphdiyne (GDY) composite TiO ₂ nanofiber with antibacterial properties.
2021	Dual-Dynamic-Bond Cross-Linked Antibacterial Adhesive Hydrogel Sealants with On-Demand Removability for Post-Wound-Closure and Infected Wound Healing ¹⁰⁴	ACS Nano	Xi'an Jiaotong University	Self-healing antibacterial containing quaternized chitosan (QCS) for wound healing after methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) infection.
2021	Anti-bacterial and wound healing-promoting effects of zinc ferrite nanoparticles ¹⁰⁵	Journal of Nanobiotechnology	University of California	Synthesis and testing antibacterial activity of zinc ferrite (ZnFe ₂ O ₄) nanoparticles against <i>S. aureus</i> and <i>E. coli</i> .
2020	Near-Infrared Light-Triggered Nitric-Oxide-Enhanced Photodynamic Therapy and Low-Temperature Photothermal Therapy for Biofilm Elimination ¹⁰⁶	ACS Nano	Chongqing University	Anti-biofilm activity of Al-MPDA Nanoparticles containing mesoporous polydopamine (MPDA), L-arginine (l-Arg), and indocyanine green (ICG).
2021	Dy ₂ BaCuO ₅ /Ba ₄ DyCu ₃ O _{9.09} S-scheme heterojunction nanocomposite with enhanced photocatalytic and antibacterial activities ¹⁰⁷	Journal of the American Ceramic Society	University of Kashan	Nanoparticles made from a semiconductor combination (Dy ₂ BaCuO ₅ /Ba ₄ DyCu ₃ O _{9.09}) were synthesized and tested for antibacterial activity against <i>E. faecalis</i> , <i>S. aureus</i> , <i>K. pneumoniae</i> , and <i>E. coli</i> .
2022	Facile formation of injectable quaternized chitosan/tannic acid hydrogels with antibacterial and ROS scavenging capabilities for diabetic wound healing ¹⁰⁸	International Journal of Biological Macromolecules	Wenzhou Medical University	Antibacterial activity of hydrogel made by introducing tannic acid (TA) into quaternized chitosan (QCS) matrix against <i>S. aureus</i> and <i>E. coli</i> .
2022	Promoting the healing of infected diabetic wound by an anti-bacterial and nano-enzyme-containing hydrogel with inflammation-suppressing, ROS-scavenging, oxygen, and nitric oxide-generating properties ¹⁰⁹	Biomaterials	Zhejiang University	Antibacterial activity of Poly (PEGMA-co-GMA-co-AAm) (PPGA) based hydrogels crosslinked with hyperbranched poly-L-lysine (HBPL)-modified manganese dioxide (MnO ₂) against methicillin-resistant <i>S. aureus</i> (MRSA) infection.
2022	Cellulose or chitin nanofibril-stabilized latex for medical adhesion via tailoring colloidal interactions ⁹⁹	Carbohydrate Polymers	Westlake University	Using cellulose and chitin nanofibrils to form adhesive tapes which exhibit antibacterial activity
2022	Multi-crosslinking hydrogels with robust bio-adhesion and pro-coagulant activity for first-aid hemostasis and infected wound healing ¹¹⁰	Bioactive Materials	Sichuan University	Hydrogels comprising carboxymethyl chitosan (CMCS), sodium alginate (SA), and tannic acid were tested for antibacterial activity against <i>S. aureus</i> and <i>E. coli</i> .
2023	Injectable wound dressing based on carboxymethyl chitosan triple-network hydrogel for effective wound antibacterial and hemostasis ¹¹¹	International Journal of Biological Macromolecules	Shanghai University	Antibacterial effect of a hydrogel comprising carboxymethyl chitosan (CMCS)/oxidized dextran (OD)/poly-γ-glutamic acid (γ-PGA).

Table 2. Notable patent publications in the field of antibacterial biomaterials in recent years.

Patent number	Publication year	Patent assignee	Title	Description of patented technology
JP2018159860A ¹¹²	2018	Tokai Optical Co Ltd	Optical product containing metal ion-carrying zeolite	An optical multilayer product with an antireflective film coated with an organic antibacterial agent.
CN107536725A ¹¹³	2018	Guangzhou Weimeizi Industrial Co Ltd	A kind of multiple-effect oral cavity composition and its application containing hyaluronic acid mixtures	Oral care composition comprising different combinations of hyaluronic acid (in some cases with zinc citrate) used as antibacterials.
JP2019065375A ¹¹⁴	2019	Harada Metal Industry Co., Ltd., National Institute of Advanced Industrial Science & Technology, Japan	Copper alloy powder having antibacterial properties and antivirus properties and article using the same	Antibacterial coating formulation containing copper alloy powder (comprising 0.10% tin, 0.01% phosphorus and remaining copper).
US10662203B2 ¹⁰⁰	2020	Hoffmann La Roche Inc	Novel pyrido [2,3-b] indole compounds for the treatment and prevention of bacterial infections	Heterocyclic compound to inhibit bacterial DNA gyrase and/or topoisomerase IV, in turn inhibiting bacterial growth.
US11065223B2 ¹¹⁵	2021	University of Texas System, USA	Antibacterial composition and its use	Antimicrobial composition in the form of wound ointment containing esterified polygalacturonic acid and a C6-12 fatty acid.
CN110067042B ¹¹⁶	2021	Donghua University	Konjac glucomannan-based antibacterial hydrogel fiber and preparation method thereof	Antibacterial hydrogel fiber comprising Konjac glucomannan polymerizable monomer, alginate, guanidine salt polymerizable monomer, deionized water, and polymerization initiator.
US11459296B2 ¹¹⁷	2022	Infex Therapeutics Ltd Medivir AB	Preparation of sulfamoyl pyrrolecarboxylic acids as antibacterial agents	Nitrogen-containing heterocyclic compounds that act as Metallo- β -lactamase inhibitors.
US11234997B2 ¹⁰¹	2022	Rottapharm SpA	Antibacterial activity of galactooligosaccharide and xylitol in dermatological treatments	Anti-biofilm activity of topical formulation comprising galactooligosaccharide and xylitol in different ratios.
US11691967B2 ¹¹⁸	2023	The Board of Trustees of the University of Illinois, USA	Antibiotics effective for gram-negative pathogens	Organic compounds with antibiotic activity, selectively against gram-negative bacteria.
CN113277563B ¹⁰²	2023	Nanjing Zhouninglin Advanced Materials Technology Co Ltd, Nanjing Normal University	Molybdenum doped cesium tungsten bronze/ montmorillonite composite powder and preparation method and application thereof	Synthesis and antibacterial activity of molybdenum doped cesium tungsten bronze/montmorillonite composites.

Challenges and perspectives

Development of novel antibiotics requires a thorough understanding of the host immune system and the interaction of host cells with antibiotics. There are various traditional antibiotic approaches/materials being used to treat bacterial infections but the major challenges in this area are:

- One common challenge in this field is the development of antimicrobial resistance in bacterial species, which happens at a much faster pace as compared to the development of any novel antibiotic.^{1, 119}
- The same levels of antibiotic treatment produce varied results in different individuals in any population, due to the differences in the host immune system.¹²⁰
- The development of antibiotics is more challenging for highly infectious, Gram-negative bacteria as compared to Gram-positive ones, due to the presence of a lipopolysaccharide (LPS) rich, outer membrane. The outer membrane acts as a barrier and prevents the entry of various drug molecules inside the bacterial cell.^{121, 122}
- The limited market size, short treatment duration, and reduced price of antibiotic agents reduce the willingness of pharmaceutical companies to invest in antibiotic drug development.¹²³

- Another major challenge is the treatment of bacterial infections if the bacteria is prone to biofilm formation, which is a densely packed community of bacteria embedded within an extracellular matrix. Biofilms prevent the entry of antibiotics and the lowest concentration of antibiotics entering the biofilm can promote the rapid development of antimicrobial resistance.^{14, 124}

Various emerging approaches such as the use of antimicrobial peptides, enzymes, bacteriophages, and CRISPR-Cas technology are being tried to enhance the efficacy of antibiotics and counter the problem of rapid antimicrobial resistance development. Artificial intelligence (AI) has slowly started entering the field of antibiotics where machine-learning based algorithms are being leveraged to identify successful antibiotic candidates. However, the widespread use of AI is still in the nascent stages, and it requires more research endeavors in the future.¹²³ In addition, continued advancements are needed in translating more antibiotic-based materials into various clinical applications.

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III. Lipid-based materials

Introduction

The field of pharmaceuticals has witnessed remarkable progress recently, driven by innovations in drug delivery technologies. Traditionally, drug delivery has been a complex puzzle, often challenged by the limited solubility, stability, and bioavailability of many therapeutic agents. These constraints have led researchers on a quest to find more effective ways to deliver drugs to their intended targets within the body. Therefore, drug delivery systems play a crucial role in optimizing the therapeutic benefits of medications while minimizing side effects and improving patient compliance. Among the transformative advancements in drug delivery technologies, lipid-based drug delivery systems have emerged as a formidable force in the world of pharmaceutical science and practice offering a dynamic range of solutions that transcend traditional pharmaceutical boundaries.

Lipid-based drug delivery systems are ingeniously designed carriers, benefitting from the inherent biocompatibility and versatility of lipids and tailored to encapsulate, transport, and release a wide array of therapeutic agents, including small molecule drugs, genes, and biologics. Their elegance lies in their ability to overcome some of the most pressing challenges in drug delivery. These challenges include improving the solubility of poorly water-soluble drugs, protecting labile compounds from degradation, and precisely targeting disease sites within the body.¹⁻⁹

Lipid nanocarriers can be divided into various categories, including solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes, lipid-based micelles, and lipid prodrugs (**Figure 1**). SLNs consist of solid lipids, while NLCs combine solid and liquid lipids, offering enhanced drug-loading capacity and

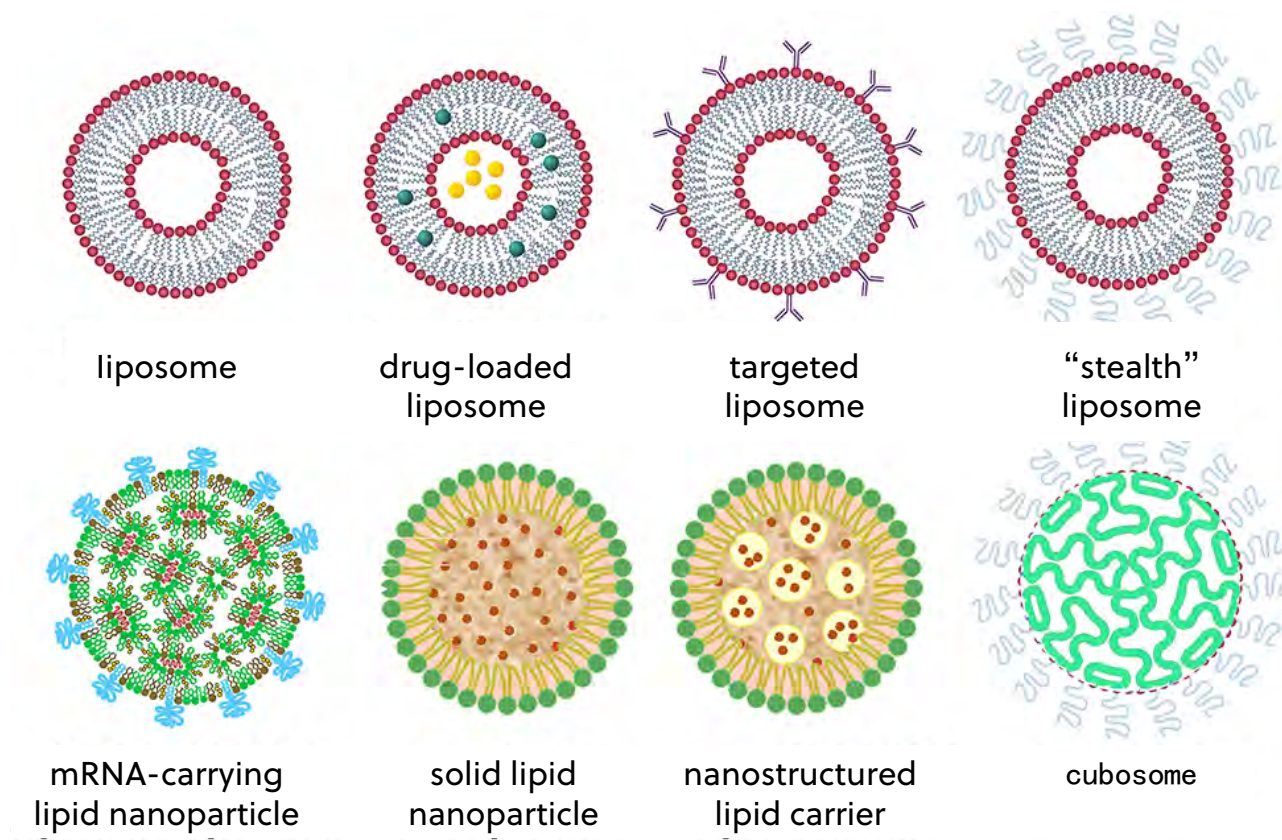


Figure 1. Schematic representation of various types of lipid nanoparticles. Adapted from Tenchov et al.¹

flexibility. Liposomes are spherical vesicles with lipid bilayers surrounding an aqueous core, while lipid-based micelles have amphiphilic molecules forming micellar structures. Lipid nanocarriers offer several advantages, such as improved drug solubility, enhanced bioavailability, controlled drug release, targeted delivery, and protection of labile drugs from degradation.^{1, 5, 8, 10, 11} Exosomes are similar to liposomes but originating from biological systems and secreted by most eukaryotic cells. They possess unique properties such as innate stability, low immunogenicity, biocompatibility, and good bio-membrane penetration capacity, making them superior natural nanocarriers for efficient drug delivery and diagnostics.¹²⁻¹⁵

Lipid nanocarriers have revolutionized drug delivery by overcoming limitations related to drug solubility, stability, bioavailability, and targeted delivery. They continue to play a pivotal role in improving drug delivery, expanding treatment options, and enhancing patient outcomes across

a wide spectrum of diseases and conditions. Their versatility, biocompatibility, and ability to address specific drug delivery challenges make them valuable tools in pharmaceutical research and development. Besides drug delivery, lipid-based materials have also found applications in other fields such as cosmetics^{16, 17} and agriculture^{18,19} among others. These diverse applications have led to a sustained interest in lipid-based materials as seen by the more or less steady increase in journal publications (**Figure 2**). Growth in patent publications have been more modest indicating unmet commercial potential (**Figure 2**).

In the present report we showcase our findings with regards to publication trends from extensive analysis of more than 46,000 documents (journals and patents) spanning across two decades (2003-2023) in the field of lipid-based materials from the CAS Content Collection. In addition to a publication trend overview, we also identified emerging materials in the field and their applications.

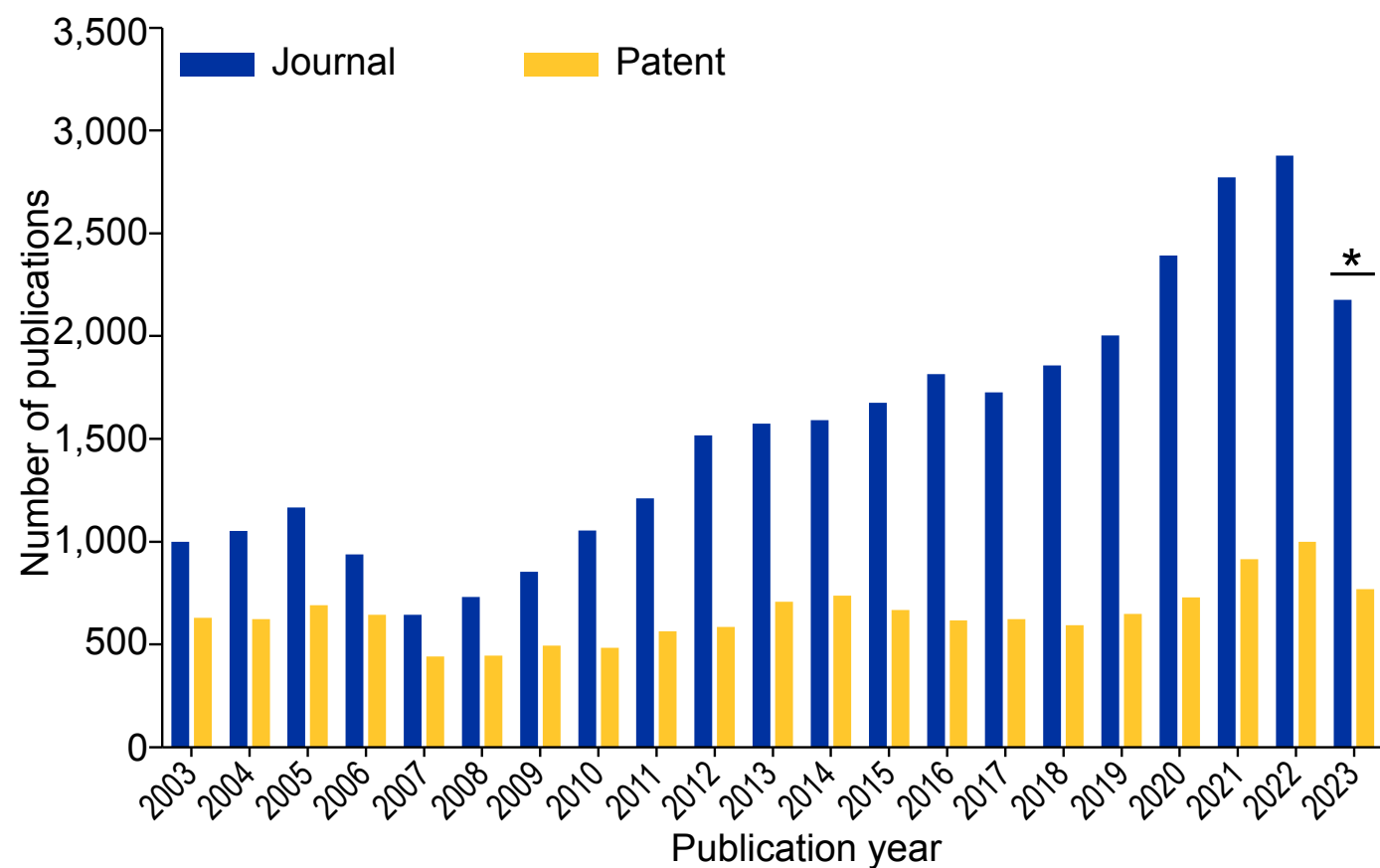


Figure 2. Number of journal and patent publications per year in the field of lipid-based materials (shown as blue and yellow bars respectively) over the period of the last two decades (2003-2023). * The data for 2023 only include months from Jan to Aug.

Journal and patent publication trends

From the top 150 organizations in terms of volume of journal publications, we identified leading organizations involved in research related to lipid-based materials on the basis of average number of citations per publications. Nearly half of the top 15 organizations originate in the USA which is followed closely by China contributing 4 institutions (**Figure 3**). The University of Alberta, the only organization originating in Canada leads the pack with an average number of citations per publication of >160 (**Figure 3**). One such highly cited article from the University of Alberta titled “Spray-freeze-dried liposomal ciprofloxacin powder for inhaled aerosol drug delivery” describes the formation and characterization of liposomal-encapsulated ciprofloxacin, a broad-spectrum antibiotic designed to be delivered via inhalation to prevent bacterial infections.²⁰

The trends in geographical distribution of patent assignees separated into commercial and non-commercial organizations show a high degree of overlap, a trend echoed in other biomaterials addressed in this report (**Figure 4**). Across both categories, the USA and China dominate with the former contributing greater numbers of patent publications in terms of commercial organizations.

On the other hand, non-commercial organizations in the USA and China have published similar numbers of patent documents. Other important/ key countries or regions in terms of volume of patent publications include: Germany (DEU), Japan (JPN), the Republic of Korea (KOR), France (FRA), Italy (ITA), India (IND) and Switzerland (CHE). More than 65% of the leading commercial organizations involved in research in lipid-based materials originate in the USA. Patents from ModernaTX, a biotechnology company from the USA, appear to be related to the use of lipid nanoparticles to deliver active payloads including drug molecules, proteins and mRNA for the treatment of cancer and other disorders (WO2021243207A1,²¹ WO2023076605A1²²) as well as development and delivery of vaccines (WO2018170260A1,²³ WO2023154818A1²⁴). Other US based companies such as Codiak Biosciences and Transdermal Biotechnology have filed patent applications relating to the use of lipid-based materials such as exosomes for drug and vaccine delivery (WO2023056468A1,²⁵ WO2020191361A2²⁶) and transdermal delivery (US20160136169A1²⁷) and wound healing (WO2014159986A2²⁸), respectively. The Japanese company, Konica Minolta Medical & Graphic, Inc. appears to have been more active in the late 2000s and was focused on the

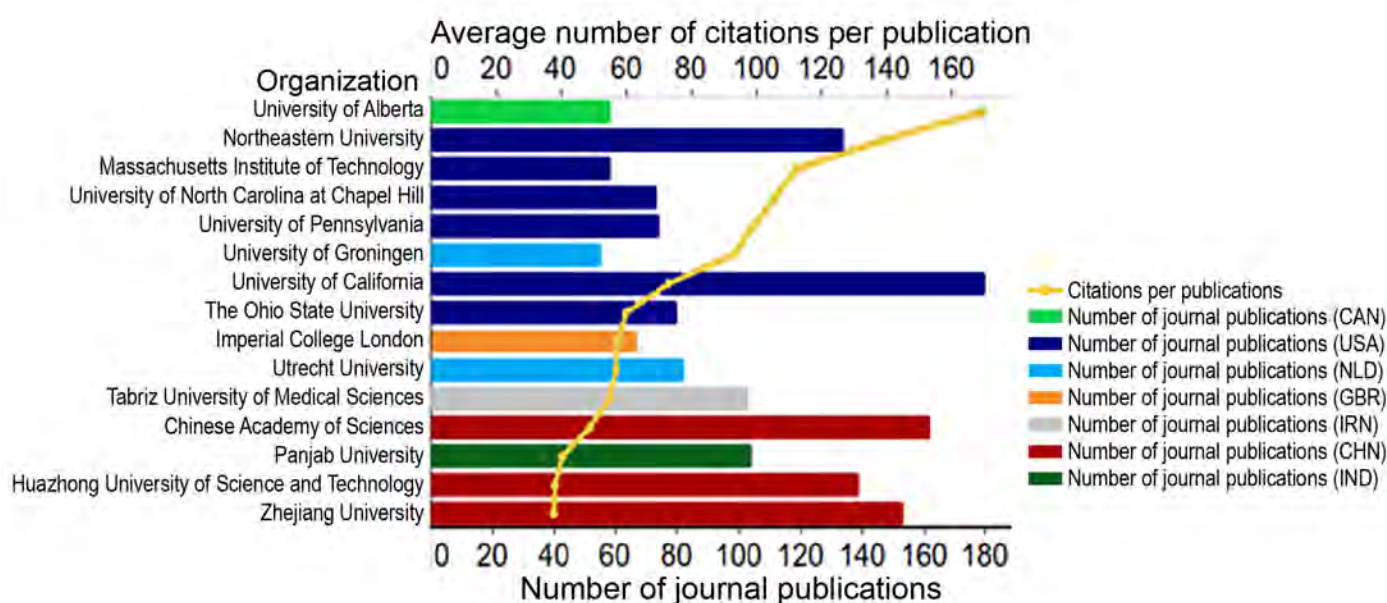


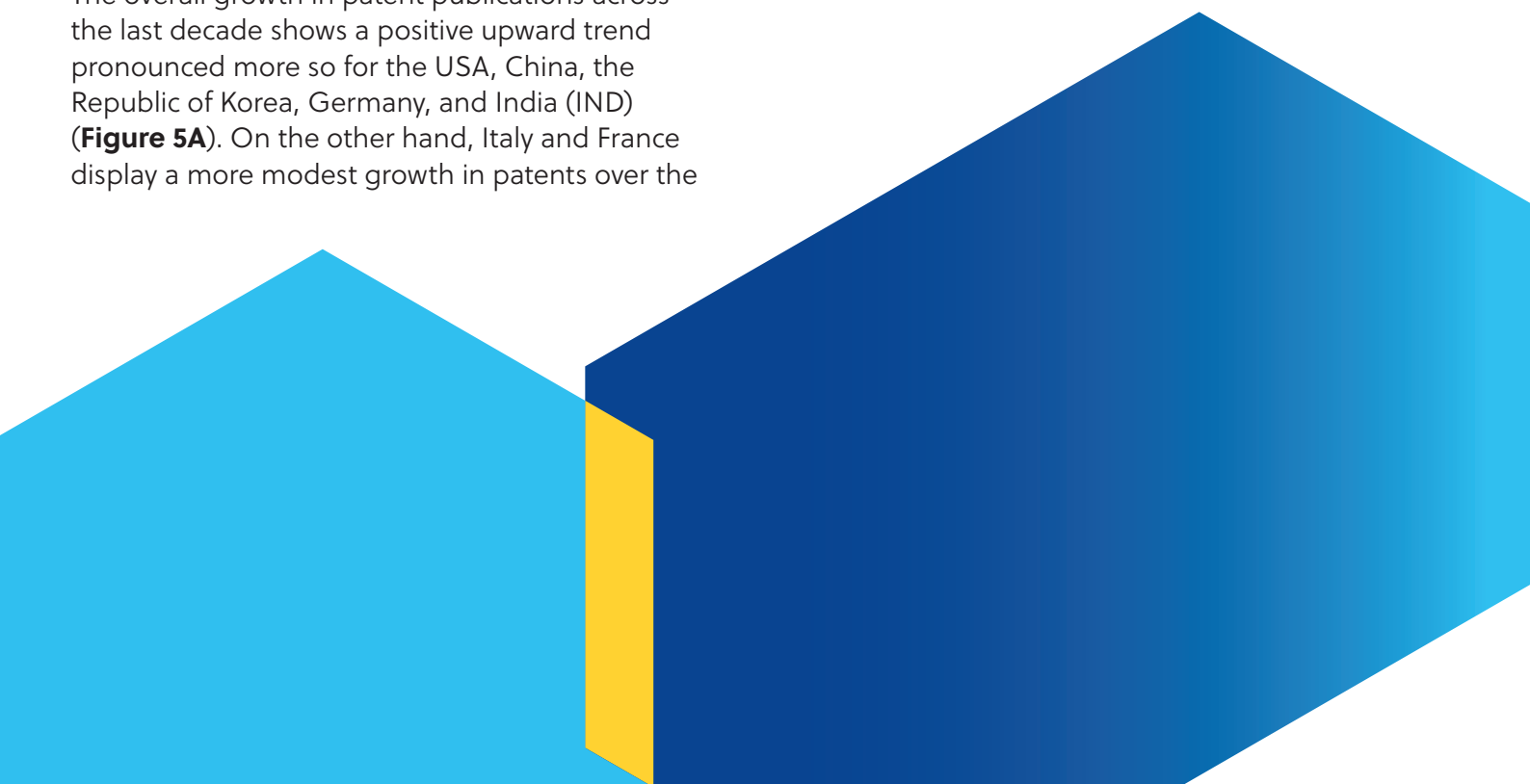
Figure 3. The top 15 research institutions in terms of average citation numbers per journal publication between 2003-2023.

delivery of X-ray contrast agents using liposomes (JP2005206540²⁹) and the use of liposomes in photodynamic therapy (EP2374825A1³⁰). Lipotec, a Spanish company, has explored the use of liposomes in cosmetics (US20130078295A1,³¹ EP2740484A1,³²) such as for the delivery of peptides and botulinum toxin.

Distribution for the top 15 commercial organization appears to split between China and the USA with 9 organizations originating in China (**Figure 5**). Among the non-commercial organizations in China, Shenyang Pharmaceutical University leads with >90 patent publications, closely followed by China Pharmaceutical University. Patents by Shenyang Pharmaceutical University appear to be centered around manufacturing liposomes (CN102552142A³³) as well as their application in drug delivery (WO2021043231A1³⁴) especially cancer therapy (CN109718228A,³⁵ CN116440287A³⁶). Examples of patent publications by China Pharmaceutical University include designing remdesivir liposomes to be administered by inhalation route (CN111991375A³⁷), liposomes for targeted delivery (CN111001011A³⁸), as well as other drug delivery applications (CN107837234A³⁹). Patent documents filed by the University of California seem to be related to use of lipid nanocarriers for drug delivery for cancer immunotherapy (WO2021076630A1⁴⁰) as well as Alzheimer's disease (WO2018081085A1⁴¹) and viral infections (WO2021207632A1⁴²).

The overall growth in patent publications across the last decade shows a positive upward trend pronounced more so for the USA, China, the Republic of Korea, Germany, and India (IND) (**Figure 5A**). On the other hand, Italy and France display a more modest growth in patents over the

last decade. Despite this upward trend, the actual number of patents for lipid-based materials is relatively low. Detailed analysis of patent family data showing the complex flow of patents from patent assignee countries or regions (left) to the patent office wherein the first application in a given family is filed (center) and the patent office where the individual patent publication activity takes place (right) is shown in **Figure 5B**. Unlike other biomaterials, for patents related to lipid-based materials a majority of applications were first filed at the European Patent Office (EPO). This is especially true for the USA, Germany, Japan, Canada, Israel (ISR) and the United Kingdom (GBR) wherein nearly half of the patent applications were filed at the EPO first (**Figure 5B**). In contrast, patent applications originating from China and Spain (ESP) appear to show only a minor preference for home office (CHN) and EPO, respectively, while a majority of the patents were filed more or less evenly across WIPO, their respective home offices as well as other patent offices across the world (**Figure 5B**). For USA, the rest of the patent application filings are split between their home office (US) and the World Intellectual Patent Office (WIPO). In terms of the final destination patent office, more than a third of the patents initially filed at the EPO make their way to the United States Patent Office (USA) followed by the EPO itself. Other important/key/major destinations offices include the Japanese, Canadian, Chinese, Korean, Indian, Spanish, Mexican, and Brazilian patent offices.



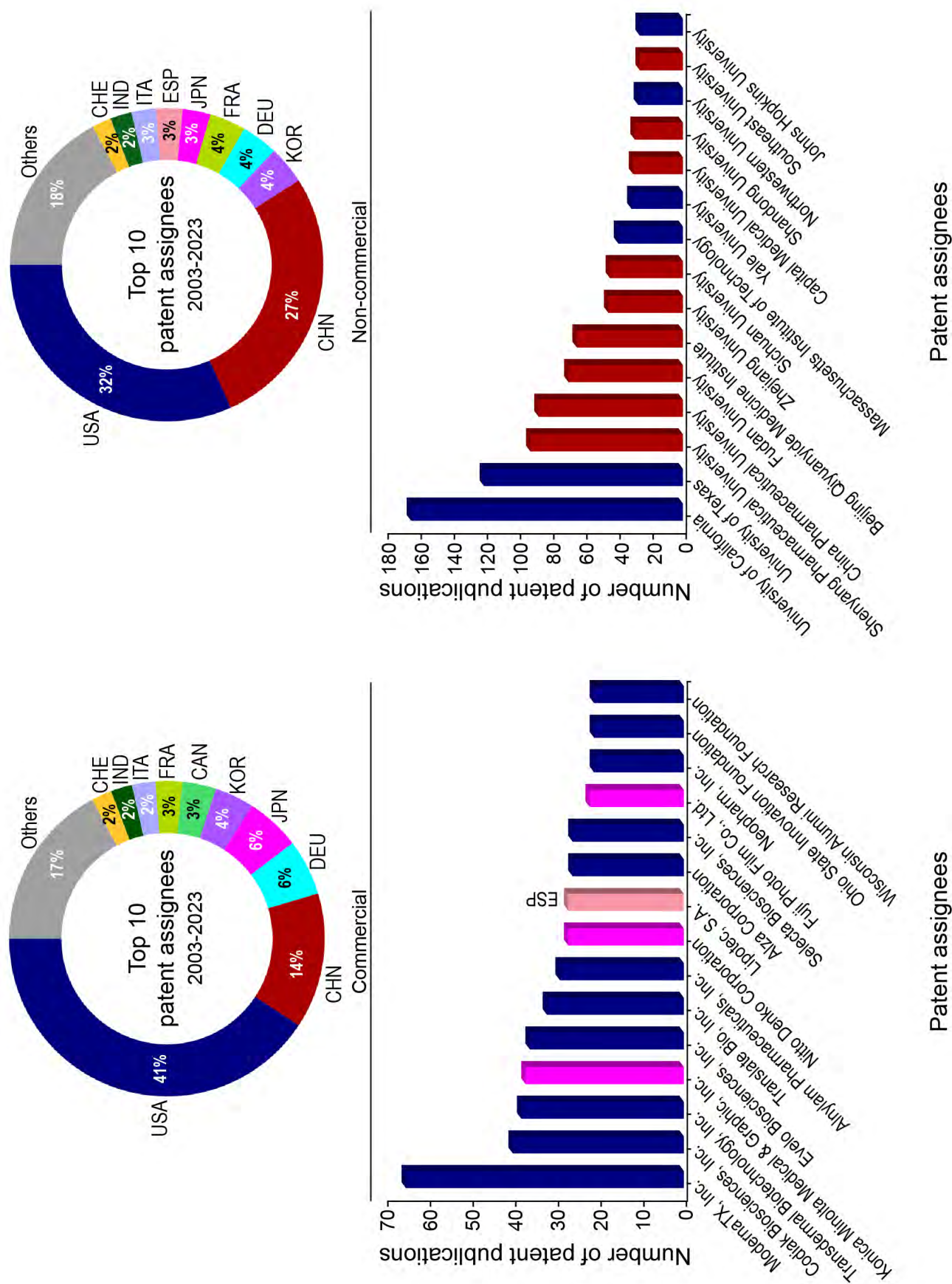


Figure 4. Geographical distribution (top panel) and leading patent assignees in the field of lipid-based materials in terms of numbers of patent publications between 2003-2023. Patent assignees have been separated in to two groups: commercial and non-commercial. Bar graphs have been color coded by country/region to match color scheme used in donut charts. Standard three letter codes used to represent countries/regions.

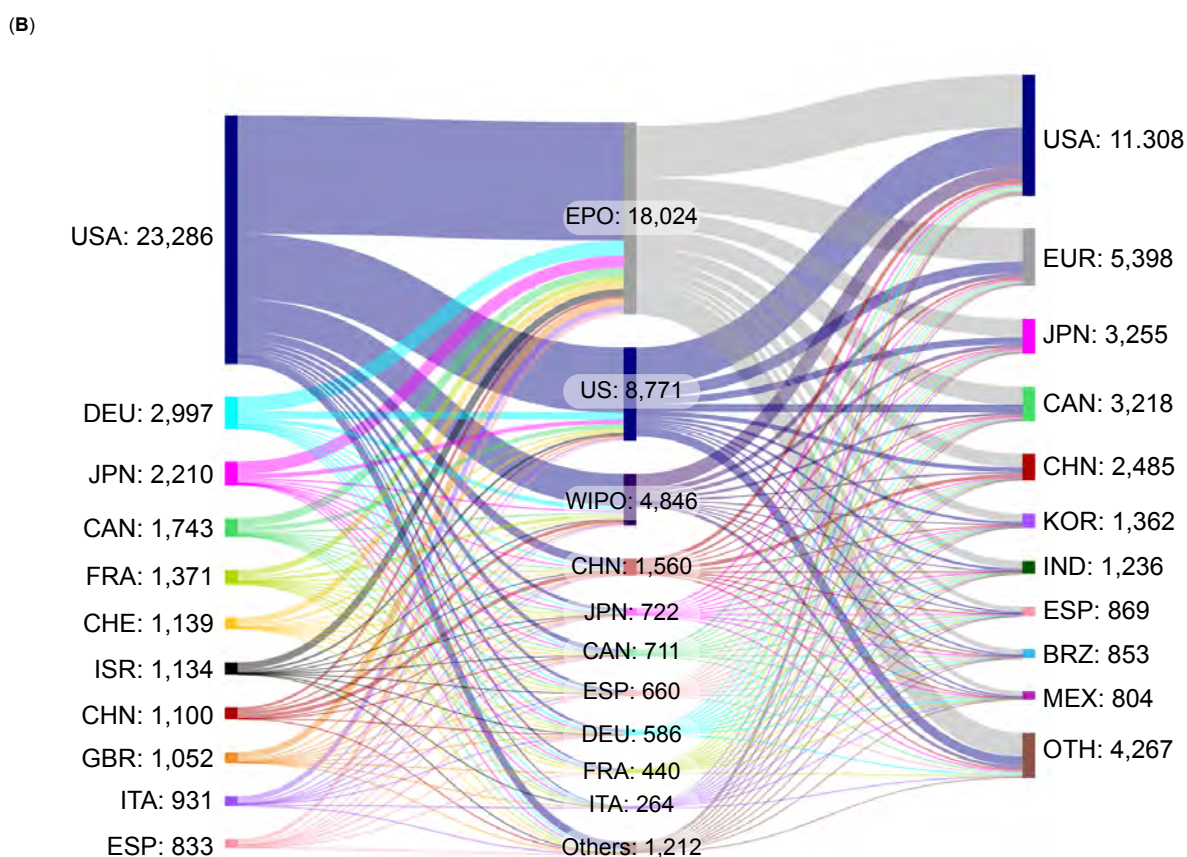
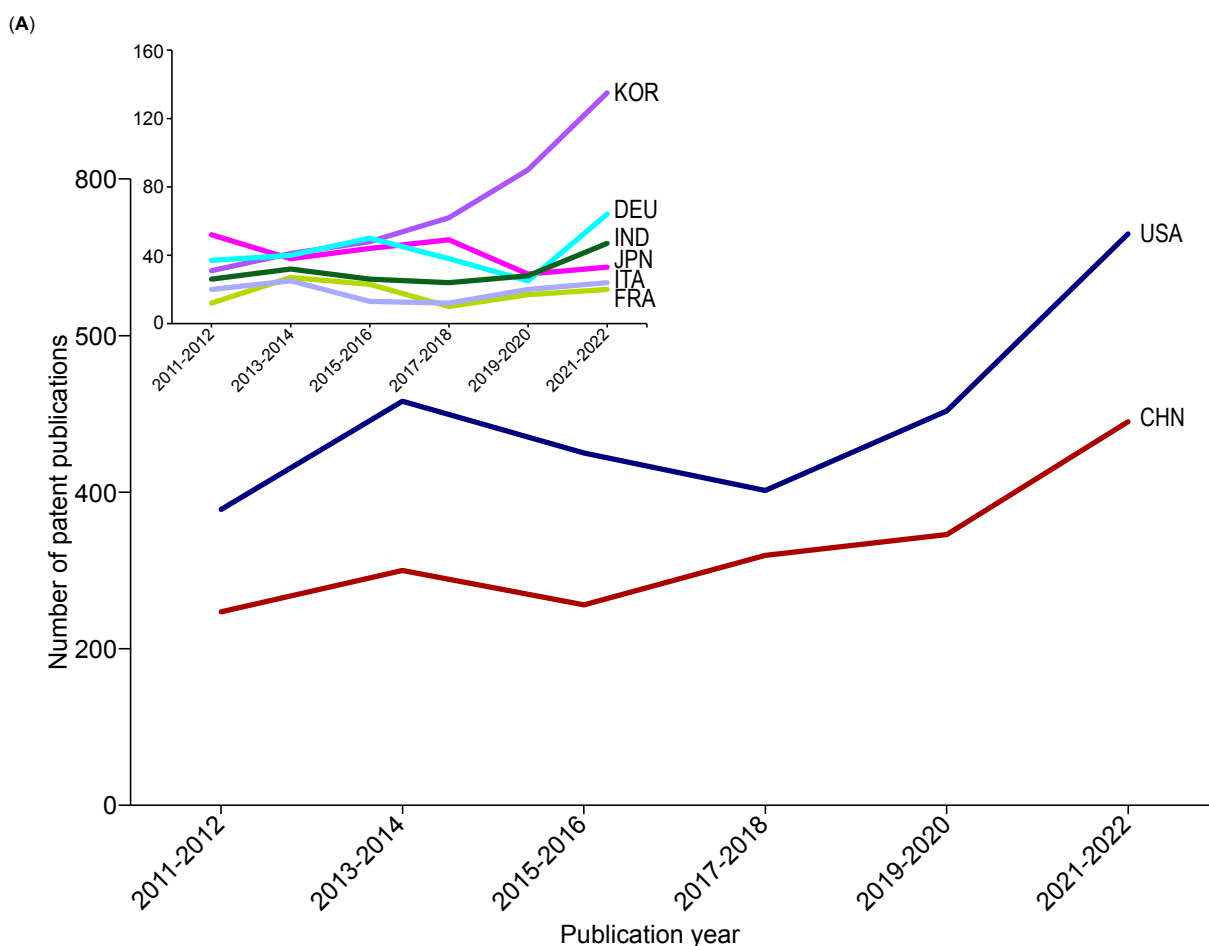


Figure 5. (A) Growth in patent publications over the last decade (2011-2022) in the field of lipid-based materials. **(B)** Sankey graph depicting flow of patent families in the lipid-based materials field between assignee countries (left), office where the first application in a family is filed (center) and the office where individual patent publication activities take place (right).

Key materials, forms and applications

A detailed and comprehensive exploration of our document and substance data from the CAS Content Collection aided in the identification of key materials across three major categories utilized in the development and application of lipid-based materials. Broadly speaking, these include:

- Lipids
- Payloads
- Emulsifiers

Figures 6 and 7 show a detailed breakdown of materials across these categories. The category of lipids was further sub-classified into the following general classes:

- Sphingolipids
- Sterols
- Phospholipids
- Glycerides
- Cationic lipids
- Oil and waxes
- PEG-lipid conjugates

In order to identify lipids that have seen an increase in interest over time, we plotted the relative publication growth rates for >50 lipids over 2012-2023 and used this information to shortlist key lipids shown in **Figure 8**. The biggest takeaway from our data analysis was that of the identified lipids, cationic lipids such as 2,3-dioleoyloxy-N-[2-(sperminecarboxamido)ethyl]-N,N-dimethyl-1-propanaminium (DOSPA; CAS number: [282533-23-7](#)), dimyristyloxypropyl-3-dimethyl-hydroxyethyl ammonium (DMRIE; CAS number: [153312-64-2](#)), 1,2-dioleoyl-sn-glycero-3-ethylphosphocholine (EDOPC; CAS number: [183283-20-7](#)) and dioctadecylamidoglycylspermine (DOGS; CAS number: [124050-77-7](#)) and the PEG-lipid conjugate DMPE-mPEG (CAS number: [474922-82-2](#)) show a sharp increase in publications post 2018 (**Figure 8A**). Phospholipids such as 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE, CAS number: [4004-05-1](#)) and 1,2-dioleoylphosphatidylserine (DOPS, CAS Number: [70614-14-1](#)) and sphingomyelin (CAS number: [85187-10-6](#)), a sphingophospholipid, also show an increase in publications after 2018 but the increase was of a more modest magnitude as compared to the cationic lipids listed above

(**Figure 8A**). Finally, publications related to the phospholipid 1,2-dierucoyl-sn-glycero-3-phosphatidylcholine (DEPC, CAS number: [51779-95-4](#)) grew rapidly from 2018 to 2020 and then appears to have plateaued (**Figure 8A**).

During the COVID-19 pandemic, a number of lipids were utilized in the delivery of vaccines being developed. The growth in interest (in terms of relative growth in publications) for these diverse lipids belonging to classes such as cationic lipids, PEG-lipid conjugate, phospholipids and sterols are shown in **Figure 8B**. Of particular note are the cationic lipids – ALC-0315 (CAS number: [2036272-55-4](#)) and SM-102 (CAS number: [2089251-47-6](#)) – and the PEG-lipid conjugates – 2-[(Polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159, CAS number: [18496164-2-7](#)) and DMG-PEG (CAS number: [160743-62-4](#)) which show a ~5-6-fold and 3-fold increase in publications, respectively.

The above-mentioned lipids can all be utilized to form various types of lipid nanocarriers including liposomes, lipid nanoparticles, exosomes, and emulsions, among others. We conducted a systematic search for the various types of lipid nanocarriers and their associated terms and showcase their distribution and growth in the lipid-based materials document dataset in **Figure 9**. Liposomes, consisting of vesicles, PEGylated, echogenic, stimuli-responsive, and bubble liposomes account for more than half while lipid nanoparticles comprising of solid nanoparticles (solid NPs), nanostructured lipid carriers (nanostructured LCs), ethosomes, cubosomes, and hexosomes account for a quarter of publications of the overall distribution (**Figure 9A**). Exosomes, a type of nanosized vesicles enclosed by a lipid bilayer membrane that can be used as drug delivery systems, and emulsions account for about 12% and 10% of publications. Virus-like particles (VLPs), well-ordered complex structures composed of viral proteins that do not retain the pathogenicity of viruses, have been increasingly explored in nanomedicine.^{43, 44} While first discovered in the late 1960s,⁴⁵ the use and exploration of VPNs appears to have proceeded in a modest fashion and accounts for a small fraction of overall publications in our dataset. Noteworthy, recently a selective endogenous encapsulation platform for cellular delivery has been developed

based on mammalian capsid protein homologs that form virus-like particles, and a long terminal repeat retroviral-like protein, which preferentially binds and facilitates vesicular secretion of its own mRNA.⁴⁶ This modular platform, engineered to package, secrete, and deliver specific RNAs, has been demonstrated to be suitable for development as an efficient therapeutic delivery unit, which potentially provides an endogenous vector for RNA-based gene therapy. In terms of growth and time trends, among the subtypes of liposomes, stimuli-responsive liposomes^{47, 48} show a sharp growth after 2016 while vesicles show a more controlled/modest but sustained growth for the last two decades (**Figure 9B**). Interest in PEGylated liposomes⁴⁹ appears to be more or less steady with neither a sharp increase nor decrease. Finally, echogenic and bubble liposomes appear to show a slight decline in interest around the same time (i.e., post 2018) however the volume of publications associated with these subtypes are much smaller than the others.

The diverse stimuli that have been utilized in the context of lipid nanocarriers can be broadly categorized into exogenous and endogenous with the former accounting for nearly 2/3rd of publications related to stimuli-induced release (**Figure 10A**). Of the various exogenous stimuli magnetic field based^{50, 51} and light or photosensitive/photo responsive⁵² release systems appear to be more popular than temperature⁵³ and ultrasound^{54, 55} based signaling. In terms of growth over time, publications related to endogenous stimuli, especially enzyme^{56, 57} and redox,^{58, 59} appear to show a sharp growth after 2014 (**Figure 10B**) while those related to pH⁶⁰ showed a more modest increase. Publications related to exogenous stimuli show a more or less sustained increase over the last two decades.

The diverse types and subtypes of lipid nanocarriers are utilized for formulations for various routes of administration, including oral (enhancing drug absorption in the gastrointestinal tract), topical and transdermal (improving drug permeation through the skin), inhalation (for respiratory diseases), and parenteral (bypassing second pass metabolism and improving bioavailability as well as allowing for targeted systemic delivery). Distribution of publications

pertaining to modes of delivery show more or less even contributions from parenteral, transdermal, and otic delivery routes (**Figure 11A**). The next most abundant route is oral accounting for 12% of the publications, followed by comparable contributions by inhalation, ophthalmic and nasal routes. Other routes such as rectal, vaginal, sublingual, and buccal contribute to a smaller extent than the rest. A further breakdown of parenteral routes indicate preference for intravenous which accounts for nearly a third of the parenteral data, followed by subcutaneous and intramuscular. Intraperitoneal administration (injection into the abdominal cavity) is a common method of administration used in laboratory animals for drug discovery research⁶¹ and probably accounts for data corresponding to testing of lipid formulations. Intrathecal⁶² and epidural⁶⁴ administration (injection into the spinal cord), intracerebroventricular⁶³ administration (injection into the brain), and intracardiac⁶⁵ administration (injection into the heart) are less common and used in limited circumstances. A heat map showing co-occurrences between lipid nanocarriers, and the various routes of administrations are shown in **Figure 11B**. Listed below are a few key observations from the heat map:

1. Most of the lipid nanocarriers show a distinct preference for any one administration route over others. This was especially pronounced for exosomes and ethosomes having highest co-occurrences with otic and transdermal routes of administration, respectively. Indeed, ethosomes – soft malleable vesicles comprising ethanol – have been specifically developed to improve the delivery of various drugs via the skin.⁶⁶ Exosomes, on the other hand have been shown to increase the delivery efficiency of locally administered inner ear therapies, such as the exosome-associated adeno-associated virus.⁶⁷
2. PEGylated liposomes are most appropriate for intravenous delivery closely followed by the otic route. Indeed, PEGylation has been specifically invented in an effort to improve systemic circulation time of drug carriers, thus improving their delivery efficiency after intravenous injection.⁶⁸

- Non-lamellar structured lipid nanoparticles such as cubosomes and hexosomes comprising lipids in bicontinuous cubic or hexagonal liquid crystalline phases, respectively, are becoming popular drug carriers for transdermal/topical delivery because of their ability to perturb the structure of the skin's outermost layer – the stratum corneum, thus enhancing the drug permeation.⁶⁹

Perhaps one of the biggest applications of lipid-based materials is in the delivery of various payloads including small molecules (drugs)^{70, 71} and biologics such as siRNA^{72, 73} as well as vaccine delivery^{74, 75} and gene therapy (safe and efficient gene transfection).^{76, 77} **Figure 12A and 12B** show the distribution of various applications and their growth over the years for lipid-based materials. In terms of drug delivery, lipid nanocarriers have been utilized in cancer therapy to reduce systemic

toxicity and enabling targeted delivery⁷⁸⁻⁸⁰ as well as in the treatment of infectious diseases with an aim to improve drug stability and selectively delivery to infected tissues.⁸¹⁻⁸³ Besides these, lipid nanocarriers are employed also in the treatment of neurological disorders (overcoming blood-brain barrier challenges),⁸⁴ ophthalmic conditions (enhancing drug retention in the eye),⁸⁵ cardiovascular therapies (improving drug solubility and controlled release),⁸⁶ and more.⁸⁷ The application of LNPs has also been extended to other fields, such as medical imaging, cosmetics, nutrition, agriculture, and other innovative areas such as nanoreactors. Lipid nanocarriers have been used to deliver contrast agents in X-ray and other types of imaging.^{88, 89} The use of lipid nanocarrier in the food industry^{90, 91} also shows an upward trend (**Figure 12**). Cosmetics^{92, 93} is another commercial sector where the use of lipid-based materials have shown a sharp increase (**Figure 12**).

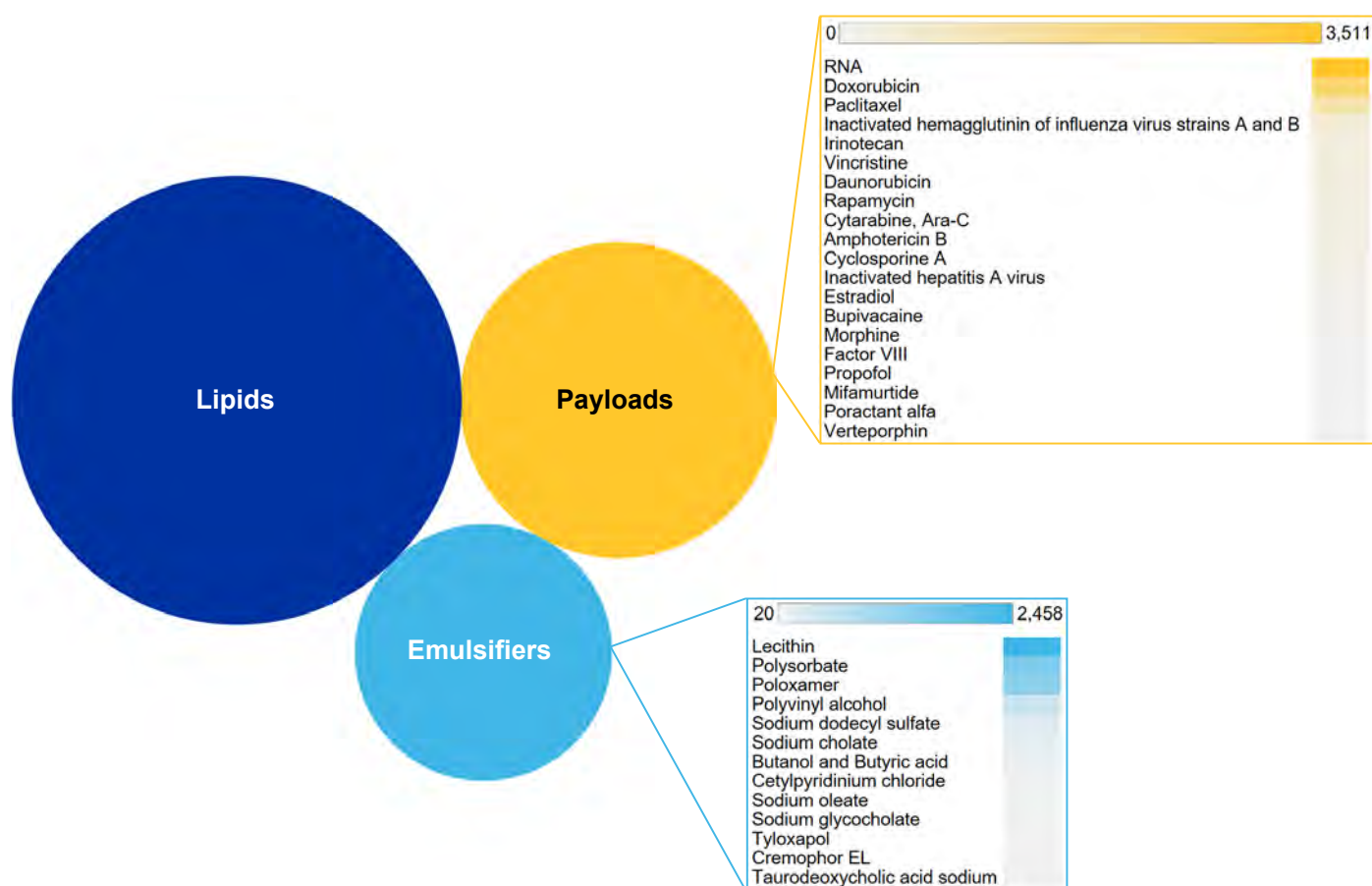


Figure 6. Distribution of key materials in lipid-based nanoparticles in terms of publications (journals and patents) based on data obtained from the CAS Content Collection for the period 2012 to 2023. A further breakdown of key lipids is shown in Figure 7.

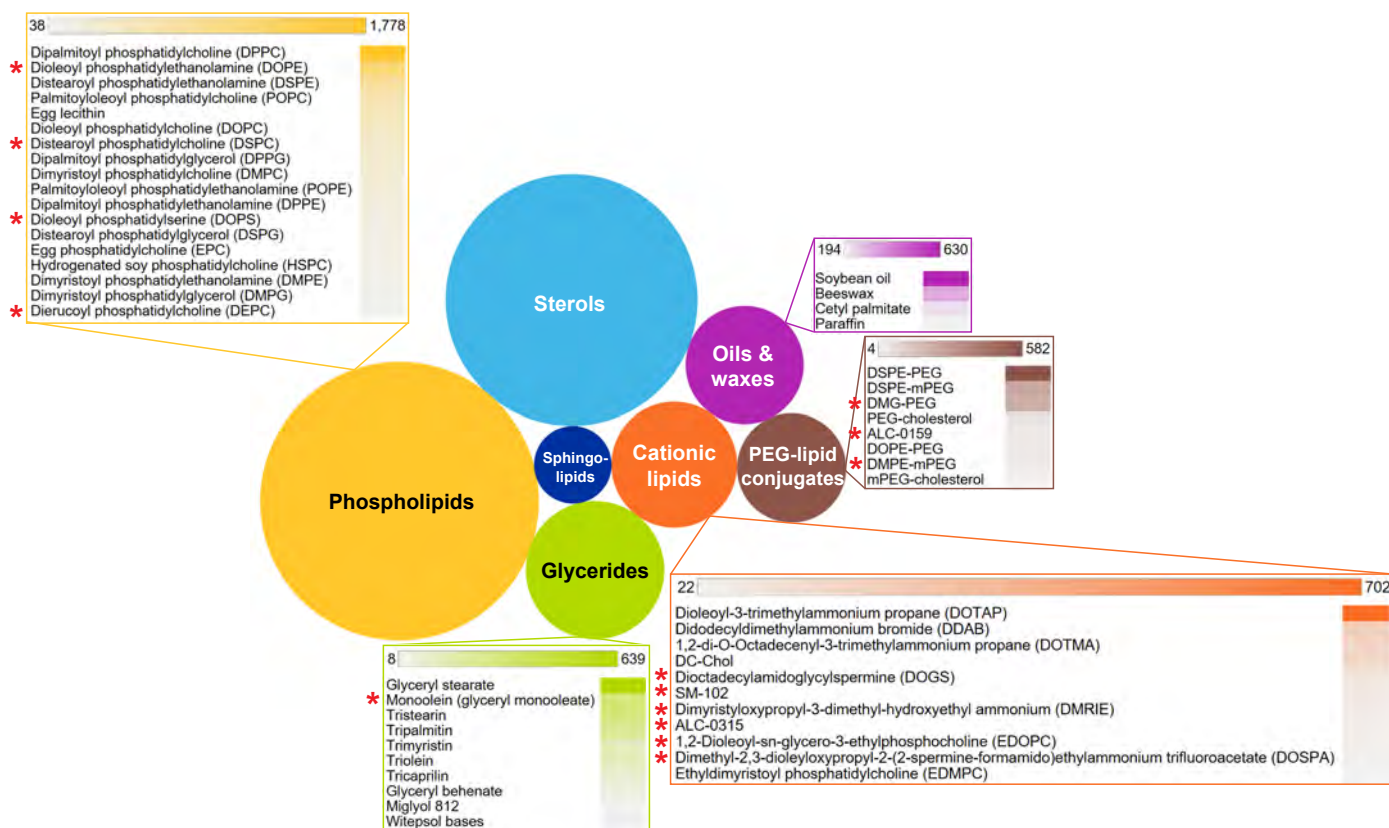


Figure 7. Detailed distribution of lipids in terms of publications (journals and patents) based on data obtained from the CAS Content Collection for the period 2012 to 2023. Size of the circle corresponds to number of publications (journals and patents). The growth of materials marked with an asterisk are shown in **Figure 8**.

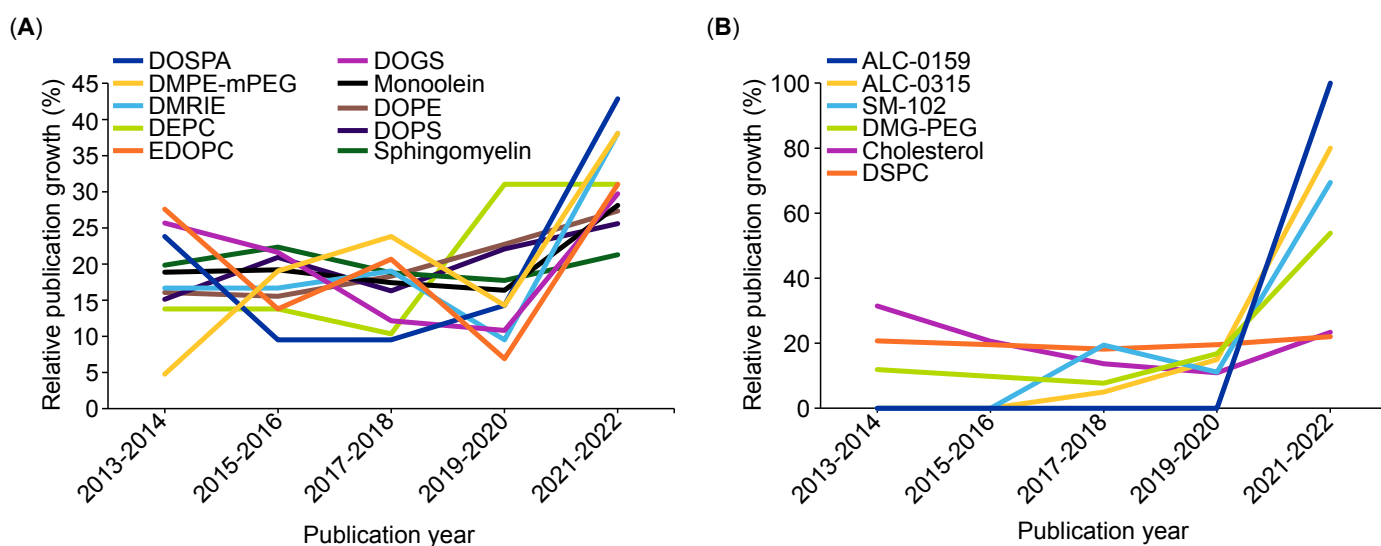


Figure 8. Growth of a **(A)** few select lipids emerging over the last decade and **(B)** lipids used in COVID-19 vaccine LNPs. Data includes journal and patent publications over the last decade (2012 to 2023) obtained from the CAS Content Collection.

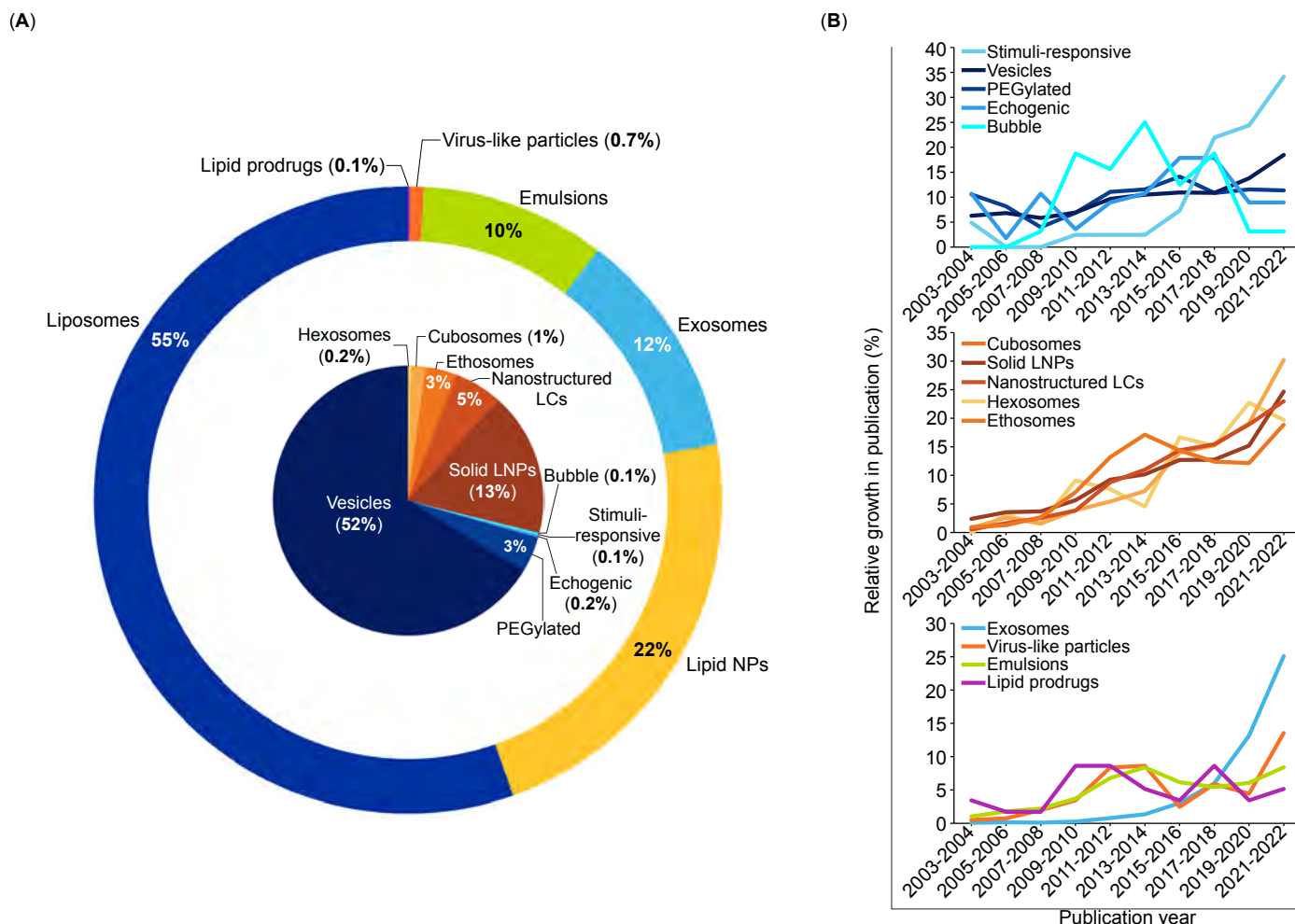


Figure 9. (A) Distribution of various types and subtypes of nanocarriers comprised of lipid-based materials. Outer donut chart shows the broader classification – liposomes, lipid nanoparticles (lipid NPs), exosomes, emulsions, virus-like particles, and lipid prodrugs, while inner pie chart depicts the breakdown across liposomes and lipid NPs. **(B)** Growth in publications (journals and patents) of the different types of lipid-based materials. Data includes journal and patent publications over two decades (2003 to 2023) obtained from the CAS Content Collection.

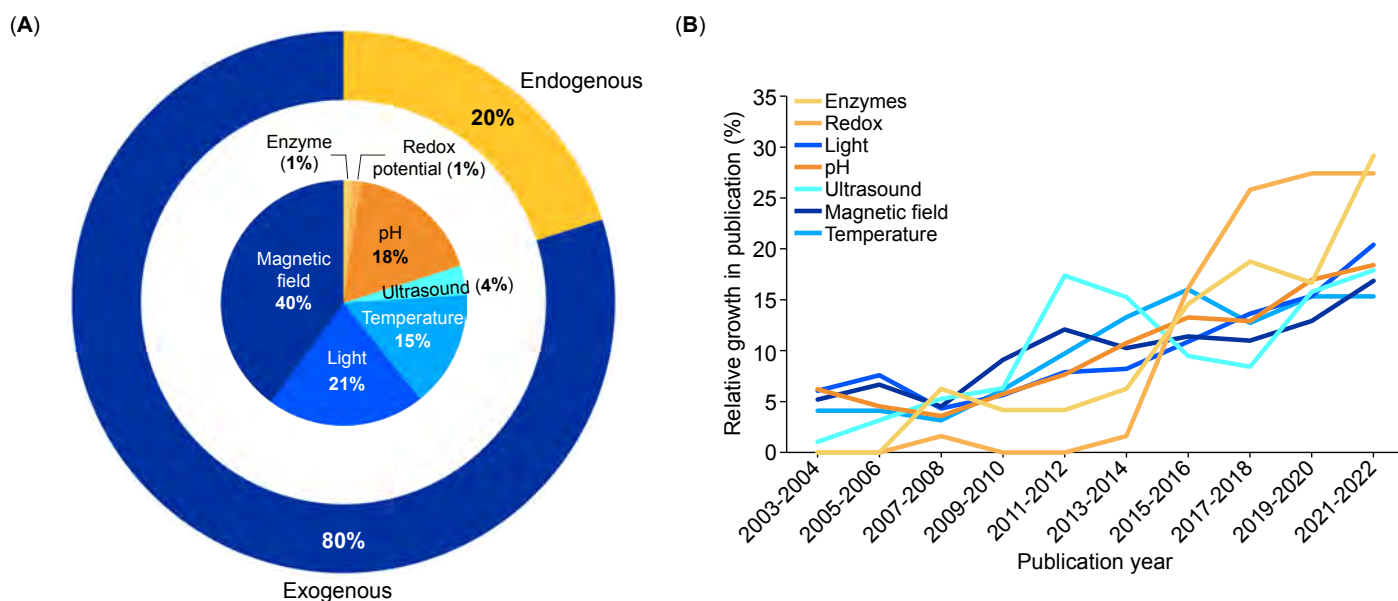
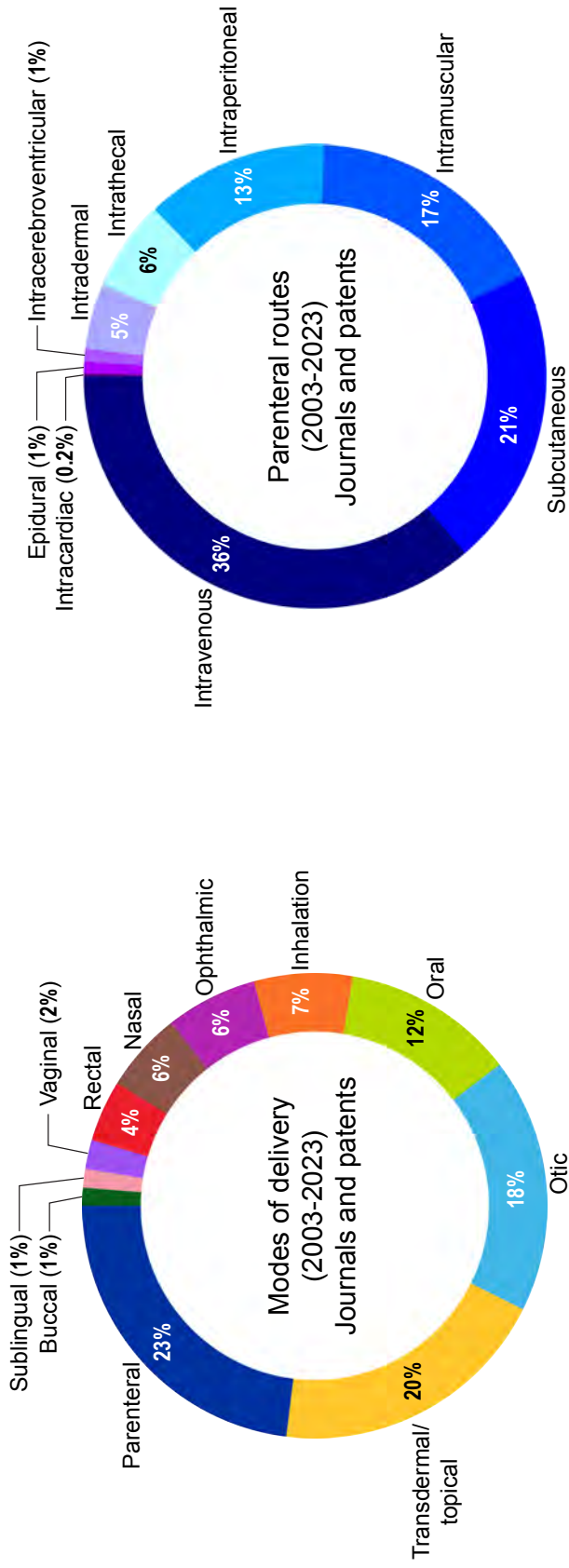


Figure 10. (A) Distribution of various types of stimuli-responsive lipid-based materials. Outer donut chart shows two major categories of stimuli – exogenous and endogenous while inner donut chart shows the breakdown across those categories. **(B)** Growth of specific stimuli utilized in stimuli-responsive lipid nanocarriers. Data includes journal and patent publications over two decades (2003 to 2023) obtained from the CAS Content Collection.

(A)



(B)

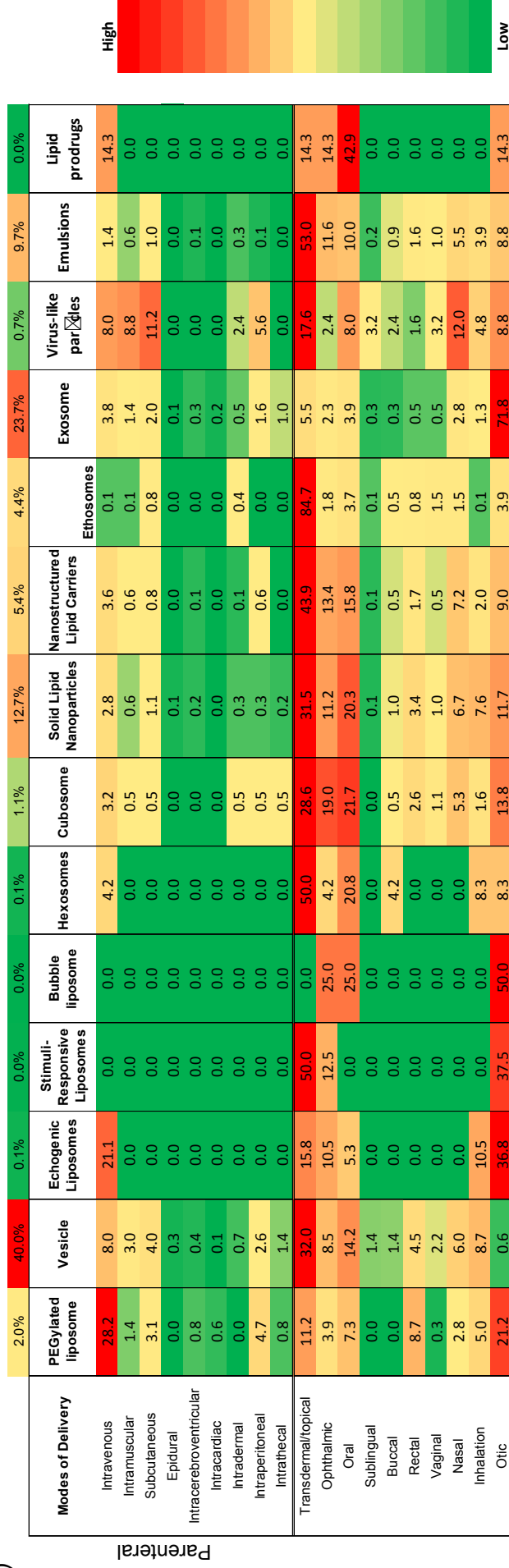


Figure 11. (A) Distribution of publications (journals and patents) with respect to various modes of delivery utilized for administration of lipid nanoparticles (left panel) with a further breakdown of parenteral routes (right panel). (B) Heat map depicting co-occurrences of various types of lipid-based materials with modes of delivery in the field of lipid-based materials based on data obtained from the CAS Content Collection for the period 2003 to 2023.

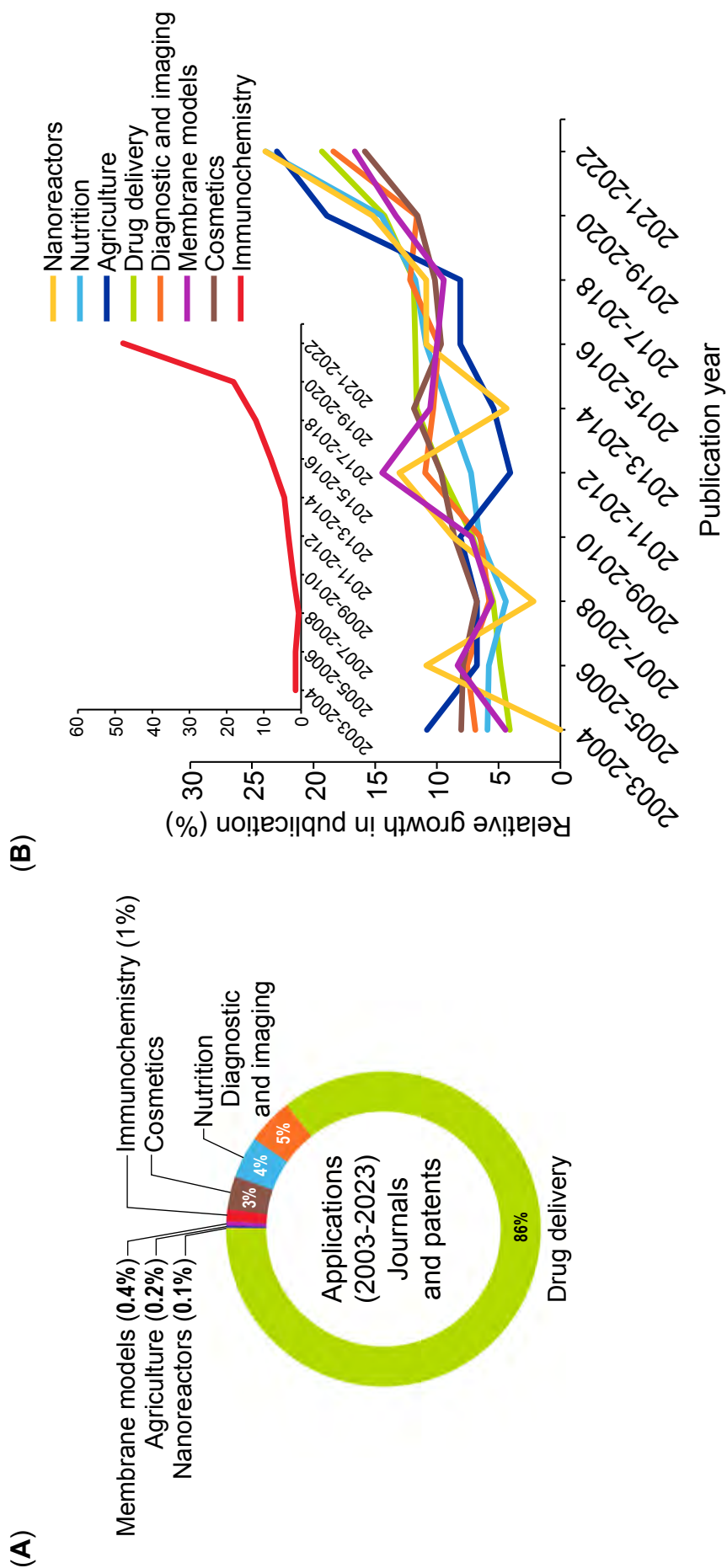


Figure 12. **(A)** Distribution of major applications of lipid-based materials **(B)** Growth in applications of lipid-based materials over last two decades (2003 to 2022). Data includes journals and patent publications obtained from the CAS Content Collection.

Notable journal articles and patents

Table 1 consists of a set of research articles published from 2020-2023 that are representative of emerging trends in this field. Articles were selected on the basis of the collective factors such as journal impact factor, citations, and type of study. These articles provide the usage of different forms of lipids examples including vesicles, liposomes, cubosomes, hexosomes, and ethosomes for varied applications. Notable examples from **Table 1** include an article titled "Theranostic combinatorial drug-loaded coated cubosomes for enhanced targeting and efficacy against cancer cells" by the Tian group at Jilin University, China describes assembly of structured lipid nanoparticle known as cubosomes encapsulating a combination of anticancer drugs - cisplatin and paclitaxel. Cubosomes were coated with poly- ϵ -lysine to avoid their premature bursting and targeted drug release. These were found to be nontoxic in human hepatoma HepG2 cell line and exhibited anticancer activity against HeLa cells *in vitro*.⁹⁴

In another example, an article titled "Selective organ targeting (SORT) nanoparticles for tissue-specific mRNA delivery and CRISPR-Cas gene editing" by Seigwart et al. describes a Selective Organ Targeting (SORT) strategy to selectively target different kinds of cargoes which could be either Cas9 mRNA, Cas-9 single guide RNA (sgRNA) or Cas9 ribonucleoproteins (RNPs) or Cre recombinase mRNA, to target organs such as the liver, kidney, and spleen in mice. It is accomplished by adding an additional molecule called SORT which helps in tissue-specific delivery and editing using CRISPR-Cas based method.⁹⁵

In another recent example, an article titled "CAR T cells produced *in vivo* to treat cardiac injury" explains generation of messenger RNA (mRNA) encoding CAR against FAP protein present on

activated fibroblasts. This mRNA is packaged in lipid nanoparticles (LNPs) targeting CD5 present majorly on T cells. These LNPs were tested for their efficacy of targeting T cells *in vitro*, where they improved cardiac function after injury upon intravenous administration.⁹⁶

Table 2 shows notable patents in the field of lipid-based materials published from 2018 to 2023. Patents were selected based on relevance, novelty, applicability, and field of study. Most of these involve different forms of lipids, methods of analysis and their applications. For instance, CN110960507B⁹⁷ describes synthesis of calcium phosphate-lipid nanodrug system using lipids like distearoylphosphatidylethanolamine-polyethylene glycol 2000 (DSPE-PEG2000) and (2, 3-dioleoyl-propyl)-trimethylamine (DOTAP). These nanoparticles encapsulate heparin and anti-breast tumor drugs which could be co-delivered to the tumor site.

In another example, US11207269B2⁹⁸ describes the liposomes for delivery of small molecule based antitumor drug. The study describes the synthesis of secretory phospholipase A2 (sPLA2) hydrolysable liposomes. sPLA2 levels are elevated in cancerous or inflamed tissues, making these liposomes potentially useful for delivering antitumor agents.

In another recent example, CN115869262A⁹⁹ provides synthesis methodology for a new polyethylene glycol (PEG) lipid compound which was combined with a cationic lipid, distearoylphosphatidylcholine, and cholesterol to generate lipid nanoparticles. These LNPs can be used for targeted drug or nucleic acid delivery.

Table 1. Notable journal publications in the field of lipid-based materials in recent years.

Year	Title	Journal	Research Institute	Application
2020	Theranostic combinatorial drug-loaded coated cubosomes for enhanced targeting and efficacy against cancer cells ⁹⁴	Nature Cell Death & Disease	Jilin University	Combinatorial drug-loaded cubosomes which can diagnose and treat cancer
2020	Selective organ targeting (SORT) nanoparticles for tissue-specific mRNA delivery and CRISPR-Cas gene editing ⁹⁵	Nature Nanotechnology	University of Texas	Using selective organ targeting (SORT) strategy to engineer multiple lipid nanoparticles each capable of selectively delivering different cargoes to liver, spleen, and lungs in mice.
2021	Characterization of Lipid Nanoparticles Containing Ionizable Cationic Lipids Using Design-of-Experiments Approach ¹⁰⁰	Langmuir	University of British Columbia	Lipid nanoparticle -short interfering RNA system (LNP-siRNA) and its optimization using design of experiments (DOE) approach.
2021	Mammalian retrovirus-like protein PEG10 packages its own mRNA and can be pseudotyped for mRNA delivery ⁴⁶	Science	Massachusetts Institute of Technology	Designing a retroviral-like protein, PEG-10 which binds mRNA to form capsids and secretes it at the target site, this tunability becomes the basis of selective endogenous encapsidation for cellular delivery (SEND) delivery platform.
2021	Ionization and structural properties of mRNA lipid nanoparticles influence expression in intramuscular and intravascular administration ¹⁰¹	Communication Biology	University of California	Using theoretical and experimental methods to determine pKa of lipid nanoparticles by calculating pKa of ionizable lipids to minimize off-target LNP delivery.
2022	CAR T cells produced <i>in vivo</i> to treat cardiac injury ⁹⁶	Science	University of Pennsylvania	Anti-fibrotic CAR-T cells based on mRNA-loaded LNPs directed towards cardiac CD5-cells
2022	Anti-PEG Antibodies Boosted in Humans by SARS-CoV-2 Lipid Nanoparticle mRNA Vaccine ¹⁰²	ACS Nano	University of Melbourne	Monitor Anti PEG antibody response by SARS-CoV-2 Lipid Nanoparticle vaccine
2022	Engineered exosomes as an in situ DC-primed vaccine to boost antitumor immunity in breast cancer ¹⁰³	Molecular Cancer	Wuhan University	Engineered breast derived cancer exosomes to form in situ dendritic cell (DC) vaccines
2023	Glucose-Responsive Charge-Switchable Lipid Nanoparticles for Insulin Delivery ¹⁰⁴	Angewandte Chemie	Zhejiang University	LNP-insulin complexes that can sense glucose and exhibit prolonged glucose release

Table 2. Notable patent publications in the field of lipid-based materials in recent years.

Patent or Publication number	Publication year	Patent assignee	Title	Description of patented technology
US10429302B2 ¹⁰⁵	2019	Scintillon Institute For Biomedical And Bioenergy Research, USA	Optical analyses of particles and vesicles	Method of analyzing vesicles based on addition of optical labels to obtain optical signals for their detection.
US10851372B2 ¹⁰⁶	2020	University of Ottawa, Canada	Exosome packaging of nucleic acids	Method for packaging interfering messenger RNA (mRNAi) into exosomes to produce exosomes with an increased nucleic acid content.
WO2021262879A1 ¹⁰⁷	2021	Chameleon Biosciences, Inc., USA	Extracellular vesicles with immune modulators	Preparation of extracellular vesicles (EVs) comprising a lipid bilayer containing immunosuppressive agents/ immune check point proteins.
US11207269B2 ⁹⁸	2021	Bio-Bedst ApS, Denmark	Medical use of sPLA2 hydrolysable liposomes	Preparation of secretory phospholipase A2 (sPLA2) cleavable liposomes encapsulating cancer drug for targeted delivery of anti-cancer medication.
US11021745B2 ¹⁰⁸	2021	Roche Sequencing Solutions Inc. USA	Methods for forming lipid bilayers on biochips	Assembly of biochips layered with lipid bilayer for use in sensing applications.
CN113101280B ¹⁰⁹	2021	Harbin University of Science and Technology, China Suzhou Hualancheng New Biomaterial Technology Co., Ltd., China	Solid lipid nano bacterial cellulose eye care patch and preparation method and application thereof	Preparation of composite from solid lipid nanoparticles and bacterial cellulose (1:5 ratio) to be used for eye healthcare.
CN110960507B ⁹⁷	2022	Fudan University, China	Calcium phosphate-lipid nano-drug co-delivery system composed of low-molecular-weight heparin and natural drug prodrug	Development of calcium phosphate-lipid nano-drug co-delivery system for treatment of breast cancer.
US11510872B2 ¹¹⁰	2022	Northwestern University, USA	Nanoparticle-lipid composite carriers and uses thereof	Synthesis of nanoparticles and lipid composites which anticancer drugs in hydrophobic core. These composites can also be derivatized and used for cancer theranostics.
CN115894555A ¹¹¹	2023	Wenzhou Research Institute Of Guoke, Wenzhou Institute Of Biomaterials And Engineering, China	Lipid prodrug nano-assembly based on dynamic covalent chemistry and preparation method and application thereof	Construction of lipid-based prodrugs by dynamic covalent chemistry such that the prodrug can later be attached to antibacterial/ antiviral/anticancer drugs.
CN115869262A ⁹⁹	2023	Guangzhou Anovent Pharmaceutical Co. Ltd., China	Novel PEG lipid compound, preparation method, composition and application thereof	Preparation of a novel polyethylene glycol (PEG) based lipid which could be used in drug and nucleic acid delivery.

Challenges and perspectives

Challenges in the development of lipid nanocarriers include drug loading and encapsulation as well as stability issues, scale-up complexities, biocompatibility concerns, limited drug loading capacity, drug release control, regulatory hurdles, cost considerations, and long-term storage requirements.

1. Achieving high drug-loading capacity while maintaining the stability of the lipid-based system can be challenging. It is necessary to achieve a delicate balance between high drug loading and particle size distribution and stability of the lipid carriers.⁸⁷ It is also essential to ensure that the drug is uniformly distributed within the lipid matrix.²
2. Lipid-based systems can be susceptible to phase separation and drug crystallization over time.¹¹² Maintaining the physical stability of these systems throughout their shelf life is a significant challenge.
3. Lipids are susceptible to oxidation and hydrolysis, which can lead to the degradation of both the lipid matrix and the encapsulated drug.¹¹³ Special care is required to prevent these reactions.
4. Controlling the release of the drug from the lipid carrier is essential for achieving the desired pharmacokinetics.¹¹⁴ Achieving the desired release profile can be challenging, especially for sustained or controlled release formulations.
5. Although lipid-based systems can improve drug solubility, the enhancement of bioavailability can be variable.¹¹⁵ Factors such as the type of lipid used, drug properties, and patient-specific factors can impact the overall bioavailability of the drug.
6. The production of lipid-based drug delivery systems may be more complex compared to traditional dosage forms, requiring specialized equipment and expertise.¹⁰
7. Ensuring good compatibility between the lipid-based system and the drug, as well as any excipients, is crucial. Incompatibilities can lead to drug degradation, reduced stability, or altered drug release profiles.¹¹⁶
8. Meeting regulatory requirements and obtaining approval for lipid-based drug delivery systems can be challenging due to the need for extensive safety and efficacy data, especially if they involve novel lipid formulations.¹⁰
9. Transitioning from laboratory-scale production to large-scale manufacturing can pose challenges, as maintaining product quality, consistency, and stability at a larger scale may require extensive process optimization.¹¹⁷
10. Lipid-based drug delivery systems can be more expensive to develop, and manufacture compared to conventional dosage forms, which can affect the overall cost of the drug product.¹¹⁸
11. Traditional approach of lipid-based drug development and testing is time consuming and labor intensive. To overcome these difficulties, AI and machine-learning based approaches in conjunction with traditional synthesis methods can help in efficient synthesis of lipids; However, structurally lipids are at the interface of small molecules which have a well-defined structure and large polymeric molecules complicating AI driven efforts. Despite this, in recent years efforts have been made in this direction.¹¹⁹

Ongoing research and innovation in lipid-based drug delivery systems aim to overcome these challenges and harness the full potential of these systems for improving drug delivery. This requires a multidisciplinary approach involving combined efforts of pharmaceutical scientists, chemists, engineers, and clinicians.

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IV. Bioinks

Introduction

Bioinks are biomaterials composed of a complex mixture of substances, often containing desired cell types with natural or synthetic polymers and other supporting materials. Bioprinting, as a method, often utilizes bioinks with a goal to fabricate biological structures in three-dimensional scaffolds, tissues and organs. While the term “bioprinting” is relatively recent, the idea itself dates back to the late 90s and was a natural extension of 3D printing in the biomedical domain. Bioprinting has diverse applications, including tissue engineering, wound healing,¹⁻³ disease modeling,⁴⁻⁶ personalized medicine,^{7,8} drug testing and development,^{9,10} and even drug delivery.¹¹⁻¹⁴ Interest in bioinks has been on a steady increase in the last two decades with an acceleration around 2015 (**Figure 1**). In general, journal publications outnumber patent publications in this field with a ratio of 5:1 in 2022 indicating that the field is still in its nascent stages. This continuously accelerated interest has led to an expansion in the different aspects of bioprinting

including the types of materials utilized in bioinks, bioprinting techniques themselves, as well as fields of applications.

Live cells are one of the primary building blocks of bioink. They can include various cell types: (1) stem cells¹⁵⁻¹⁸ – highly versatile and can differentiate into various cell types. They can be derived from sources like bone marrow, adipose tissue, or induced pluripotent stem cells (iPSCs); (2) endothelial cells¹⁹ – essential for vascularization and ensuring that the newly bioprinted tissue receives an adequate blood supply; (3) tissue specific cells – for example: keratinocytes and fibroblasts^{20, 21} for skin bioprinting, chondrocytes²² for cartilage bioprinting, and muscle cells for contractile tissues. The incorporation of live cells into bioink allows for the creation of functional tissues because these cells can proliferate, differentiate, and interact with the surrounding environment, mimicking the behavior of natural tissues.

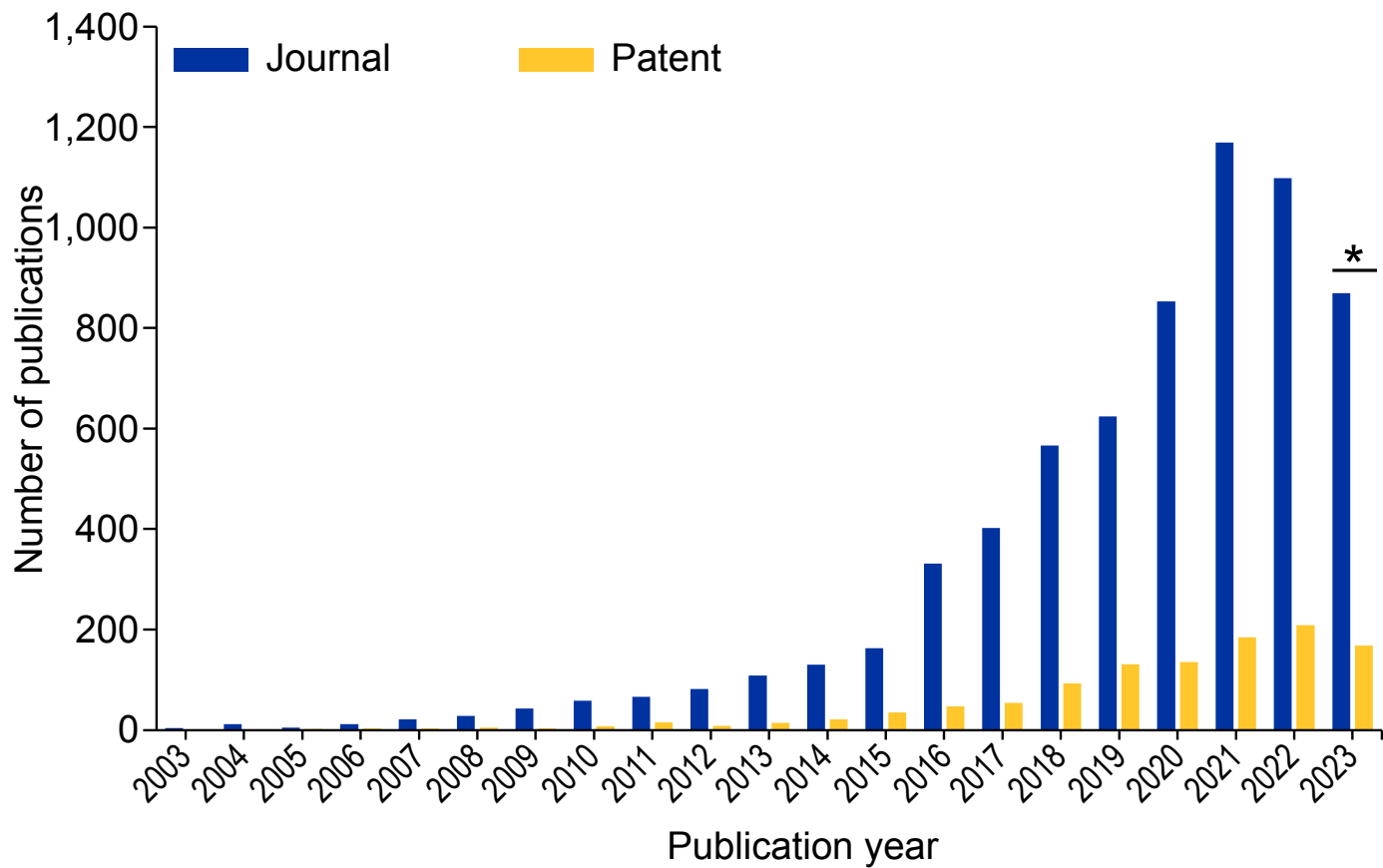


Figure 1. Number of journal and patent publications per year in the field of bioinks (shown as blue and yellow bars respectively) over the period of the last two decades (2003-2023). * The data for 2023 only include months from Jan to Aug.

Growth factors are signaling molecules that regulate various cellular processes, including cell proliferation, differentiation, cell-cell/cell environment interaction, tissue development, and tissue repair. In bioink, growth factors are typically added to stimulate specific cellular behaviors and enhance tissue development. Some common growth factors used in bioprinting include: transforming growth factor-beta (TGF- β),²³⁻²⁵ vascular endothelial growth factor (VEGF),^{26,27} epidermal growth factor (EGF),²⁸ platelet-derived growth factor (PDGF),²⁹ and fibroblast growth factor (FGF).^{26, 27} These growth factors can be incorporated into the bioink formulation in controlled concentrations to guide cell behavior and tissue formation. They help create a microenvironment that promotes cell proliferation and differentiation, ultimately leading to the development of functional and structured tissues.

However, live cells are fragile and lack the necessary structural framework to grow and maintain intricate connection and desired form. Synthetic polymers, such as polyethylene glycol (PEG) and its derivative polyethylene glycol diacrylate (PEGDA)³⁰⁻³² and polycaprolactone (PCL),³³⁻³⁵ are often incorporated into bioinks to provide the necessary mechanical strength and scaffold-like structures that help maintain the desired tissue shape. These synthetic polymers can be precisely tuned for properties like stiffness and degradation rate, ensuring they match the specific requirements of the target tissue. Meanwhile, natural polymers like collagen,³⁶⁻³⁹ fibrin,⁴⁰ and gelatin⁴¹⁻⁴³ offer bioactivity and biocompatibility, closely resembling the extracellular matrix (ECM) of native tissues. Many of these polymers can form hydrogels which possess characteristics such as oxygen and nutrient permeability, the ability to absorb substantial amounts of water without compromising their structure, biocompatibility, and biodegradability, among others. Importantly, hydrogels offer cells the freedom to migrate, creating a dynamic environment akin to the extracellular matrix ECM, rendering them indispensable components of bioinks. This biomimicry enhances cell adhesion, proliferation, and differentiation within the printed tissue. The

combination of synthetic and natural polymers in bioinks optimally balances structural support with the biological environment necessary for the successful 3D bioprinting of functional tissues and organs.

The realm of bioprinting encompasses various established methods, including laser-assisted, droplet-based, and extrusion-based techniques.⁴⁴⁻⁴⁶ These broad methods further branch into subcategories like inkjet, acoustic, or micro-valve droplet-based bioprinting.⁴⁷ Selecting the appropriate bioink and bioprinting technique hinges on several factors, such as the intended structure, and the mechanical design of the bioprinter, as well as the material's inherent properties.^{44, 46, 48} For instance, while rapid gelation is often a universal requirement, extrusion-based bioprinting proves more accommodating of varying viscosities, contrasting with droplet-based bioprinting, which performs optimally with low-viscosity bioinks.⁴⁶ In terms of the intended structure, whether hard (e.g., cartilage and bone) or soft (e.g., skin) tissue engineering, the demands on bioink characteristics tend to be distinct. Soft tissue engineering, for instance, necessitates a delicate balance of elasticity, flexibility, and structural integrity, a challenge often difficult to achieve. Light-based techniques such as photo-cross-linking can enhance better mechanical property in existing constructs upon in-situ crosslinking or produce a scaffold in a bioresin reservoir using computed axial lithography.⁴⁹

Within this chapter, we present our findings stemming from a comprehensive examination of approximately 7,000 documents, comprising both journal and patent publications, spanning the period from 2003 to 2023 in the field of bioinks. Our analysis centers on the overarching publication trends, with a particular emphasis on uncovering emerging materials, elucidating their interactions with key properties, and exploring their potential applications.

Journal and patent publication trends

To identify the leading research institutions in this field, we analyzed the average citation numbers per publications among the top 150 organizations in terms of total journal publications associated with bioinks. The top 15 research organizations with highest average citation per paper are shown in **Figure 2**. Among the 15 institutions, 6 of them are from the US, 4 from China, and 2 from Korea. Harvard Medical School, with an average of 110 citations per publication, leads the top 15 organizations.

The geographical distribution of patent assignees across both commercial and non-commercial entities reveals a substantial overlap, as illustrated in **Figure 3**. The United States (USA) and the Republic of Korea (KOR) dominate as leaders in both commercial and non-commercial sectors. China (CHN) exhibits a slightly more favorable position in the non-commercial sector compared to its standing in the commercial sector. Beyond these frontrunners, other noteworthy countries/regions include Sweden (SWE), France (FRA), India (IND), Israel (ISR), Germany (DEU), Australia (AUS), Russia (RUS), Spain (ESP), and Switzerland (CHE). Among the top patent assignees, the Sweden-based company Cellink is a leading

commercial entity in 3D bioprinting. They provide bioinks and bioprinters tailored for applications, such as tissue engineering regenerative medicine, disease modeling, drug delivery, and so on. For instance, patents US1186736B2, SE1950711A1^{50, 51} by Cellink describe important advances in the field of bioinks. The US company Organovo is dedicated to creating functional human tissues and organs using 3D bioprinting techniques. Their technology allows them to print intricate cell structures layer by layer with the goal of ultimately creating tissues and organs for transplantation and drug testing. For example, WO2018035138 A1,⁵² EP3215603B1⁵³ patents by Organovo describe the development of *in-vitro* bioprinted human tissue models such as tumor models and 3D printed models of skin respectively, which could help in the assessment fo biological responses to test drugs. Notably Organovo has used its proprietary 3D-printed human tissue models to develop a lead therapeutic molecule FXR314, which is currently in Phase II clinical trials for ulcerative colitis.⁵⁴

It is not surprising to see that the growth of patent publications prior to 2013 remained flat, probably due to its relatively nascent stage in those years. Over the past decade, the United States (USA), China, and Korea have consistently demonstrated

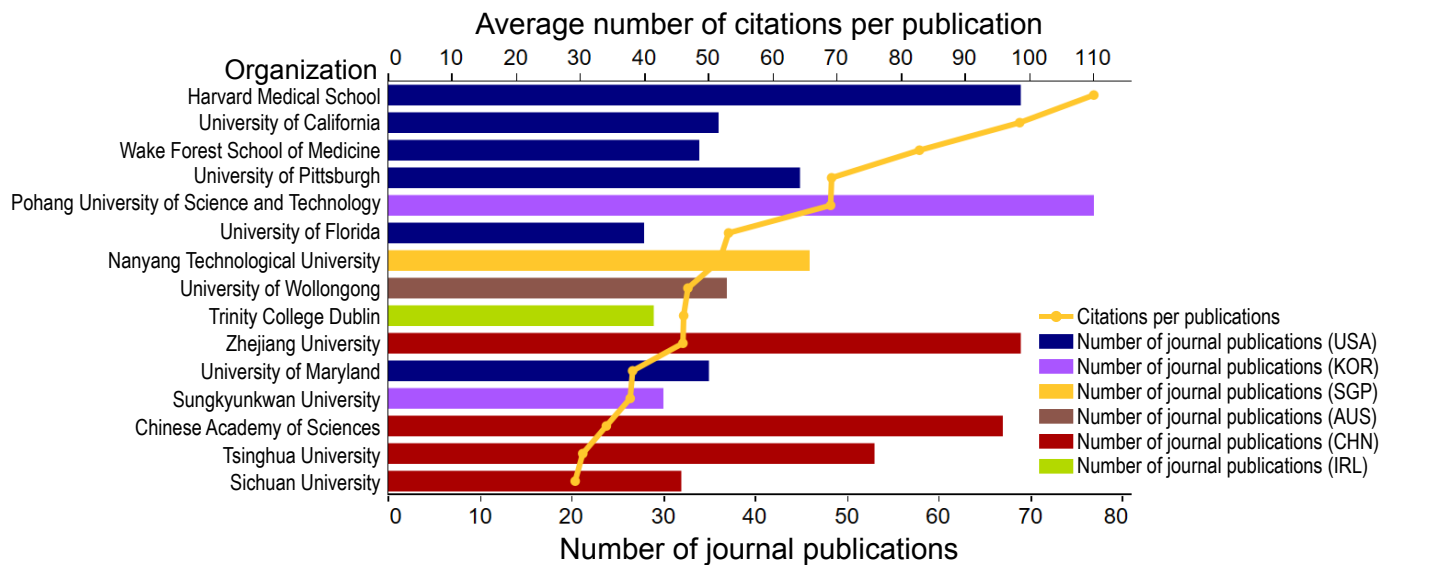


Figure 2. The top 15 research institutions in terms of average citation numbers per journal publication between 2003-2023. The different colors of the bars represent institution's country/region: blue (USA), red (China), yellow (Singapore), purple (Korea), brown (Australia), green (Ireland) institutions; and the yellow line represents the average number of citations per publication.

an upward trend in patent publications, as evident in **Figure 4A**. While countries such as India, France, Germany, and Sweden have shown moderate publication growth since 2017, their overall share of the publication volume is small. The flow of patent activities between assignee countries (left), the first patent filing office for a given family (center), and the patent office for individual patent publications (right) is shown in **Figure 4B**. This analysis indicates that applicants in China, Korea, and France typically had the first filing in for each patent family in their national patent offices, while applicants in the US and

Australia more frequently filed initial patents through WIPO/PCT.

To provide an overview of how research effort has been distributed among different types of tissue, organs, or types of cells in the field of bioinks, a comprehensive analysis was conducted with the associated terms and their frequencies appearing in the published documents. **Figure 5A** shows the distribution of most commonly used cell types in bioinks by counting the publications using CAS indexed terms. Publication volumes indicate that mesenchymal, induced pluripotent, neural,

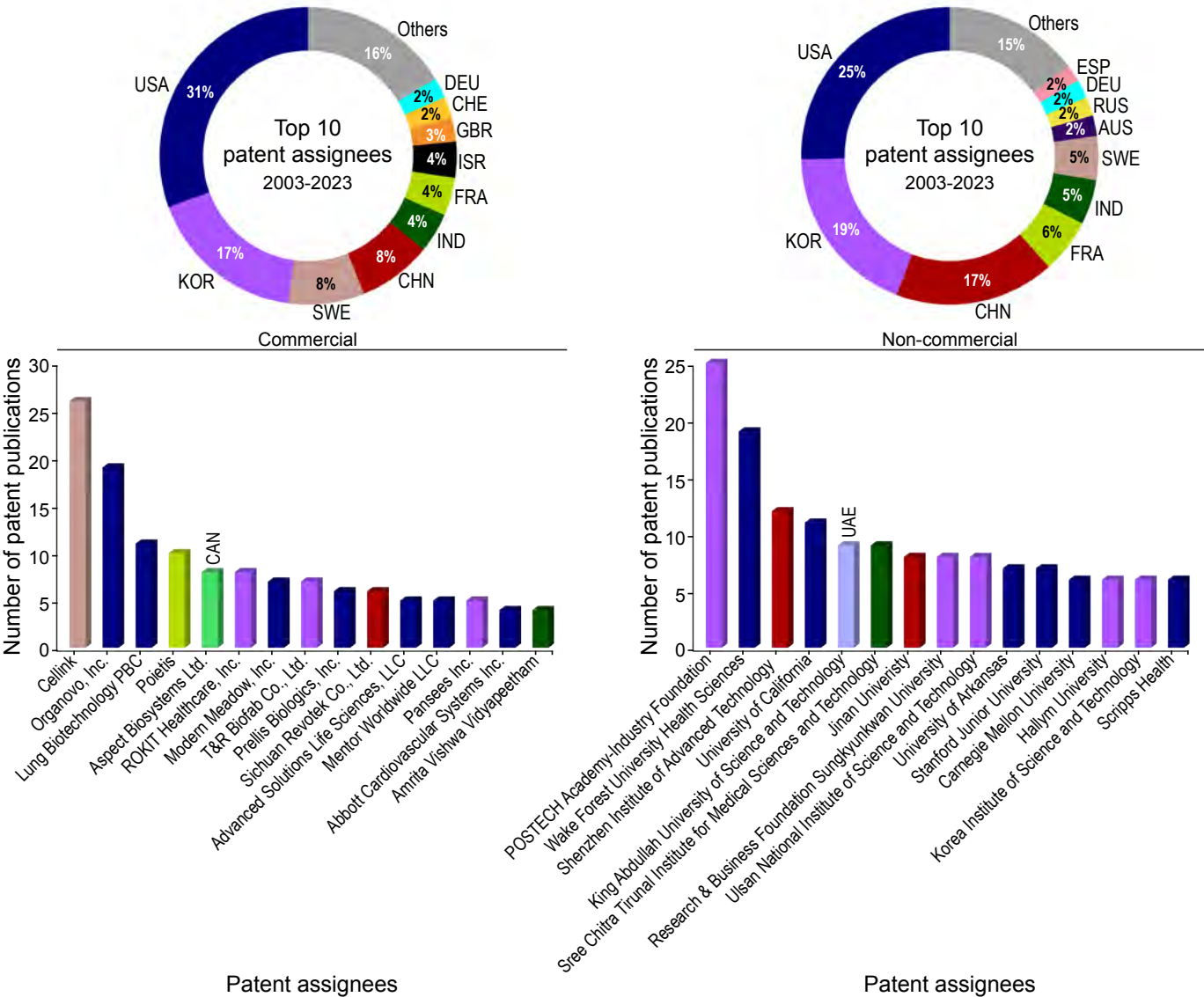


Figure 3. The geographic distribution of patent assignees (top panels) and the leading patent assignees in terms of the number of patent publications (bottom panels) from 2003-2023. Leading patent assignees were presented in two groups, commercial and non-commercial. Bar graph has been color coded by country/region to match color scheme in donut charts. Standard three letter codes used to represent countries/regions.

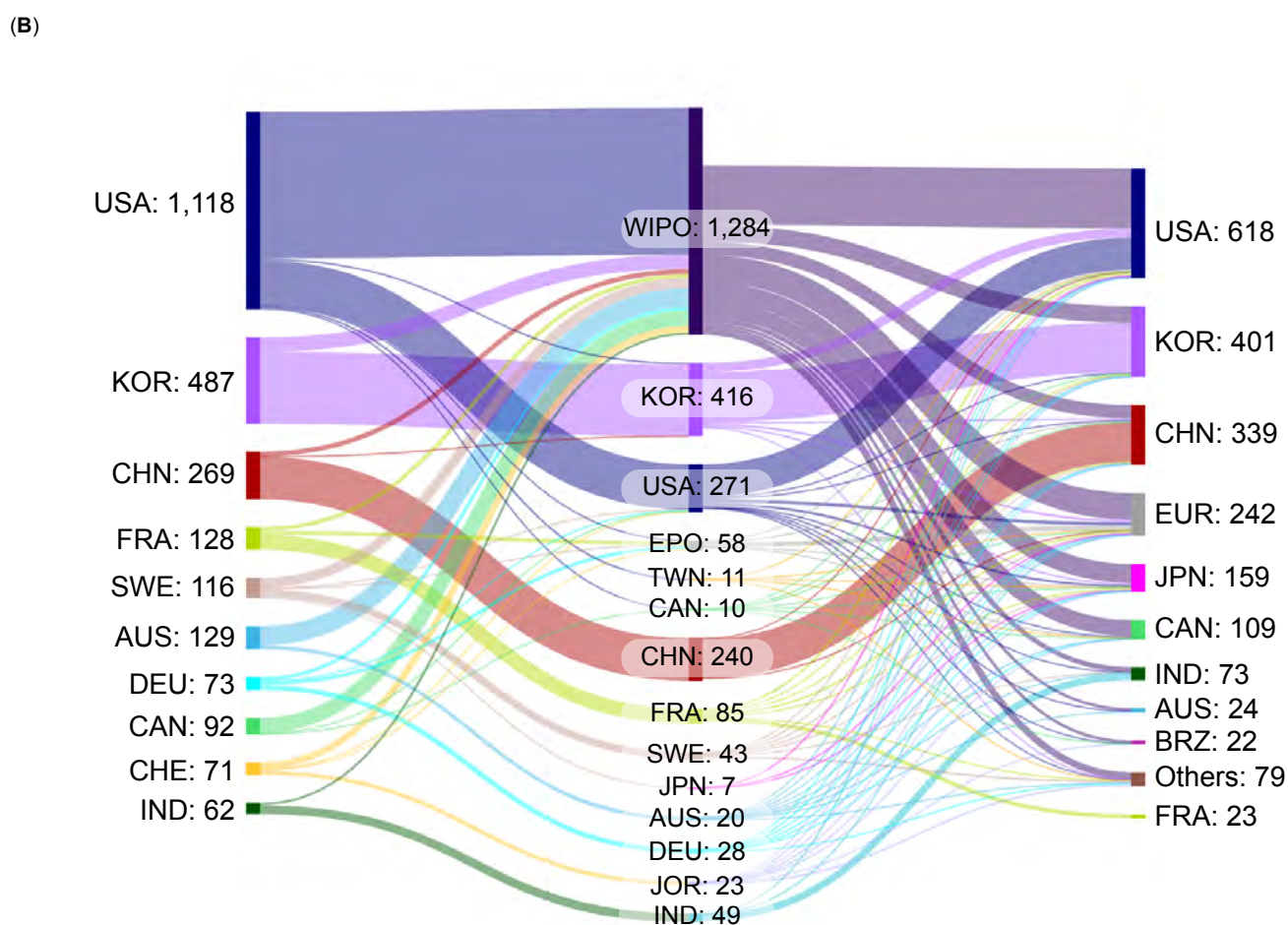
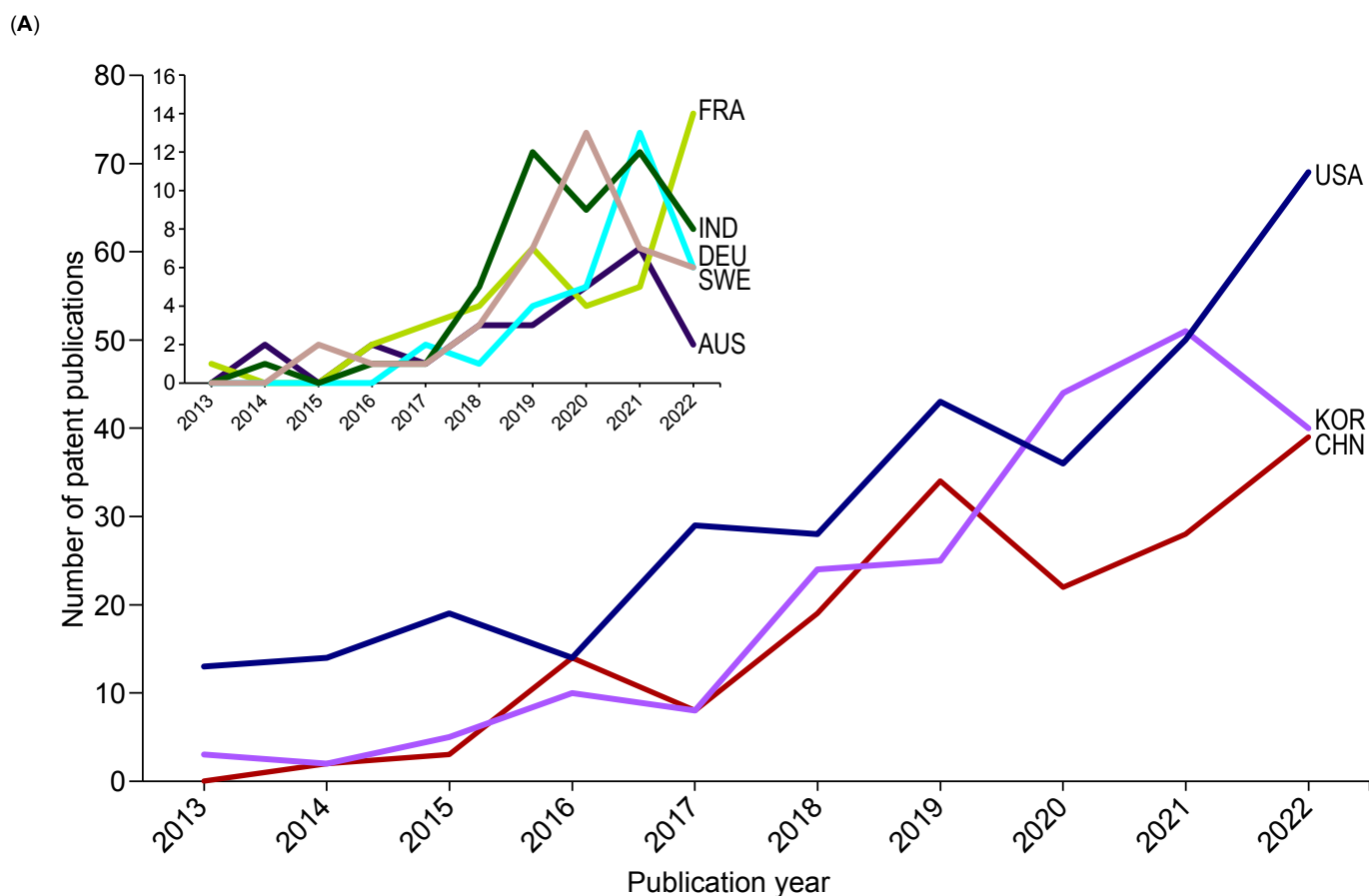


Figure 4. (A) Growth in patent family publications between 2003-2022 for the top 8 most prolific countries/regions. **(B)** Sankey graph depicting flow of patent families in the bioink field between assignee countries (left), office where the first application in a family is filed (center) and the office where individual patent publication activities take place (right).

and hematopoietic stem cells are important for bioinks.¹⁵⁻¹⁸ Besides stem cells, other major cell subtype that co-occur in the bioink dataset include blood cells (RBCs,⁵⁵ platelets,⁷ blood cells) and pancreatic cells. Schwann cell,⁵⁶ a type of neuronal cell co-occurs in much smaller fraction of publications. **Figure 5B** shows the distribution of publications in the field of bioinks across cell lines derived from different species – human, mouse, plant, hamster, rat and monkey cell lines. Our dataset shows distribution of publications across a wide variety of tissues and organs wherein bioinks are utilized to generate tissue constructs. The biggest contributor is the wider group of organs,

followed by bone, muscle, and skin. Bioinks appear to be utilized to a smaller extent for other tissues such as nerves, joints, tendon and ligament (**Figure 5C**). Further breakdown of organs into sub-categories indicates that in ~50% of cases, bioinks are utilized in liver-related constructs. The next most abundant categories are blood vessels, consisting of veins, arteries and capillaries, and cardiac tissue. In recent years, bioinks have also been utilized to create tissue constructs pertaining to other organs such as kidney, lungs, mammary gland, pancreas, and ocular/ophthalmic (**Figure 5D**).

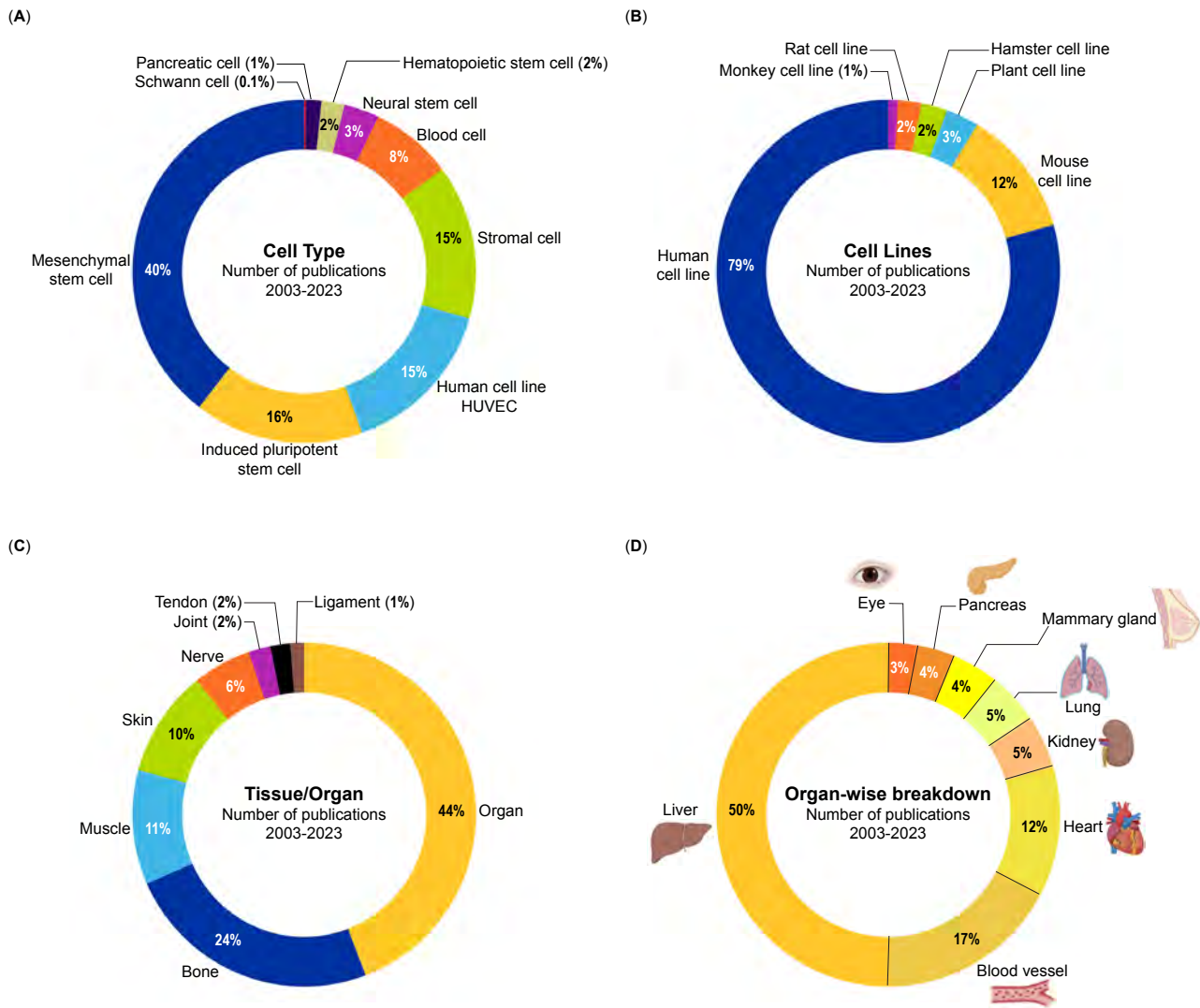


Figure 5. Distribution of publications (journals and patents) in terms of **(A)** cell type, **(B)** cell lines, **(C)** organ and tissue systems (left panel) with a further breakdown across different **(D)** organ systems (right panel) over the time period of 2003-2023. Organ illustrations sourced from biorender- www.biorender.com

Key materials, properties and applications

A deep dive into our substance and publication data pertaining to bioinks allowed us to identify materials that serve as components of bioinks.

Figure 6 shows identified materials for bioinks that have been classified into 4 major categories:

- Natural polymers
- Synthetic polymers
- Cell-based materials
- Others

One of the biggest categories of materials, natural polymers have been further sub-divided primarily into polysaccharide and protein-based materials.

Polysaccharides are a type of carbohydrates composed of multiple monosaccharide units connected by glycosidic bonds. Among them, alginate, cellulose, hyaluronic acid, and chitosan,^{3, 57} outrank other polysaccharide materials by a considerable margin. In the protein-based materials, the distribution is slightly more even-keeled across materials such as peptides,^{58, 59}

silk,^{60, 61} agarose,⁶²⁻⁶⁵ fibrins, and fibrinogen,⁴⁰ though gelatin⁴¹⁻⁴³ and collagen³⁶⁻³⁹ appear to lead in terms of number of publications associated with them. Live cells or cell-derived materials are at particular interest in this field – most commonly stem cells such as mesenchymal, pluripotent, embryonic among others,¹⁵⁻¹⁸ tissue specific cells, growth factors, and extracellular matrix (ECM).⁶⁶⁻⁶⁹ For example, fibroblasts, a type of connective tissue cells that are responsible for producing collagen fibers, have been incorporated into a hydrogel-based bioink and show potential for tissue engineering.^{20, 21} Chondrocytes, cells that are vital for production of collagen, are of increasing interest and have been used to bioprint 3D constructs of human ear.²² Other cellular materials such as human platelet lysates are still in nascent stages of development and are starting to be incorporated into bioinks.^{70, 71} Osteocytes have been incorporated into bioinks with potential utilization in creating bone constructs.⁷² To shed light on the growth in popularity of materials over time, the growth rates in the number of the publications were assessed in those



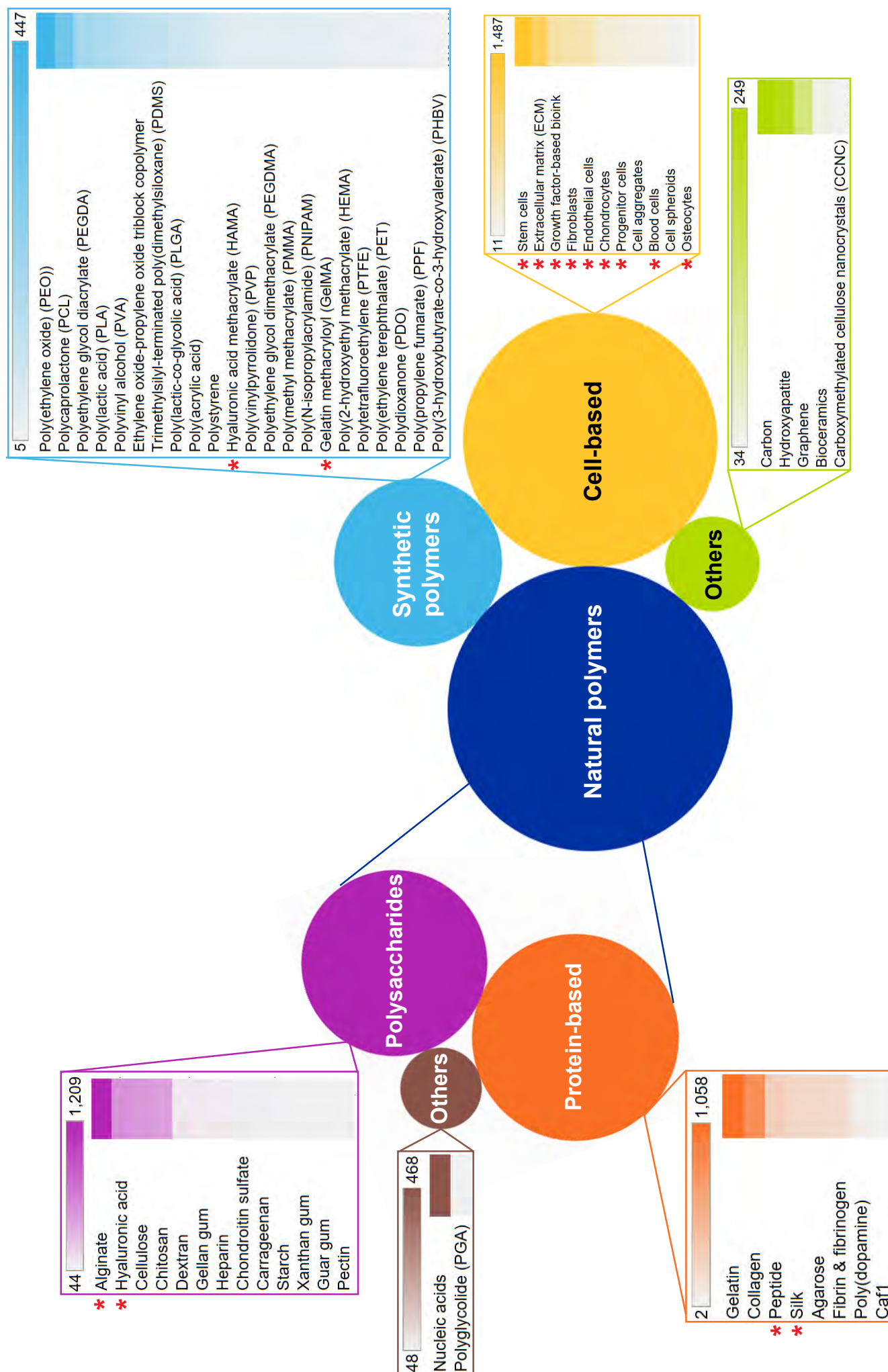


Figure 6. Distribution of materials in the field of bioinks over 2003-2023 obtained from the CAS Content Collection. Size of the circle corresponds to number of publications (journals and patents). Growth of materials marked with an asterisk are shown in **Figure 8**.

documents mentioning the specific materials. The number of publications or the relative publication growth rates are shown in **Figure 7**. Among the different cell-based materials, stem cells and ECM show steady growth in the last decade, with an acceleration around the year 2017 (**Figure 7A**). Other cell types such as chondrocytes, fibroblasts and endothelial cells show a modest growth. Materials based on progenitor cells and blood cells, show a conservative but upward growth trend. Among the polymers, polysaccharides such as alginate⁷³⁻⁷⁵ and hyaluronic acid^{76, 77} show consistent growth in the field of bioinks with alginate leading by a wide margin (**Figure 7B**). Protein-based natural polymers such as silk and silk-based polymers^{60, 61} and other peptides^{58, 59} have seen sustained interest in the last decade. Synthetic derivatives of natural

polymers, methacrylated gelatin (GelMA)⁷⁸⁻⁸⁰ and methacrylated hyaluronic acid (HAMA)^{81, 82} start to appear in 2016 and seem to have doubled between 2021-2022.

Incorporating cell-based materials into bioinks is a complex endeavor, requiring the utilization of a multitude of growth factors to foster and expedite cell growth.⁸³ Notably, growth factors such as FGF^{84, 85} and TGF^{23, 24} have exhibited a significant surge in research interest between 2020-2022, as indicated in **Figure 7C**. Conversely, EGF²⁸ and VEGF^{26, 27} have experienced a more moderate increase in relative publication growth rates during the same period. Additionally, growth factors like connective tissue growth factor (CTGF),⁸⁶ insulin-like growth factor (IGF),⁸⁷ hepatocyte growth factor (HGF),⁸⁸ platelet-derived growth factors

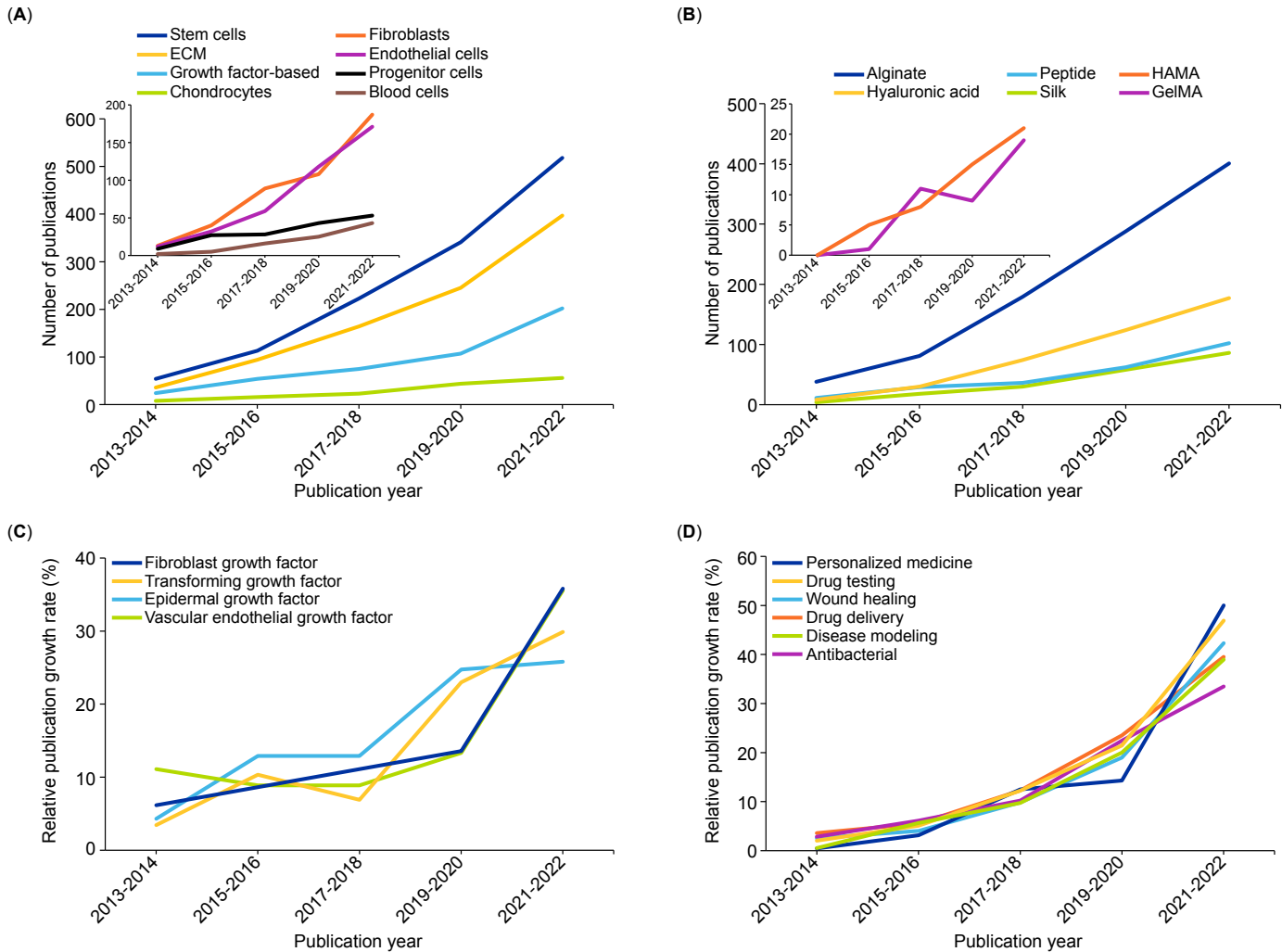


Figure 7. Emerging trends of materials in the field of bioinks over 2013-2022 obtained from the CAS Content Collection with respect to (A) cell-based materials and (B) natural and synthetic polymers used as components of bioinks. Increase in relative publication growth rates for (C) growth factors used as enhancers in bioinks for optimum cell growth and (D) applications associated with bioinks.

(PDGF)²⁹ and others⁸⁹ are still in the early stages of potential emergence. Each of these growth factors possesses distinct roles and is frequently used in combination with each other^{90, 91} and specific cell types.

While the predominant application of bioinks remains focused on tissue engineering, it's worth noting the existence of diverse potential applications beyond this domain. Our dataset unveils documents associated with a range of applications, including drug delivery,^{11, 12} wound healing,^{1, 2} personalized medicine,⁷ antibacterial,⁹² drug testing and development,^{9, 10} and disease modeling⁴⁻⁶ as depicted in **Figure 7D**. For instance, a recent study for the combined applications of drug delivery and wound healing involved loading gelatin-alginate hydrogel based bioink with chlorhexidine acetate, a small molecule bactericidal agent, to allow fabrication of wound dressings.¹¹ Another interesting application involved loading curcumin, a naturally occurring alkaloid isolated from *Curcuma longa* well known for its anti-inflammatory properties, as encapsulated nanoparticles onto an alginate-gelatin hydrogel-based bioink with potential applications in drug delivery.¹² Self-gelling bioinks composed of chitosan derivatives have been designed for wound healing.³ Platelet-rich plasma obtained from patients containing a mixture of several growth factors has been utilized to try and create personalized bioink.⁷ An example of personalized medicine is 3D printing tumor models to test immunotherapies such as chimeric antigen receptor (CAR) T-cell therapies.⁹³

Properties of bioink have a direct influence both on the type of structure that can be fabricated as well as the type of printing technique that can be utilized. Broadly speaking, properties of materials can be arranged into the following categories:

- rheological
- biological
- surface properties
- mechanical
- physical
- chemical
- physicochemical

We generated a heat map to show connections between materials and the various properties that are studied in their context (**Figure 8**). A few observations from the heat map include:

1. Among the selected materials, ECM, stem cells, and cellulose seem to be the most extensively researched materials with respect to their properties.
2. Biological, rheological, and chemical properties are more frequently studied compared to others.
3. Surface properties, encompassing aspects like surface charge, tension, roughness, area, and wettability, appear to receive relatively less attention.
4. Within biological properties, the following properties are studied more extensively:
 - biocompatibility especially for natural polymers (silk, peptide, cellulose, fibrin) as well as synthetic polymer (GelMA and PCL) and cell-based materials such as extracellular matrix
 - cell viability more for synthetic polymers GelMA and HAMA and cell-based materials ECM, stem cells and chondrocytes
 - cell adhesion more for peptide and fibrin (types of natural polymer), and synthetic polymers GelMA, HAMA and PCL and cell-based materials ECM and stem cells.
 - Notably, the co-occurrence cell density as a property with materials in publications is low, despite recent studies highlighting its importance in bioink viscosity and shear thinning behavior.^{94, 95}
5. Rheological properties, defined as the property that accounts for a material's deformation and flow appear to be studied more or less evenly across the different material types. Rheological properties perhaps affect printability of bioinks more than any other properties.^{96, 97}
6. Among chemical properties, the ability to be cross-linked appears to be studied across almost all of the materials shown in **Figure 8** with GelMA and HAMA (unsurprisingly) leading and PCL trailing the pack.

Despite being a relatively new field, commercially available bioinks are already starting to appear on the market and include gelatin-based hydrogel bioinks such as Gel4Cell® (Amerigo Scientific⁹⁸) and BioInk® (RegenHU⁹⁹), GelMA based bioinks such as BioGel (Biobot) and Tissue Fab (Aldrich¹⁰⁰), alginate based CELLINK (CELLINK¹⁰¹), calcium phosphate based OsteoInk™ (RegenHu¹⁰²), among others. Similarly, commercially available bioprinters are also on the rise¹⁰³ – a few example include extrusion-based bioprinter R-Gen 200 (RegenHu¹⁰⁴), microfluidic technology based Biopixlar (Fluicell¹⁰⁵) and Rastrum (Inventia

Life Science Operations¹⁰⁶), among others. Currently, many companies such as CELLINK,¹⁰⁷ MilliporeSigma,¹⁰⁸ CollPlant,¹⁰⁹ RegenHu,¹¹⁰ sell bioink and bioink based products yet most commercially available bioinks are used for research purposes or for designing pilot-scale experiments. The accelerating commercial availability of both bioinks as well as bioprinters is an indicator of the interest in this area and bodes well for future development. More efforts are needed for translating bioink related products in clinical applications.

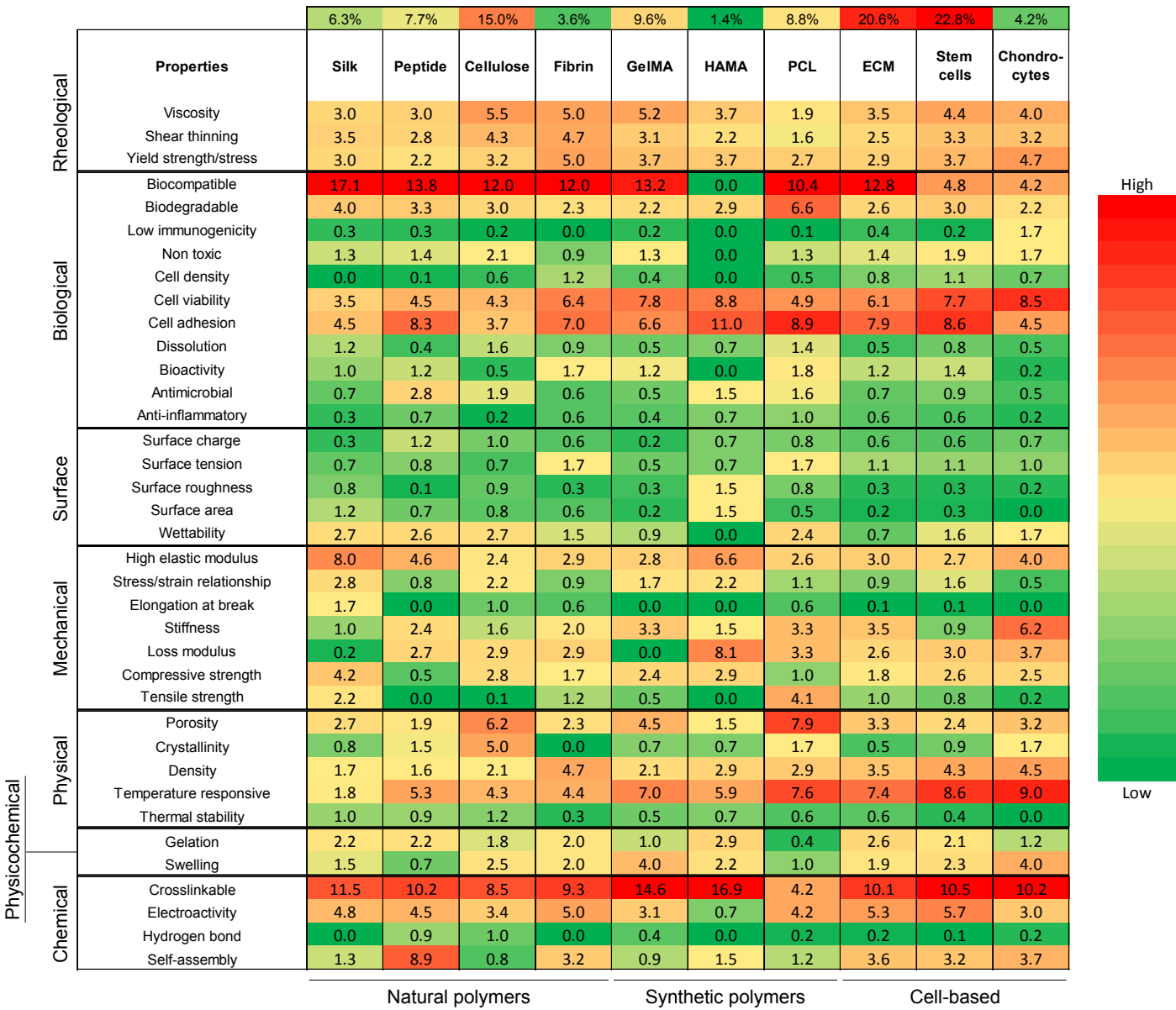


Figure 8. Heat map showing co-occurrences of selected materials and properties in the field of bioinks over 2003-2023 obtained from the CAS Content Collection. Values shown are in percentages.

Notable journal articles and patents

Table 1 consists of a set of research articles published from 2020-2023 that are representative of emerging trends in this field. Articles were selected on the basis of the collective factors such as journal impact factor, citations, and type of study. Notable examples from the table include the publication on volumetric additive manufacturing (VAM) of pristine silk-based (bio) inks by Zhang et al.¹¹¹ The article describes the use of silk-based bioinks made from silk sericin (SS) or silk fibroin (SF) to design silk-based constructs. SS and SF are used across a wide range of concentrations in conjunction with ruthenium/sodium persulphate (Ru/SPS) that enables reactions between tyrosine groups of SS and SF, under green light (wavelength) 525 nm as the photoinitiator. The resulting formulations are printed using VAM resulting in constructs that are biocompatible and can be used to grow C2C12 cells.

Another example is the study "titled" Light-Activated Decellularized Extracellular Matrix (dECM)-Based Bioinks for Volumetric Tissue Analogs at the Centimeter Scale by Jang et al. at POSTECH, Republic of Korea.¹¹² This study relies on the use of dECM for developing bioink. dECM is one of the most desired biomaterials for bioinks as it can emulate the intricacy of the native microenvironment of tissues/organs due to the similarity in components and composition of various biomolecules present in dECM and native tissues. Another journal publication by Feinberg et al. at Carnegie Mellon University, USA,¹¹³ describes the application of the Freeform Reversible Embedding of Suspended Hydrogels (FRESH) bioprinting technique to develop a complete 3D human heart. To mimic the elasticity of heart tissue, a natural polymer- alginate is used as the major component of the bioink. This breakthrough technology could further be used to develop full-size anatomical models for organs for ease of studying them. An exciting application of this down the line could be to generate artificial organs that can be used for transplantation.

Table 2 represents notable patents in the field of bioinks from 2018-2023. These patents were selected based on collective factors such as relevance, novelty, applicability, and field of study. The search was performed using CAS STN

to identify representative patents from the top commercial and non-commercial organizations across the globe and subsequent shortlisting was performed by subject matter experts (SMEs) in the field. The list reflects innovation either in terms of the use of different materials in preparation of bioinks or practical innovations involving use of hybrids from these materials for their use in 3D printing, tissue engineering and various other applications. Patents listed include a wide range of materials such as silk fibroin, undenatured collagen, extracellular matrix, derivatives of hyaluronic acid, collagen, cellulose nanofibrils etc., and their hybrids along with different additives. For instance, US11186736B2 (Cellink AB-Bico Group AB)⁵¹ describes the development of a double-network hydrogel-based bioink that contains a cross-linkable polyethylene glycol (PEG) network, a photoinitiator and a cross-linkable thickener made from either polyethylene oxide, polypropylene oxide, nanofibrillar cellulose, nanocrystalline cellulose, gelatin, collagen, glucomannan, alginate, k-carrageenan, bentonite clay, and/or xanthan gum. These facilitate the formation of an interpenetrating network and the resulting bioink can be used for a wide variety of applications by adding different additives such as fluorescent dyes.

Various patents pertaining to bioinks are related to development of 3D printed tissues such as skin, hair follicles, etc. For instance, WO2022260583A1 (Iscaff Pharma)¹¹⁴ describes the development of bioink for the reproducible production of 3D tumor tissue scaffolds. It relies on the identification of protein composition of tumor tissue and producing bioink with the corresponding protein/protein domain which can be developed into a 3D scaffold mimicking the tumor which can be used for studying the tumor. A closer look at patents shows that hydrogels are a commonly used form of bioink in several patent applications with KR102100506B1 (Medifab Co., Ltd.)¹¹⁵ describing a thermosensitive chitosan hydrogel comprising chitosan (a linear polysaccharide composed of D-glucosamine and N-acetylglucosamine) cross-linked by glycerol and phosphoric acid group. Varying the content of phosphoric acid and glycerol in the gel can induce the bioink to convert from liquid to gel state. Companies like Organovo have patented

technologies for 3D printing of human tissue models such as patent EP3215603B1⁵³ by Organovo and L'Oreal which describes development of 3D printed human skin model comprising a dermal layer comprising a dermal bioink containing

fibroblasts; and an epidermal layer comprising epidermal bioink comprising keratinocytes. Epidermal and dermal layer are in contact to replicate human skin-like communication *in-vitro*.

Table 1. Notable journal publications in the field of bioinks in recent years.

Year	Title	Journal	Research Institute	Application
2020	Nanoengineered osteoinductive bioink for 3D bioprinting bone tissue ¹¹⁶	ACS Applied Materials Interfaces	Texas A&M University	Nanoengineered ionic covalent entanglement (NICE) bioink formulation for 3D bone bioprinting
2020	FRESH 3D Bioprinting a Full-Size Model of the Human Heart ¹¹³	ACS Biomater. Sci. Eng.	Carnegie Mellon University	Hydrogel-based 3D bioprinting of human heart
2021	3D bioprinted neural tissue constructs for spinal cord injury repair ¹¹⁷	Biomaterials	Chinese Academy of Sciences	Biocompatible bioink consisting of functional chitosan, hyaluronic acid derivatives, and Matrigel for growth of neural stem cells (NSCs)
2021	3D bioprinted silk fibroin hydrogels for tissue engineering ¹¹⁸	Nature Protocols	Hallym University	Methacrylated photocurable silk fibroin (SF) bioink for digital light processing (DLP) 3D bioprinting
2021	Light-activated decellularized extracellular matrix-based bioinks for volumetric tissue analogs at the centimeter scale ¹¹²	Advanced Functional Materials	Pohang University of Science and Technology (POSTECH)	Light-activated, decellularized extracellular matrix (dECM) based bioinks with ruthenium/sodium persulfate (dERS) for constructing bioscaffolds
2021	Programmable microbial ink for 3D printing of living materials produced from genetically engineered protein nanofibers ¹¹⁹	Nature Communication	Harvard University, Northeastern University	Microbial ink that is produced entirely from the genetically engineered E. coli biofilms
2021	3D bioprinting of high cell-density heterogeneous tissue models through spheroid fusion within self-healing hydrogels ¹²⁰	Nature Communication	University of Pennsylvania	Supramolecular hydrogel-based bioink comprising hyaluronic acid (HA) modified with either adamantane (Ad) or β -cyclodextrin (CD), used for tissue engineering
2022	Molecularly cleavable bioinks facilitate high-performance digital light processing-based bioprinting of functional volumetric soft tissues ¹²¹	Nature Communication	Harvard University	Hyaluronic acid methacrylate (HAMA) mixed gelatin methacryloyl (GelMA) bioink for digital light processing (DLP) bioprinting
2022	In situ 3D bioprinting with bioconcrete bioink ¹²²	Nature Communication	Zhejiang University	Bioconcrete bioink comprising cell-laden microgels aggregate and gelatin methacryloyl (GelMA) solution as the cement
2022	Development of cellulose nanofibril/casein-based 3D composite hemostasis scaffold for potential wound-healing application ¹²³	ACS Applied Materials Interfaces	Jiangsu University	Cellulose nanofibrils (TCNFs), chitosan, and casein based bioink for wound healing
2022	Orthogonally induced differentiation of stem cells for the programmatic patterning of vascularized organoids and bioprinted tissues ¹²⁴	Nature Biomedical Engineering	Harvard University, Boston	Use of human induced pluripotent stem cells (hiPSCs) containing bioinks to generate patterned neural tissues
2023	Volumetric additive manufacturing of pristine silk-based (bio)inks ¹¹¹	Nature Communication	Harvard Medical School	Silk-based bioinks for volumetric additive manufacturing (VAM)
2023	In situ covalent reinforcement of a benzene-1,3,5-tricarboxamide supramolecular polymer enables biomimetic, tough, and fibrous hydrogels and bioinks ¹²⁵	Advanced Materials	Maastricht University	Biomimetic bioink made from 1D fibrils made from benzene-1,3,5-tricarboxamide (BTA) hydrogelator with norbornene (NB)

Table 2. Notable patent publications in the field of bioinks in recent years.

Patent or Publication number	Publication year	Patent assignee	Title	Description of patented technology
WO2018035138 A1 ⁵²	2018	Organovo, Inc.	Three dimensional bioprinted tumor models for drug testing	A cancer model that accounts for the interaction of tumor cells with surrounding stromal cells and the inherent complexity of the tumor microenvironment by using an engineered scaffold construct. A bioink used to create the engineered constructs comprises fibroblasts, endothelial cells, adipocytes, and preadipocytes among other cell types.
WO2018186611 A2 ¹²⁶	2018	Industry Academic Cooperation Foundation, Hallym University, Republic of Korea	Bioink and preparation method therefor	Bioink made of silk fibroin (SF) can help construct biostructures using 3d printing with better stability and biocompatibility.
WO2018071639 A1 ¹²⁷ KR2556540B1	2018 2019	Advanced Biomatrix Inc.	Three-dimensional (3D) printing inks made from natural extracellular matrix molecules	Bioinks composed of undenatured collagen
KR102156310B1/EP3705294A1 ¹²⁸	2020	UNIST (Ulsan National Institute of Science and Technology), Republic of Korea	Manufacture of cell spheroid using bioink	Method for creating spheroids using a combination of two bioinks – the first containing alginate and the second containing live cells – extruded one after the other. Addition of calcium chloride solution to the alginate present in the first bioink and dissolution of the second bioink in a cell culture medium results in formation of a cell spheroid from the cells.
KR102100506 B1 ¹²⁹	2020	Medifab Co., Ltd., Korea	Thermosensitive chitosan hydrogel composition and bioinks composition comprising the same	Bioink containing chitosan polymer hydrogel having two chitosan molecules form covalent and / or non-covalent bonds with glycerol and / or phosphate groups or their combination. An example of temperature-controlled bioink that can interchange from a liquid state to gel state according to the content ratio of the phosphoric acid group and the glycerol.
SE1950711 A1 ⁵⁰	2020	Cellink AB	3D bioprinted skin tissue model	3D printed skin tissue that can act as model for testing in drug development, toxicological studies, tissue engineering among others.
KR20200012723 A ¹³⁰	2020	Kyungpook National University	Sericin-based bioink composition for 3D printing without photo-crosslinking agent	Bioink comprising of protein-based material (sericin) with applications in wound healing and tissue regeneration.
US11186736B2 ⁵¹	2021	Cellink AB (Bico Group AB)	Double network bioinks	Bioink consisting of a double network including a non-crosslinkable thickener and PEG-based cross-linkable network that interpenetrates each other, photoinitiator, and/or different additives to impart desired characteristics. Potential applications include 3D bioprinting and constructing scaffolds.
EP3215603B1 ⁵³	2021	L'Oréal SA Organovo Inc, France	Engineered three-dimensional skin tissues, arrays thereof, and methods of making the same	A 3D, engineered, biological skin tissue comprising: a dermal layer comprising a dermal bioink containing fibroblasts; and an epidermal layer comprising epidermal bioink comprising keratinocytes. The epidermal layer is in contact with the dermal layer to create a 3D skin tissue.
WO2022260583 A1 ¹¹⁴	2022	Iscaff Pharma	Bioink for reproducible production of 3D tumor tissue scaffolds	Protein-based bioinks for 3D scaffolds that mimic tumor microenvironment and can be used to generate cancer models to test anti-tumor therapies
US11629329B2 ¹³¹	2023	Wake Forest University Health Sciences, USA	Bioink compositions and methods of preparing and using the same	Method for formulating bioink with 1:0.5 to 1:10 (thiolated hyaluronic acid:methacrylated collagen). This composition has an elastic modulus similar to natural tissues and can be used for cell/tissue culture and for bioprinting.
KR20230106369 A ¹³²	2023	POSTECH Academy-Industry Foundation, Republic of Korea	Biomaterial-based drug delivery patch, manufacturing method therefor, and use thereof	A multilayered patch useful for drug delivery applications, containing inner and outer layers made of extracellular matrix-based hybrid ink. Both layers have ink with different chemical crosslinking densities and contain different growth factors thereby allowing controlled release of drugs.
WO2023062111 A1 ¹³³	2023	Commissariat a l'Energie Atomique et aux Energies Alternatives	Novel bioink and uses thereof for constructing tissues	Tissue engineered esophagus via 3D bioprinting using biodegradable polymeric materials such as poly(caprolactone)-co-glycolide (PCG), polycaprolactone (PCL) and methylcellulose (MC).
US11648336 B2 ¹³⁴	2023	Bico Group AB Cellink Bioprinting AB	Preparation and Applications of 3D Bioprinting Bioinks for Repair of Bone Defects, Based on Cellulose Nanofibrils Hydrogels with Natural or Synthetic Calcium Phosphate Particles	Bioink composed of cellulose nanofibril hydrogel having calcium containing compounds (β -tricalcium phosphate (TCP), single-phase hydroxyapatite (HA), biphasic HA-TCP, or natural bone powder). This bioink can be used for tissue engineering/tissue replacement.

Challenges and perspectives

An ideal bioink should possess appropriate rheological, mechanical, chemical, and biological properties of the target tissues. Despite path breaking advances in the field of bioinks with respect to both the materials used and their wide array of applications, there continues to be various challenges:

1. Bioinks based on natural polymers lack sufficient mechanical strength in the absence of additives.^{111, 135}
2. The process of development of bioinks focuses more on designing and characterizing them for their physical, chemical, and rheological properties. However, their interaction with live cells not only affects the stability of bioinks but also hampers cell viability.
3. The addition of additives, extensive printing time, and lesser control over the printing process can impact embedded cell viability.
4. Some synthetic polymers and additives used in bioink preparation lack biocompatibility/cytocompatibility, therefore it remains a challenge to design unique bioink considering their biological competence.¹³⁶ For instance hydrogels made using synthetic polymers without ECM components support the cell but they do not promote cell growth and limit cell-to-cell interactions resulting in a non-native microenvironment.¹³⁵
5. Scaffold-free printing approaches with existing bioinks such as cell pellet-based methods often result in cellular aggregates which could limit the supply of oxygen and nutrients to cells resulting in their loss.¹³⁷
6. Bioprinting adds to the cost of the overall procedure when used in cell/tissue culture.
7. The scale-up of the biofabrication process to make bioprinted scaffolds for clinical relevance without compromising on bioink properties and cell viability and having a minimal batch-to-batch variation thereby highlighting a dire need for standardized bioink formulations.¹³⁸ Similarly, more work is needed in developing models and standards to compare and evaluate the performance of bioinks.^{138, 139}
8. The overall lack of suitable bioinks for generating suitable and larger 3D constructs that mimic original tissues can hamper the translation toward clinical applications.

Further advancements are required in the bioink technology field to increase cell viability, minimize cell loss, maximize cellular interactions, improve the physical, chemical, mechanical, and rheological properties of bioinks, and make them compatible and scalable for clinical applications.



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V. Programmable materials

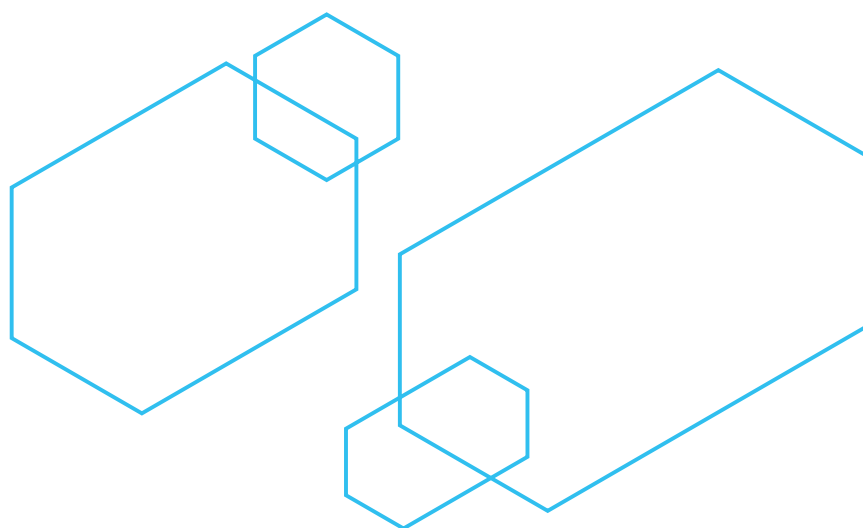
Introduction

Programmable materials can change their morphology, physical properties, and/or chemical functionalities in a pre-determined sequence in response to an external stimulus or a change in the surrounding environment.¹ Programmability in materials is highly advantageous in some applications, such as drug delivery, because it enables additional, time-dependent methods of control.² For example, mesoporous silica particles can be programmed to release a drug cargo selectively in cancer cells by capping its pores with polymeric structures that reconfigure in different pH conditions.³

Programmable materials that are used for biomedical applications include natural and synthetic polymers,⁴ as well as metal alloys, such as Ni-Ti. The programmability of these materials originates from their ability to respond to small changes in their environment, for example pH,⁵ temperature,⁷ light,^{8,9} electrical¹⁰ or magnetic fields,^{11,12} or a specific chemical or biological signal.¹³

DNA-based materials represent a special class of programmable biomaterials. One reason for this is that DNA offers precise structural tunability through Watson-Crick base pairings.^{14,15} Directed self-assembly of single-stranded DNA can lead to diverse 2D and 3D structures, the formation and dynamics of which can be controlled at the molecular level.¹⁶ In addition to the ability to generate specific structures, DNA can also be engineered to respond to specific cues or chemical environments,^{17,18} or through using CRISPR technology.¹⁹

Programmable biomaterials have found applications in drug delivery, implants, sensors, and several other areas. In this chapter, we will first review the trends in journal and patent publications in this area, then identify the most prominent substances used in programmable biomaterials, and finally provide representative examples of recent programmable biomaterial research.



Journal and patent publication trends

Figure 1 shows the number of journal and patent publications per year involving programmable biomaterials from 2003-2023. Here, we see a strongly increasing trend in journal publications up to 2022, and likely to include, 2023. The frequency of patent publications has been relatively lower, showing a flat trend from 2016-2022, suggesting that the results of academic research have not yet been fully translated to commercial applications.

Figure 2 shows the top 15 research institutions in terms of the number of citations per publication, from within the top 100 institutions in terms of total journal publications. This analysis clearly shows a trend of high research publication activity in China. Apart from the University of California, the top 15 institutions with the highest number of citations per publication are in China. The Chinese Academy of Sciences has both the highest number of citations per publication, and the highest number of overall publications on programmable biomaterials.

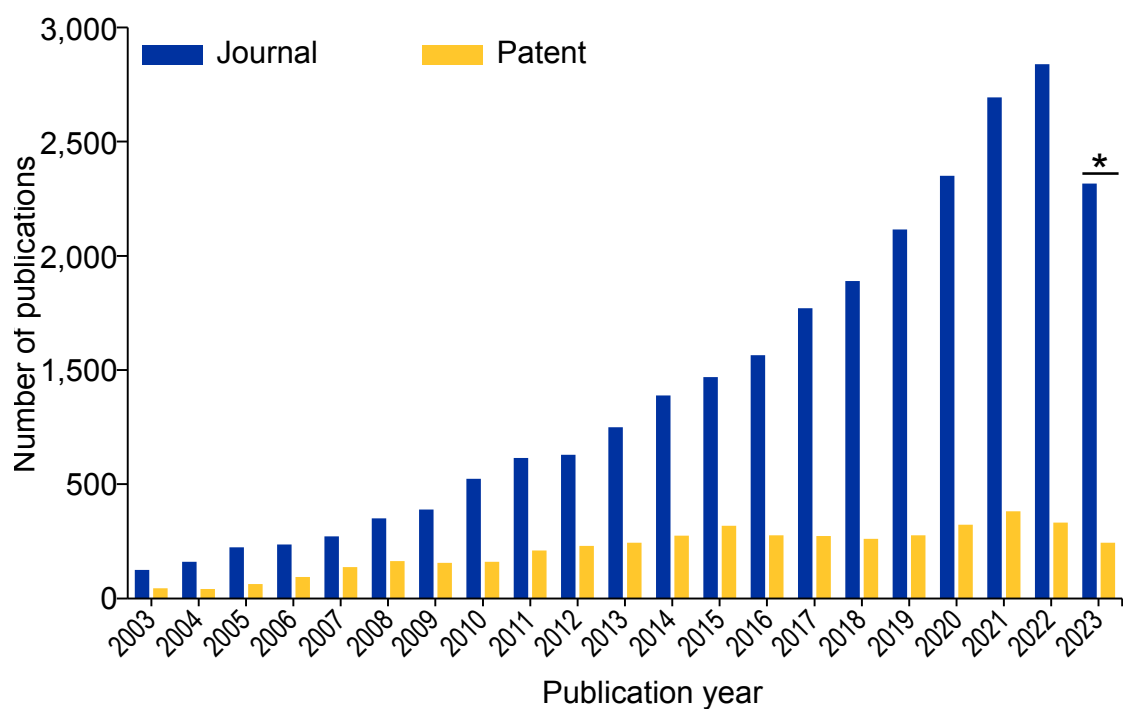


Figure 1. Number of journal and patent publications per year in the programmable biomaterials field from 2003 to 2023 (journals: blue bars, patents: yellow bars). * The data for 2023 only include the months from January to August.

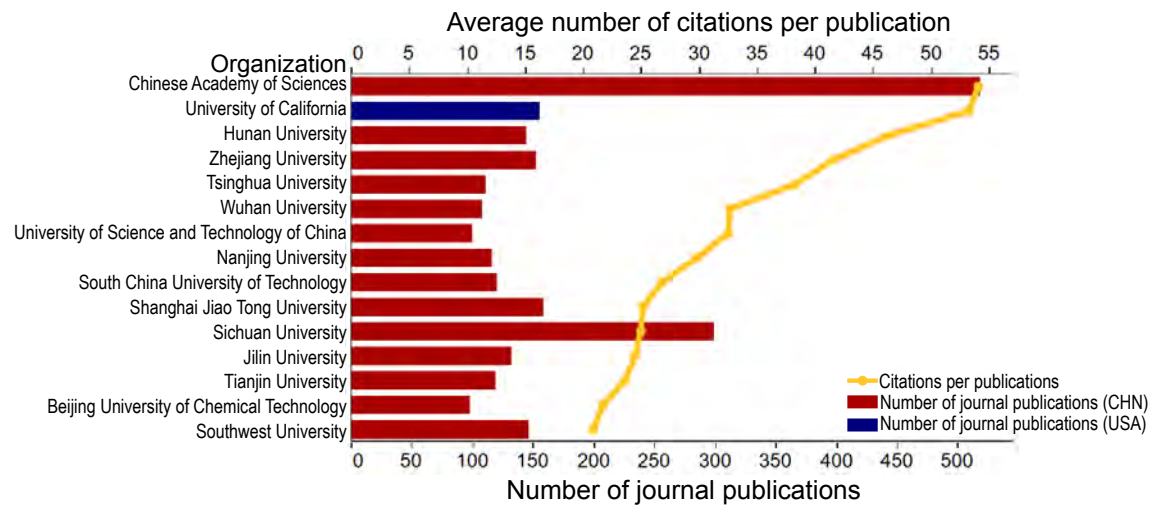


Figure 2. The top 15 research institutions in terms of average citations per publication (yellow line). Total publications from 2003-2023 shown as bars; colors of the bars indicating country/region.

Figure 3 shows a breakdown of the top assignees for patents related to programmable biomaterials. The US generally has the highest amount of patent activity by commercial entities, led by Boston Scientific, while patent activity by non-commercial entities is highest in China. Furthermore, as shown in **Figure 4A**, patent activity in both China and Korea has increased significantly over time, with the number of patent families filed by entities in China increasing by

roughly a factor of 4 over the past 10 years. Analysis of patent families, shown in **Figure 4B**, indicates that the top national/regional patent offices for filings are the US, China, EPO, Japan, Canada, and Korea. For applicants in China, Japan, and Korea, initial filing through the national patent office appears to be preferred, while initial filings through WIPO/PCT are more common for applicants in the US, Israel, and the UK.

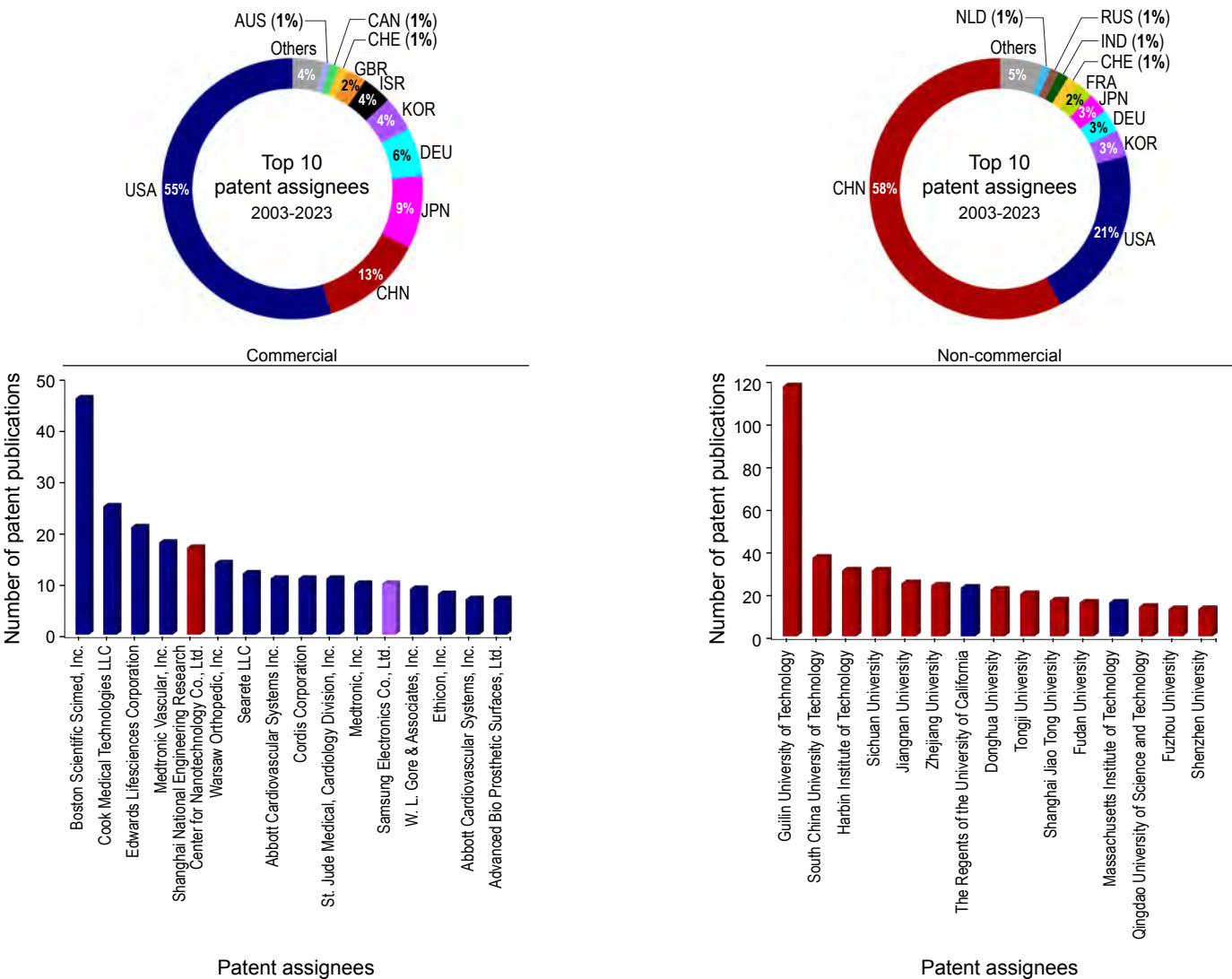


Figure 3. Top panel: The top 10 countries/regions in terms of number of patents published between 2003-2023. Lower panel: The top 15 patent assignees in the field of programmable biomaterials in the same time period. Both panels are divided into commercial and non-commercial entities. Bar graph has been color coded by country/region to match color scheme in donut charts.

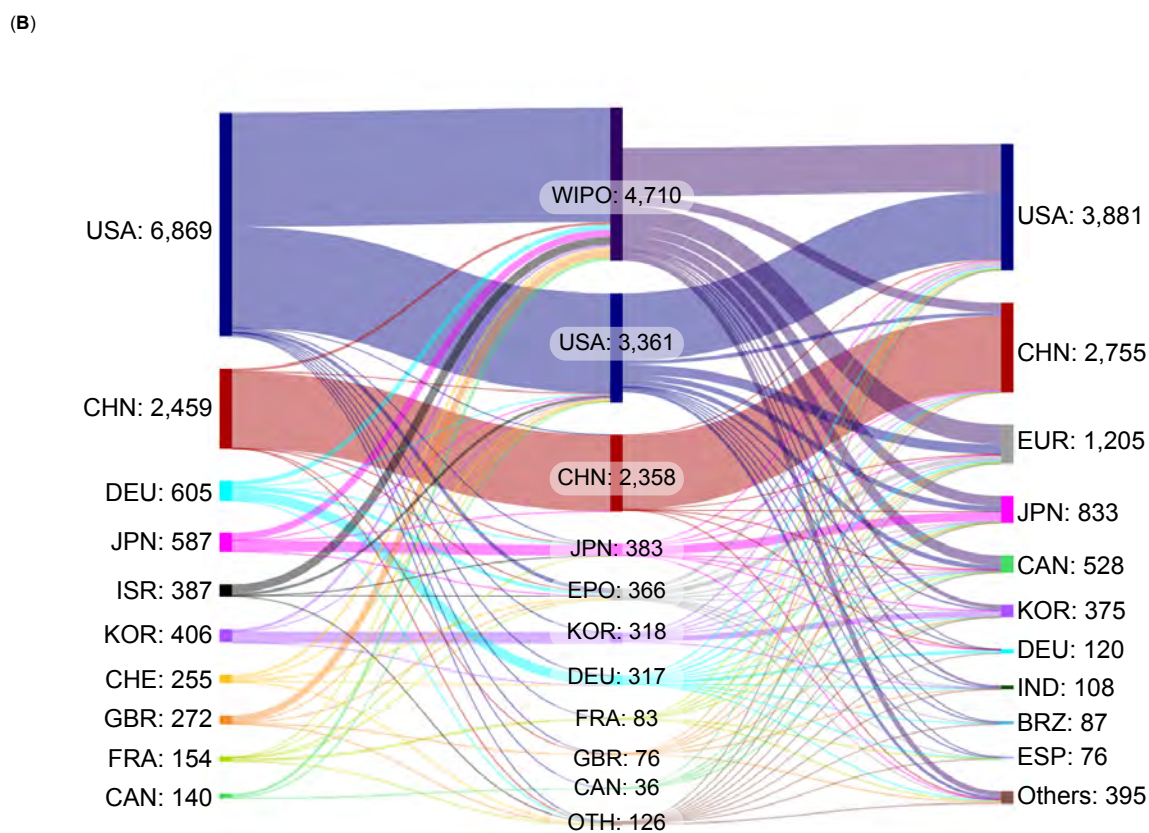
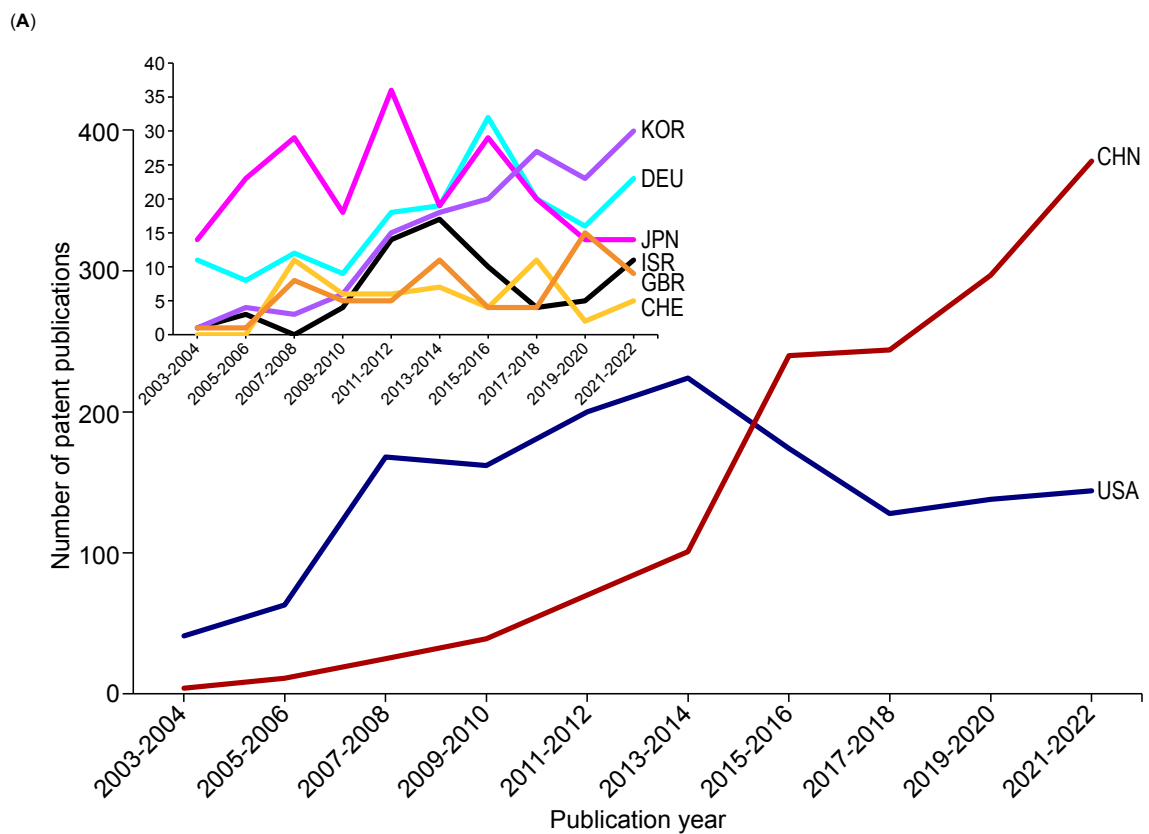


Figure 4. (A) Number of patent family publications per year between 2003-2022 for the top 8 most prolific countries/ regions. **(B)** Total patent flow between assignee countries/regions (top ten countries/regions in terms of total patent filings, left), the patent filing office where the first application in the patent family was filed (center) and the destination patent office for individual patent publication activities (right). Standard three letter codes utilized for countries/regions.

Key materials and applications

The response that happens when a programmable material is exposed to a specific stimulus can take several forms. In some materials, the stimulus can cause changes in noncovalent interactions within the material that lead to reversible physical changes like swelling or deswelling of a material, irreversible chemical degradation, or other structural changes that are required to perform certain functions. As an example, in the case of drug-delivering polymeric vesicles, response to a stimulus can lead to complete disassembly.²⁰ These responses are commonly brought about by temperature changes (which can be induced by direct heating, or indirectly by photothermal or magnetic hysteresis effects), by changes in pH or other solvent conditions that lead to protonation or deprotonation, or through more specific chemical interactions (with glucose or enzymes, for example).

Another class of programmable material is shape-memory substances.²¹ Shape memory, which is a property that can be exhibited by organic materials and alloys, is one-way (where the material only has one temporary form, and shape change back to its permanent form upon stimulus is irreversible), two-way (where the shape change is at least partially reversible), or multi-way (where the material has more than two temporary forms).^{22,23} Shape-memory materials can be used to make artificial muscles, micromachines, and implants and medical devices that reconfigure inside the body.²⁴

These basic programmable functions can in turn be used to build structures and devices with more complex behavior. For example, actuators composed of bilayer films where one layer swells much more compared to the other² leading to programmable bending or other shape-based programming. Another example of this is localized photothermal heating by a laser of temperature-responsive polymers to make a wiring-free microactuator.²⁵

In hydrogels, as another example, combinations of rigid and soft programmable materials can induce folding and other behaviors.²⁶ "Smart" hydrogels

containing stimulus-responsive polymers make up a large class of programmable biomaterials and continue to be an active area of research for biomedical applications.^{27, 28, 29}

At an even higher level of complexity are nanorobots, which can integrate programmable materials to make complex, active structures³⁰ and biomimetic materials.^{31, 32} Programmable materials are also used in so-called 4D printing, an emerging technology that involves 3D printing programmable materials, which can later be physically reconfigured, or perform actuation, biomimetic function, or some other stimulus-triggered action.³³⁻³⁵

The combined bubble chart and heat map in **Figure 5** shows the substances which have been referenced most frequently in publications on programmable biomaterials. These substances are grouped into polymers (natural and synthetic), inorganic and organic small molecules, metallic and nonmetallic elements, minerals, coordination compounds, and alloys. It is important to note that not all these materials are intrinsically programmable. Generally, the non-programmable materials found in these publications serve other complementary purposes in combination with a programmable material.

Polyethylene glycol, poly(lactic acid), and polycaprolactone are the top substances in the synthetic polymers category. Polyethylene glycol appears frequently due to its biocompatibility, and because it can be used in a variety of different ways in programmable biomaterials. These include using it to make copolymers that are responsive to pH^{36, 37} (including attaching side groups that form Schiff base bonds),³⁸ light,³⁹ glucose and other chemical environments,⁴⁰ and as a basis for programmable hydrogels.⁴¹

Poly(lactic acid) and polycaprolactone have similar versatility and well-established biocompatibility and biodegradability. Poly(lactic acid)⁴² has been used to make materials responsive to temperature⁴³ electric field,⁴⁴ as well as a matrix for a magnetically responsive material driven by embedded Fe₃O₄ particles.⁴⁵ Polycaprolactone,

notably, can be copolymerized with PEG to form thermosensitive materials for biomedical applications.⁴⁶

An important material that also appears prominently in the data set is poly(N-isopropylacrylamide) (PNIPAM),²⁷ a widely used temperature-responsive polymer. The key property of PNIPAM is that it has a lower critical solution temperature (LCST) of around 32°C with water, meaning that below this temperature, the PNIPAM-water system is a stable single phase. Above this temperature, hydrogen bonding between the PNIPAM and water become less favorable, leading to phase separation. This property has led to PNIPAM to be used in a wide range of applications recently, particularly in hydrogels.⁴⁷⁻⁵⁰

Several direct and indirect sources of heat can be used to trigger changes in PNIPAM hydrogels, including Joule heating,⁵¹ photothermal effects,⁵² and magnetic hysteresis,⁵³ as well as photoisomerization⁵⁴ and photoionization.⁵⁵ Through these methods, PNIPAM-based smart hydrogels can be made to respond to light, temperature, and magnetic and electric fields. Furthermore, copolymerization with more hydrophilic or hydrophobic polymers can be used to tune the LCST temperature and the extent of physical changes in PNIPAM-based hydrogels.⁵⁶

The primary natural polymers that appear in programmable material literature are DNA, chitosan, and cellulose.

DNA is a special case, due to its precisely defined structure and multiple types of programmability. First, DNA can be used to make intricate, nanoscale structures through programming base pair sequences. This programmability has been implemented in strategies including scaffold-free DNA self-assembly⁵⁷⁻⁵⁹ and DNA origami,⁶⁰⁻⁶² which has received significant research interest recently. In this technique, a long single stranded DNA (the scaffold) folds into predesigned structures determined by many short single stranded DNA sequences (staples). The possible applications of DNA origami include controlled drug delivery,^{63, 64} biosensing,⁶⁵ and biomimicry.⁶⁶

DNA-based materials can also have stimulus-response programmability similar to the synthetic polymers described above. Several mechanisms have been reported that lead to predictable physical or chemical reconfigurations in DNA molecules. Some mechanisms are physical, which involve a change in the secondary or tertiary structure of DNA nanostructures, through G-quadruplex formation, triggered by pH or metal ions,^{67, 68} I-switch formation, triggered by pH,⁶⁹ or duplex formation,⁷⁰ in this case triggered by the presence of Hg and glutathione.

The mechanisms can also be chemical, such as DNA strand cleavage by DNazymes or restriction enzymes,^{71,72} or polymerase-mediated DNA amplification.⁷³ In addition, molecular programming can be integrated with the dynamics of reconfigurable DNA nanostructures using toehold-mediated strand displacement and toehold exchange.⁷⁴

Chitosan, the next most commonly referenced natural polymer, is naturally pH sensitive, through its amino and imine groups, which become protonated at low pH.⁷⁵ Thermal programmability can be incorporated into chitosan by combining it with thermally responsive polymers,⁷⁶ for example by grafting with PNIPAM.⁷⁷

Cellulose is notable due to its abundance as a bio-derived material, and because of its wide range of properties and functions.⁷⁸ Cellulose can function as a stimulus-responsive programmable material, through the disruption of hydrogen-bonded anhydroglucose units within cellulose structures by water,⁷⁹ or through chemical modification that enables other types of stimulus response.⁸⁰ Cellulose hydrogels can also be combined with other responsive polymers, for example PNIPAM,⁸¹ to make materials that respond to multiple stimuli.⁸² Nanoscale cellulose materials, such as nanocrystals and nanofibers, have also seen increased research activity due to their versatility, mechanical properties, and the potential to use them as building blocks for more complex structures.⁸³⁻⁸⁶

Cellulose has also been used to make biomimetic actuators and other structures that are inspired by

plant behavior.^{87, 88} A notable example of this is a 3D printed acrylamide-based hydrogel containing cellulose fibrils reported by Gladman et al.³²

Anisotropic swelling of the fibrils on exposure to water caused the hydrogels to take on complex three-dimensional shapes determined by their placement in the gel.

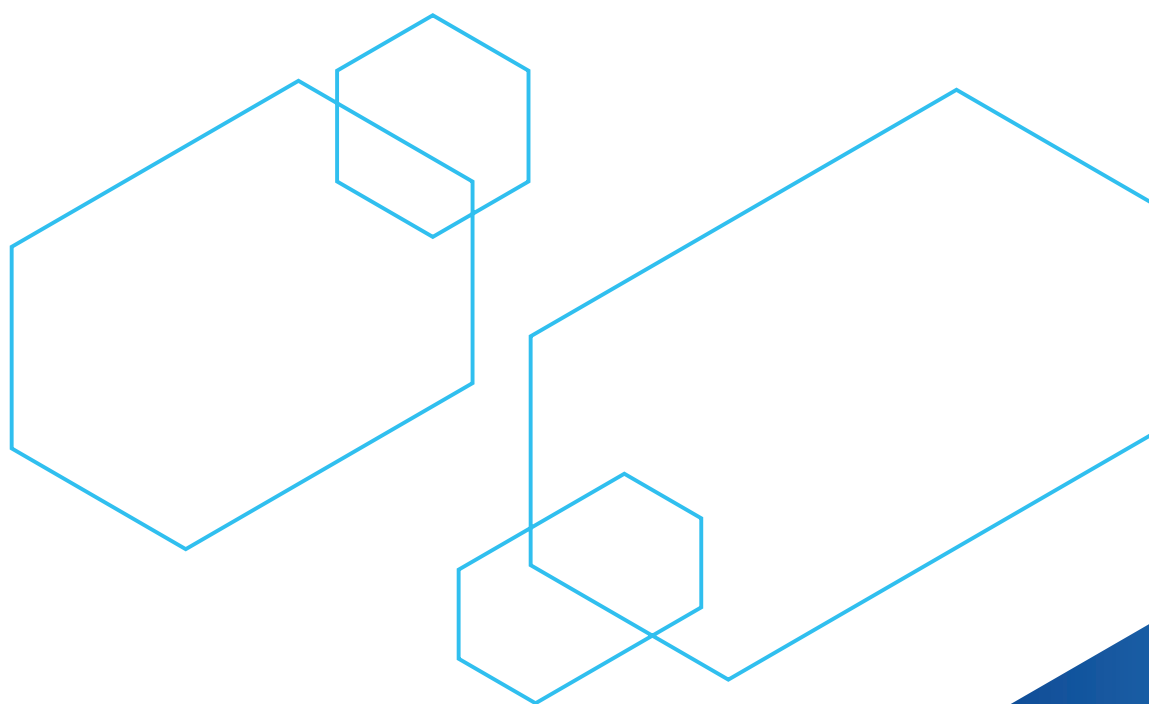
Turning to the small organic molecules, the material that appears most prominently is doxorubicin, likely due to its use as a representative chemotherapy drug in programmable drug delivery materials.^{89, 90}

N-isopropylacrylamide is used primarily as a monomer to synthesize temperature-responsive homo- and copolymers.^{91, 92}

Outside of organic materials, a notable programmable material is the Ni-Ti alloy (nitinol), which has shape-memory properties triggered by temperature, driven by the solid-state austenite-martensite phase transition. Nitinol is well known

for its use in biomedical applications,^{93, 94} due to its combination of shape memory properties, biocompatibility,⁹⁵ and superelasticity.

Silica is the most extensively used inorganic substance used in programmable materials, with particular focus on the use of mesoporous silica for drug delivery.⁹⁶ Through chemical functionalization,⁹⁷ mesoporous silica has been demonstrated to release drugs in response to changes in pH,^{98, 99} ultrasound,¹⁰⁰ and other types of stimuli.¹⁰¹ Within pure metals, gold and silver are the most prominent. These materials can be used for their electrical properties, or as part of a programming strategy where they are used as photothermal agents.^{102, 103} Silver can have the added benefit of conferring antimicrobial properties.¹⁰⁴



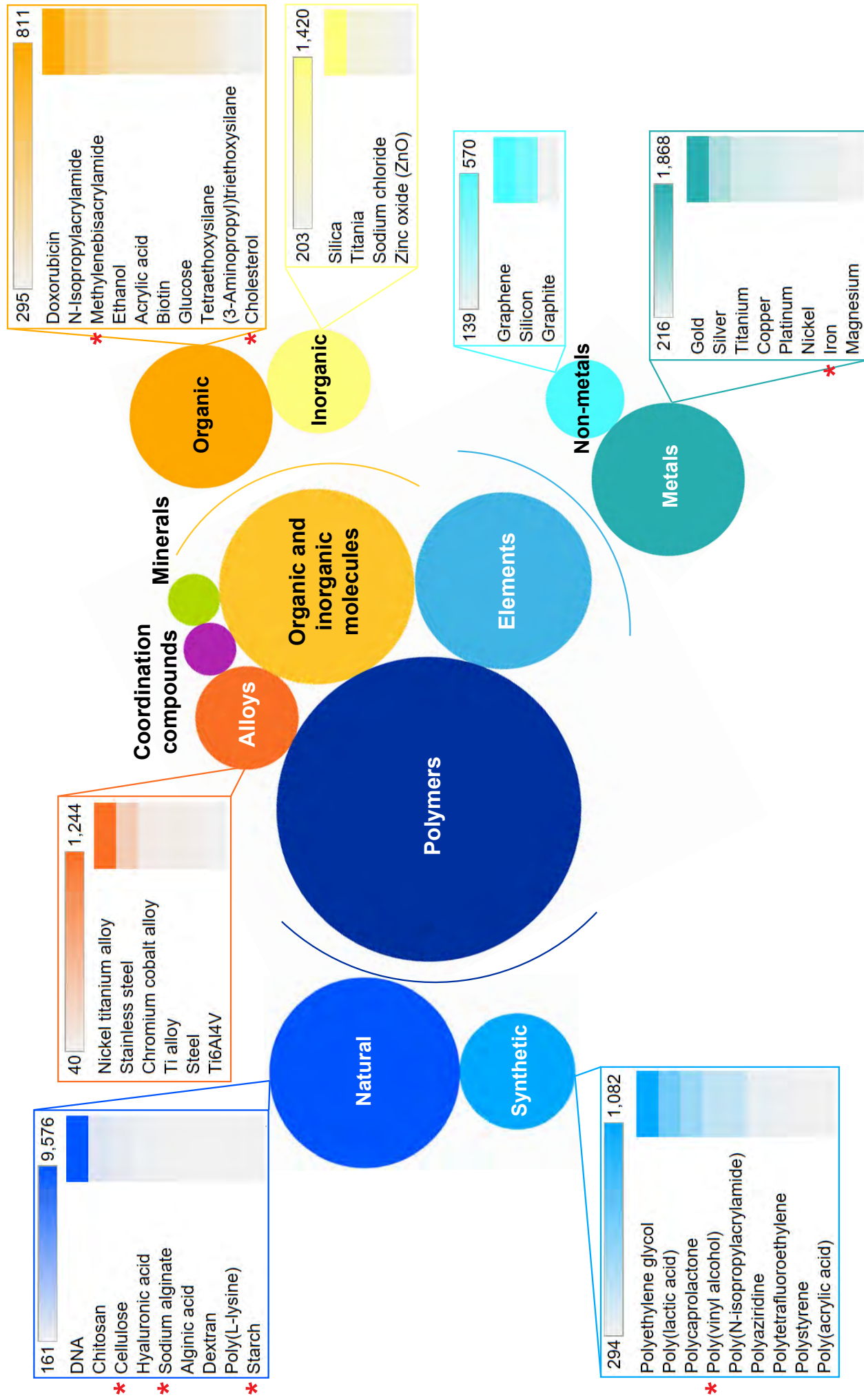


Figure 5. Bubble chart and heat maps showing distribution of substances used in programmable biomaterials in terms of number of publications (journals and patents) from 2003-2023. Materials with a relatively high rate of growth in their use in journal and patent publications are indicated by an asterisk.

Figure 6 shows a plot of the frequency of the use of several material terms in journal and patent literature, normalized by their average use frequency from 2013-2018. Materials with a high increase in normalized frequency (identifying them as emerging materials) were selected for this plot.

Within this set, two materials are particularly prominent. Lignin has seen increased research activity due to its natural abundance, biodegradability, and the ability to confer a wide range of stimulus responses (pH, light, temperature, electric field, ions) through chemical modification.^{105,106,107,108} Metal-organic frameworks have the dual advantages of finely controlled pore structure and stimuli-response, making them versatile drug delivery materials.¹⁰⁹ Recent work in the area of programmable MOFs includes functionalizing them with oligonucleotides,¹¹⁰ and combining MOFs with temperature-responsive hydrogels for multi-drug delivery.¹¹¹ Polydopamine is also used for its combination of photothermal and pH-responsive properties and high drug loading capacity.¹¹²⁻¹¹⁴

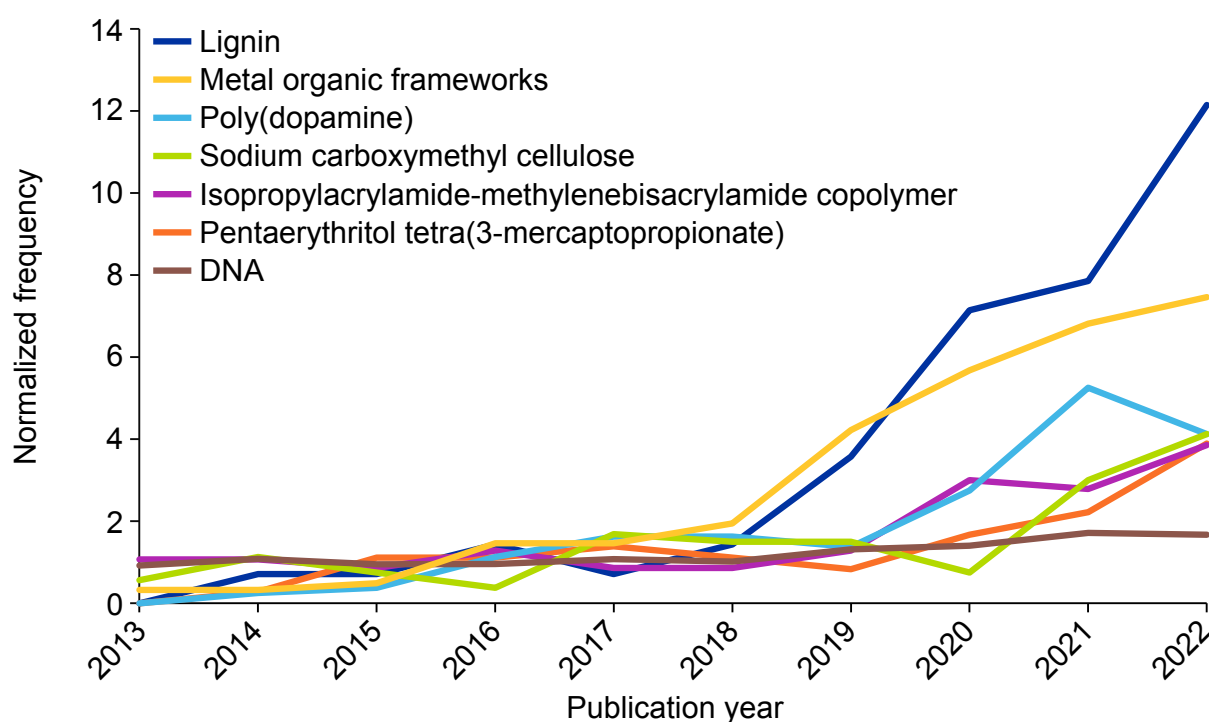


Figure 6. Normalized frequency of representative materials in journal and patent publications from 2013-2022.

Figure 7 is a heat map showing the relationship between the most prominent biomedical applications for programmable materials (top rows) and the substances used in these applications (left column). The green to red color scale reflects the relative frequency that each substance is referenced within each application. Because DNA is not a single chemical substance, it is treated separately in this figure. For DNA, the green to red color scale represents the distribution of the use of DNA-based materials across the 7 applications in the top row.

Addressing the non-DNA materials first, there are a number of notable applications and application-substance pairings. First, we note that drug delivery is the most common biomedical application for programmable materials, due to the potential of programmable materials to localize drug delivery and in some cases penetrate tissue.¹¹⁵⁻¹¹⁷ Within this category, silica, PEG, and chitosan are frequently referenced. (Note that lipids are another widely used drug delivery platform, some types of which are used clinically for anticancer drug delivery.¹¹⁸) For silica, this

reflects the use of functionalized mesoporous silica as discussed above, while PEG and chitosan are frequently used in stimuli-responsive drug delivery hydrogels^{119, 120} and in composites or copolymers.¹²¹

Within implantable devices, metallic materials including nitinol, stainless steel, and titanium are commonly used, due to their mechanical strength and shape-memory properties in the case of nitinol. Poly(lactic acid) and polycaprolactone are also frequently used in this area. While they are not as mechanically strong as metals, they are bioresorbable.⁴⁴ Both materials can be engineered to have stimulus response, either through shape memory,^{122, 123} or by incorporating other materials, for example magnetic particles to remotely control devices after implantation.^{45, 124} Sensors heavily use conductive materials

including gold, silver, copper, and graphene. Gold nanoparticles are also used as scaffolds in sensor applications.^{125, 126}

Based on the data in **Figure 7**, the most frequent uses of DNA are in drug delivery and sensors, which is likely related to the highly precise structural characteristics and programmability of DNA-based materials.^{63, 65, 127}

The evolution in the use of DNA for programmable biomaterial applications over time is shown in **Figure 8**. Here again we see the prominence of drug delivery and sensor/diagnosis, with sensor/diagnosis applications increasing quickly since 2018.

Notable examples include a DNA nanorobot developed by Ravan et al. that can simultaneously detect the cancer biomarkers miR21 and

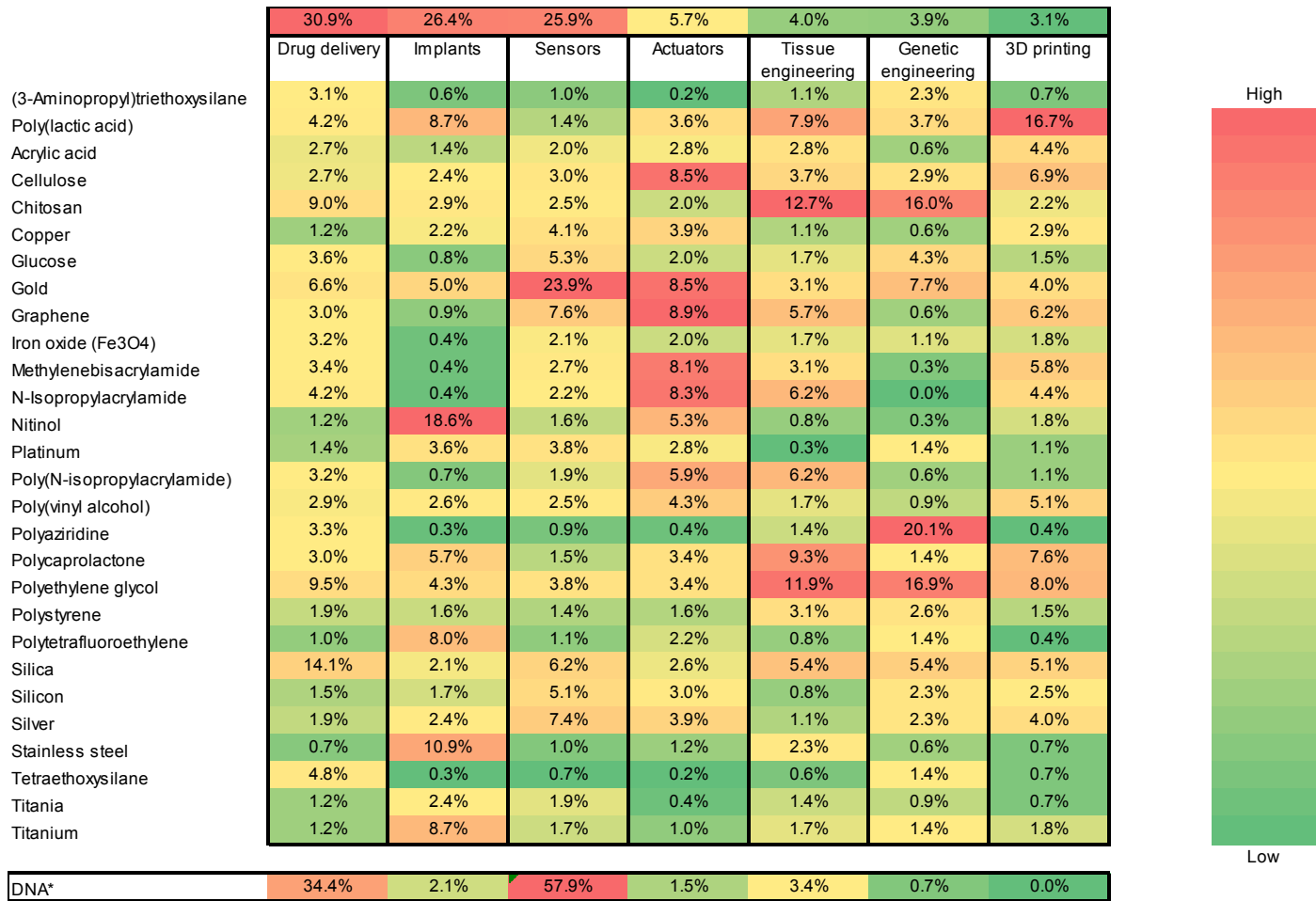


Figure 7. Heat map of the relationship between the most commonly used substances in programmable materials (left column) and the most common material applications (top rows). Relative frequencies of each substance have been calculated within each application category. DNA is treated separately in this figure because it is not a single chemical substance (further details in text).

miR125b.¹²⁸ The nanorobot was programmed through toehold-mediated strand displacement and logic gate operation, where DNA cues acted as the stimulus. Ke et al. fabricated a series of DNA hydrogels based on a single-stranded DNA that contained multiple domains and studied the cargo release profile.¹²⁹ The hydrogel enabled control of mechanical properties, thermal stability, and cargo loading capacity through modifying the sequence and lengths of the DNA domains.

A major advantage of DNA nanovehicles for drug delivery is that they provide several strategies of drug incorporation based on the nature of the drug or therapeutic molecule. Small molecule drugs like metal complexes¹³⁰ and anthracyclines¹³¹ can be carried via intercalation within the DNA double strand. For nucleic acid sequences such short interfering RNAs (siRNA) or CpG motifs, the sequences can be synthesized as a part of a staple, or hybridized with a complementary strand that is partially involved in forming the

DNA nanostructure.^{132, 133} In the case of large biomolecule cargoes and nanoparticles, the cargo can be attached to the extensions of the staple strands using complementary strands, or they can be covalently attached.¹³⁴

Chu et al. reported a DNA nanocarrier that enables targeted codelivery of doxorubicin (a chemotherapeutic drug) and two antisense nucleotides in the drug-resistant cancer cells.¹³⁵ This nanovehicle is able to penetrate the Hela/adriamycin cells and avoid lysosomal degradation. The targeting property of the nanocarrier originated from the attachment of MUC1 aptamers as the MUC1 protein is generally overexpressed in several tumors. The two antisense strands were attached to the origami via disulfide linkage, which is cleaved by the high level of endogenous glutathione present inside the cancer cells. Here, glutathione acts as the stimulus that leads to the release of the antisense strands inside the target cells.

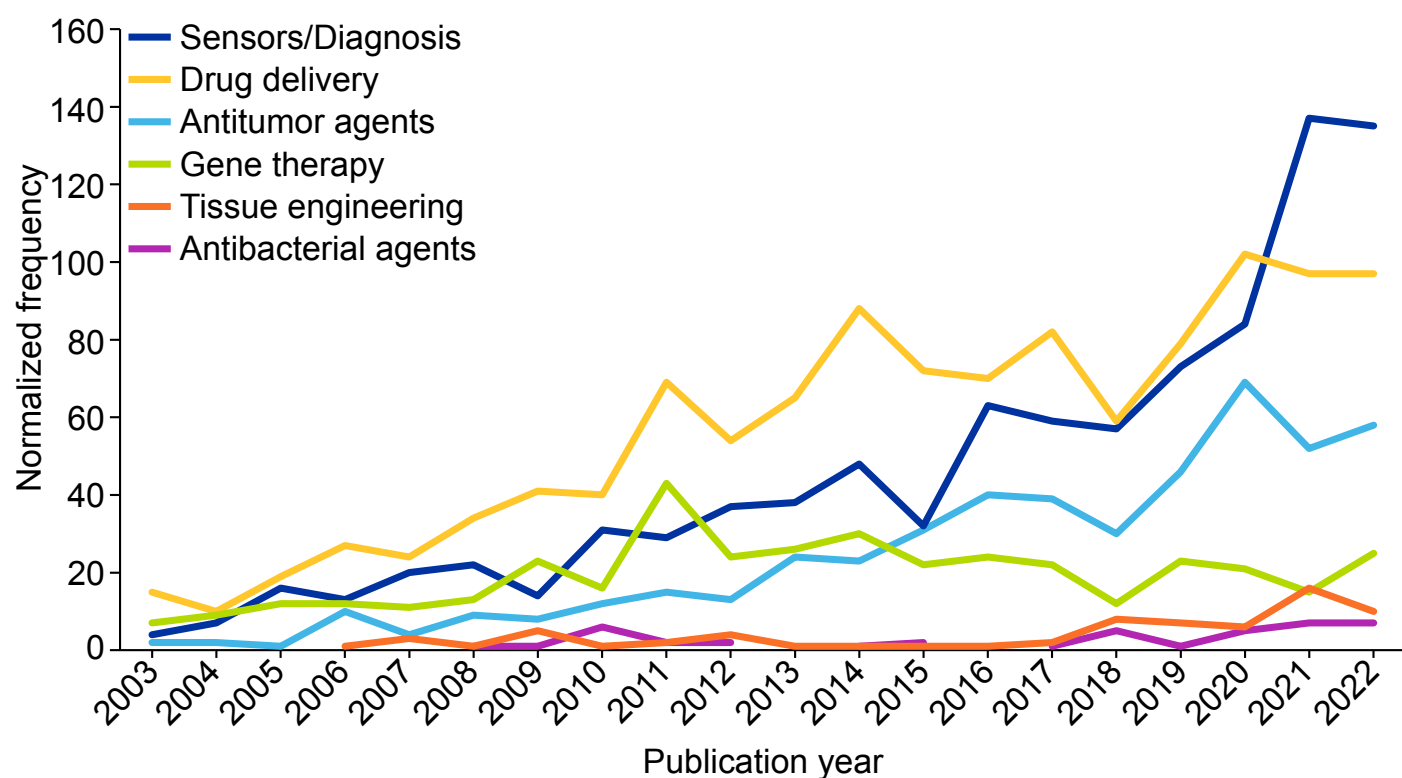


Figure 8. Overall publication (Patents + Journals) trend in selected top concepts involving DNA between 2003-2022

Notable journal articles and patents

Table 1 is a set of research articles published from 2020–2023 that represents emerging trends in the field of programmable biomaterials. These references provide examples of the materials and applications which appear prominently in our analysis of the literature in this area as presented in Section III. Selection criteria for these examples also included high citation count, and/or publication in high impact factor journals.

As discussed in earlier sections, DNA-based structures are receiving significant research attention because of their programmability through nucleotide base pairing. However, these structures can become destabilized due to environmental changes.¹³⁶ In a study by Macfarlane et al., DNA-grafted nanoparticles were stabilized using a polyelectrolyte hydrogel composed of poly(dimethylaminoethylacrylate-methylene bis-acrylamide) (P(DMAEA-MBAAm)), which formed electrostatic bonds between positively charged DMAEA from the hydrogel and sugar-phosphate groups on the backbone of DNA.¹³⁷ The resulting DNA-crystal-embedded hydrogel retains its crystallinity under hydration, drying, and compressing conditions for five cycles. This study is an example of enhancing DNA-based programmable material through combination with a polyelectrolyte hydrogel.

Biosensors were noted as a prominent application for programmable DNA materials in the previous sections. An example of this is the use of a tetrahedral DNA structure to detect miRNA-196a, a cancer biomarker,¹³⁸ through combining it with CuS and $\text{Fe}_3\text{O}_4@\text{SiO}_2@\text{CdS}$ composite particles. The fully assembled structure has a weak photocurrent response, due to photon capture by CuS. In the presence of the target, the $\text{Fe}_3\text{O}_4@\text{SiO}_2@\text{CdS}$ particles separate from the tetrahedral DNA and CuS through toehold-mediated strand displacement. After additional magnetic separation, they can be detected through photocurrent measurements. In this study, programmability was important in forming the tetrahedral DNA, which has several advantages over the more commonly used methods involving hairpin DNA, including better sensitivity, enzyme-free use, and better resistance to degradation.¹³⁹

Bone defect repair under complex medical conditions, such as inflammation, is challenging.¹⁴⁰ Recently, a magnetoelectric membrane consisting of $\text{CoFe}_2\text{O}_4@\text{BaTiO}_3$ core-shell nanoparticle embedded in poly(vinylidene fluoride-trifluoroethylene) was reported for bone regeneration.¹⁴¹ This membrane triggers osteogenesis with its highly efficient magnetoelectric conversion based on the core shell $\text{CoFe}_2\text{O}_4@\text{BaTiO}_3$ induced charge density increase in an external magnetic field, followed by beta-phase transition in the polymer that increases the membrane surface potential. This increased surface potential further activates bone regeneration, even when co-morbidity conditions are present. This *in vivo* study provides a method to reactivate skull regeneration under medical treatments that impede osteogenesis, or when inflammatory conditions are present.

Trainable stimuli-responsive materials are a special class of programmable materials that evolve over repeated cycling of strain, temperature, or other conditions.^{142, 143} An example of this type of material are dual network hydrogels whose physical properties change over the course of thermal cycling in ways that depend on their design. In a recent study, two hydrogels were constructed, one composed of poly(N-isopropylacrylamide) (PNIPAm)/agarose, the other an interconnected interpenetrating network made by PNIPAm/acrylated agarose (ac-agarose), both crosslinked by PEGDA.¹⁴⁴ After thermal training, the PNIPAm/agarose hydrogel became softer and the PNIPAm/ac-agarose became stiffer. These two thermo-responsive hydrogels can perform cooperatively as artificial muscles after thermally trained. Furthermore, this study provides a general approach to build actuators using thermally trainable materials.

One aspect of synthetic biology, another emerging field of research, is the use of engineered bacteria to synthesize and process chemicals.^{145, 146} Pokorski et al. provide an example of combining programmability with synthetic biology, with a biocomposite material made by 3D printing an engineered cyanobacteria-alginate scaffold.¹⁴⁷ This printed alginate scaffold can be swollen to accommodate nutrients and gases for further

bacterial growth and the photosynthesis expressed by cyanobacteria embedded on the scaffold. The composite material also shows its response to external chemical stimuli, for example plasmid pAM4909, and forms Yellow Fluorescent Protein (YFP). Another aspect of programmability in this material is controllable cell death.

Table 2 contains a set of patents and patent applications in the field of programmable materials from 2019-2023 that represent the material trends discussed in Section III. For example, US20220160901A1 describes mesoporous silica nanoparticles loaded with a cargo, drugs or contrast agents, where the openings of the pores are capped with stimuli-responsive polymers (including PEG and others). Under a stimulus, which could be to light, heat, ultrasound, or magnetic field, the polymers reconfigure to allow the cargo to be released. CN115887684A also describes a drug delivery system. Here, a rectangular DNA origami structure is complexed with an adriamycin prodrug that is released in an acidic environment, then activated by NQO1 enzyme expressed in tumor cells. The goal of this approach is to improve targeting and reduce the toxicity of anticancer drugs.

As discussed in Section III, hydrogels are commonly used as programmable biomaterials. An example of this is provided in CN116474093A, which describes a hydrogel containing a phenylboronic acid-modified hyaluronic acid/poly-N-phenylglycine nanocomposite, crosslinked with tannic acid. This hydrogel undergoes a gel-sol transition through a photothermal process in the NIR II range, and also in response to changes in pH, both of which can be leveraged for drug delivery in postoperative skin cancer treatments.

Shape memory is another important class of programmability. CN113683770A provides an example of a shape-memory material which is made of a blend of polyaryletherketones with different glass transition temperatures, which allows the material to have multiple shape memory states corresponding to different temperatures. This provides the ability to program more complex or multi-step behaviors compared to standard shape memory materials with a single transition temperature.

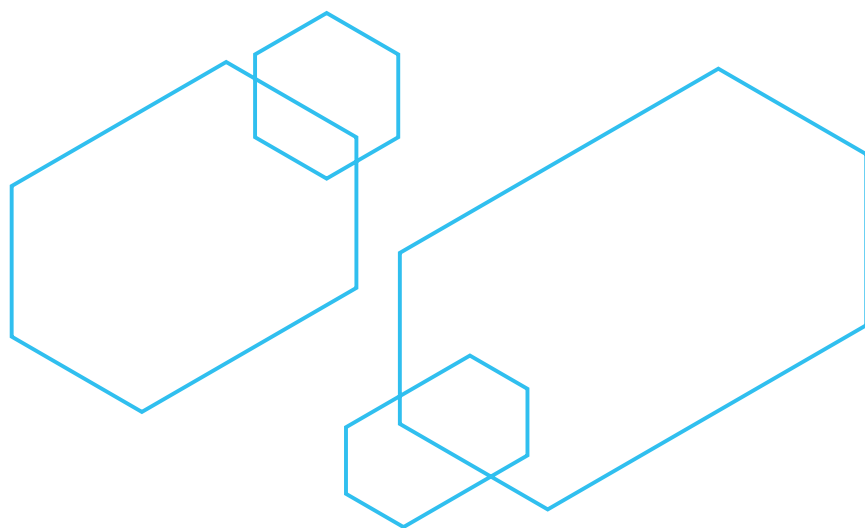


Table 1. Notable journal publications in programmable biomaterials in recent years.

Year	Title	Journal	Research Institute	Summary
2018	Programmable Metal/ Semiconductor Nanostructures for mRNA- Modulated Molecular Delivery ¹⁴⁸	Nano Letters	University of Toronto	Self-assembled DNA-based metal/ semiconductor nanomaterials embedded with therapeutic agent; the drug release triggered by target mRNA upon a strand-displacement reaction
2021	Biomimetic high performance artificial muscle built on sacrificial coordination network and mechanical training process ¹⁴⁹	Nature Communications	South China University of Technology; Guangdong University of Technology	Use of poly(ethylene-propylene-diene monomer)/lignin composite and zinc dimethacrylate (ZDMA) to make an artificial muscle
2021	Dynamic Manipulation of DNA- Programmed Crystals Embedded in a Polyelectrolyte Hydrogel ¹³⁷	ACS Applied Materials & Interfaces	Massachusetts Institute of Technology	Stabilization of DNA-based structures under different conditions using polyelectrolyte hydrogel
2022	Networking of Block Copolymer Nanoassemblies via Digital Light Processing Four-Dimensional Printing for Programmable Actuation ¹⁵⁰	ACS Applied Polymer Materials	Nanyang Technological University	Use of various monomers to afford photocurable and pH-responsive copolymer, followed by nanoassembly and digital light processing to produce a pH-responsive material
2022	Biomimetic heterodimerization of tetrapeptides to generate liquid crystalline hydrogel in a two-component system ¹⁵¹	ACS Nano	Westlake University	Controllable self-assembly of tetrapeptides upon substitution of peptides to achieve desired mechanical properties for specific uses
2023	Polymer-dispersed liquid crystal elastomers as moldable shape-programmable material ¹⁵²	Nature Communications	Jožef Stefan Institute	Shape programmability of a main-chain liquid crystal elastomer (MC-LCE) dispersed in a polymer matrix
2023	Phenotypically complex living materials containing engineered cyanobacteria ¹⁴⁷	Nature Communications	University of California San Diego	Engineered cyanobacteria incorporated with alginate to form a stimuli-responsive biocomposite material capable of bioremediation
2023	In situ activation of flexible magnetoelectric membrane enhances bone defect repair ¹⁴¹	Nature Communications	Peking University, Sun Yat-sen University, Huazhong University of Science and Technology	CoFe ₂ O ₄ @BaTiO ₃ /poly(vinylidene fluoridetri fluoroethylene)-based membrane with magnetic response enhancing bone cell regeneration
2023	Thermally trainable dual network hydrogel ¹⁴⁴	Nature Communications	Aalto University	Two thermoresponsive polymers-, agarose and poly(N-isopropylacrylamide), applied to form a trainable material with established training strategy under thermal conditions

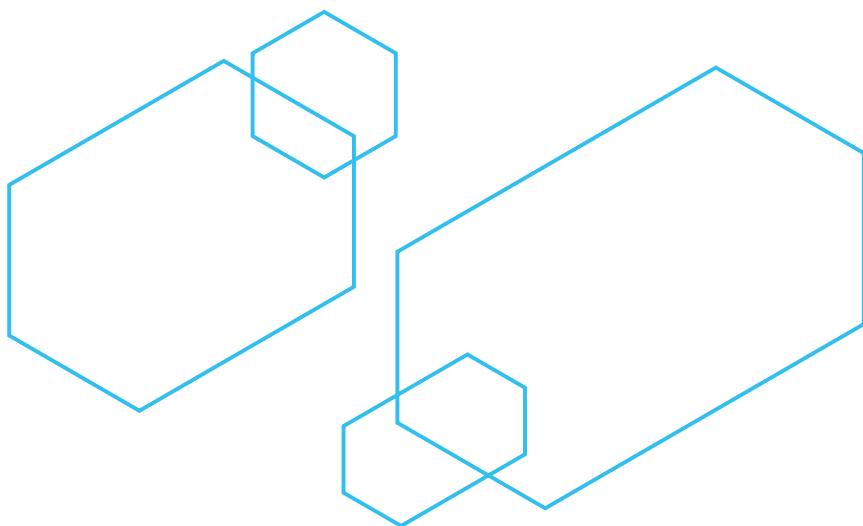


Table 2. Notable patent documents in programmable biomaterials in recent years.

Patent or publication number	publication year	Patent assignee	Title	Description of patented technology
EP3453411 A1 ¹⁵³	2019	Cook Medical Technologies LLC	Endovascular device configured for controlled shape memory deployment in a body vessel	Endovascular device made of nitinol, where the shape-memory temperature varies along the length of the device
WO2020241819 A1 ¹⁵⁴	2020	Tokyo Inst. of Technology; Kawasaki Inst. of Industrial Promotion	Complex, medicine, therapeutic agent for cancer, kit and conjugate (pH)	pH-responsive drug delivery material based on PEG (or other biocompatible polymers) modified with a boronic acid group, and a compound with a diol structure, including tannic acid and gallic acid.
US20220160901 A1 ¹⁵⁵	2020	University of California	Stimuli-Responsive Compositions, Imaging Systems, and Methods for Using the Same for Biomedical Applications	Porous silica particles loaded with active agents (for therapy or as a contrast agent), where the pores are capped with a stimulus responsive polymer that is designed to release the active agent when exposed to light, heat, ultrasound, or magnetic field
CN112011069 A ¹⁵⁶	2020	Harbin Institute of Technology	Nano filler/PNIPAM composite hydrogel, preparation method and application in smart window, actuator and remote light control device	Hydrogel including PNIPAM with a nano-scale filler such as MXenes, graphene, carbon nanotubes, MoS ₂ , VO ₂ , and others, which can be used for near-IR irradiation triggered drug delivery
CN113831453 A ¹⁵⁷	2021	South China University of Technology	Temperature response hyaluronic acid, hydrogel and its preparation method and application	Hyaluronic acid based hydrogel that releases mesenchymal stem cell-derived exosomes for treating corneal injuries when triggered by temperature
CN110801433 B ¹⁵⁸	2021	Jiangnan University	Targeted pharmaceutical composition loaded with amphotericin B and adriamycin together and application thereof (pH)	pH-responsive micelles made of mannose-modified beta-cyclodextrin, loaded with amphotericin B and adriamycin as a treatment for leishmaniasis
CN113683770 A ¹⁵⁹	2021	Harbin Institute of Technology	Preparation of poly(aryl ether ketone) with multiple shape memory effects and its application	Temperature-triggered shape memory polyaryletherketones, mixtures of which have different transition temperatures are used to generate multiple responses
CN112980165 B ¹⁶⁰	2022	Sichuan University	Self-repairing shape memory composite material with photo-magnetic response and preparation and application thereof	Polycaprolactone-based shape memory material that responds to light or magnetic stimuli (or to both, cooperatively) through the inclusion of Fe ₃ O ₄ particles
WO2022119868 B ¹⁶¹	2022	University of California	Injectable biodegradable polymeric complex for glucose-responsive insulin delivery	Poly-L-lysine modified with 4-carboxy-3-fluorophenylboronic acid, which complexes with insulin and releases it when glucose levels are high
US20220297374 ¹⁶²	2022	Xerox Corporation	Structure that compresses or expands a volume in response to an applied magnetic field	Elastomer loaded with magnetic particles (along with compatibilizers and fillers) that mechanically responds to magnetic field
US11219502 B2 ¹⁶³	2022	Medtronic Advanced Energy LLC	Transformative shape-memory polymer tissue cavity marker devices, systems and deployment methods	Bioresorbable, shape-memory medical device used to mark tissue cavities after cancer surgery to target radiation treatment based on poly(lactic acid), poly-L-lactide, poly-L-glycolic acid, or polycaprolactone, that is inserted through a small incision, then takes on a permanent shape as triggered by body temperature.
CN116474093 A ¹⁶⁴	2023	Guilin University of Technology	Near-infrared II zone photoresponsive hyaluronic acid-based multifunctional hydrogel for postoperative treatment of skin cancer	Hydrogel incorporating boronic acid-modified hyaluronic acid poly-N-phenylglycine that is light (NIR II), thermal, pH-responsive, to be used as a postoperative drug delivering and antimicrobial material
WO2023133546 A2 ¹⁶⁵	2023	Arizona State University	Folding mRNA into a nanoscale delivery vehicle	DNA nanostructures as delivery vehicles for mRNA and single-stranded DNA
CN115887684 A ¹⁶⁶	2023	Nanjing University of Posts and Telecommunications	Drug delivery nano system and method constructed based on DNA origami and adriamycin prodrug	DNA origami-based drug delivery system that selectively releases a prodrug in acid environments

Challenges and perspectives

Despite the many advantages of programmable materials, several challenges need to be addressed to enable their more widespread use in biomedical devices. The challenges identified in recent literature include:

- Scale-up and cost optimization of fabrication methods, particularly lithography.² Photolithography, electron- and ion-beam lithography, and nanoimprint lithography have all been used to pattern programmable polymer materials, but all have drawbacks. Photolithography is limited to photo-sensitive materials, while the other two forms of lithography have practical limitations on scaling, specifically long processing times and issues with mold durability.
- Combining multiple independent functions in a single material, using orthogonal, simultaneous responses or sequential responses to a single stimulus, or incorporating different responses to different stimuli while reducing interference between functions has proven to be difficult.^{26, 167} This represents a significant opportunity for new material development.
- Coupling the direction of the stimulus to the direction of the response, for example reproducing the response of plants to move in the direction of sunlight.¹⁶⁷ While this continues to be a challenging area, recent work has demonstrated that the incorporation of photoresponsive liquid crystal elastomers in a material can enable the selective triggering of multiple shape-morphing modes, and even continuous, oscillating motion in actuators and robots.¹⁶⁸⁻¹⁷⁰
- Low response speed and slow kinetics are significant limitations for shape-morphing hydrogels, mainly because actuation is typically constrained by the movement of water or ions.²⁶ Introducing porosity on a scale conducive to generating faster responses, as has been demonstrated by using electrospun hydrogel fibers, and is a possible route toward a practical solution.¹⁷¹
- Concerns exist regarding the use of programmable materials in complex biological systems such as the human body. Extensive *in vivo* testing would be required before proof-of-concept demonstrations can be applied in clinical settings, as most studies have been conducted *in vitro*. For example, programmable folding behavior may become unpredictable in complex physiological environments,² while programmable responses may be affected by the presence of multiple, unpredictable stimuli present in the body.
- The lack of clear evidence supporting the biomedical effects of DNA nanostructures and their potential immunostimulatory properties raises concerns about their long-term safety.^{15, 172}
- Nuclease degradation in the body is a common obstacle for all DNA-nanostructure based *in vivo* applications.¹⁵ To prevent this degradation, strategies involving modification and encapsulation, for example by proteins or lipids are being explored.¹⁷³ Notably, many of these stabilization techniques are not adaptable to the dynamic switching needed in several stimuli-responsive DNA nanorobots that are as *in vivo* delivery vehicles.¹⁸ Although some DNA nanostructures are intrinsically nuclease resistant, their effectiveness can also be reduced by renal filtration,¹⁵ though conjugation with bulky groups might help to address this issue.

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- (165) Folding mRNA into a nanoscale delivery vehicle. WO2023133546A2, 2023.
- (166) Drug delivery nano system and method constructed based on DNA origami and adriamycin prodrug. CN115887684A, 2023.
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VI. Protein-based materials

Introduction

Materials consisting of proteinaceous components are referred to as protein-based materials and include well-known examples such as silk,¹⁻³ collagen,^{4,5} keratin,⁶⁻⁸ etc. Desirable properties such as biocompatibility, biodegradability, bio-absorbability and self-assembly have meant that the use of protein-based materials in itself is an age-old practice.¹ However, the development of new hybrid/composite materials based on naturally occurring protein materials^{12,13} is a much more recent endeavor. Proteins are complex molecules consisting of long polypeptide chains often folded to form highly complex and dynamic structures. Classified as natural or biopolymers, proteins possess mechanical and physical properties with the use of protein-based materials in the biomedical field. Due to their natural origin, proteins are biocompatible and offer ideal mechanical and physical properties for being used in the biomedical field, finding a place in applications such as drug delivery,¹⁵⁻¹⁷ tissue engineering,¹⁸⁻²¹ hydrogels,^{13,22,23} wound healing,^{24,25} surface functionalization of implants,²⁶⁻²⁸ electronic skin^{29,30} among others. This sustained increase interest in protein-based materials is evident in the growing number of publications (journals and patents) over the last two decades (**Figure 1**). While the growth in journal publications

has been more or less on the rise, the growth in patent publications appears to be somewhat stagnant (**Figure 1**).

In this report we present our findings from evaluation of more than 122,000 documents (journals and patents) spanning across two decades (2003-2023) in the field of protein-based materials from the CAS Content Collection. Along with providing publication trends, our analysis is also centered around identifying emerging materials in the field and their applications.

The three-dimensional structures of a few protein molecules and their corresponding amino acid compositions are shown in **Figure 2** and **Table 1**, respectively. Diversity in amino acid compositions of proteins confers characteristic properties to the materials based on those proteins. For instance, a recent study found correlations between amino acid compositions of silk and properties, including wetting behavior. This could have a direct bearing on the use and design of engineered recombinant silk types depending on the desired applications.³¹ In another study, the amino acid composition of silk sericin extracted from three different moth species was determined to be more or less similar with all three of them displaying/possessing antibacterial and antioxidant properties.³²

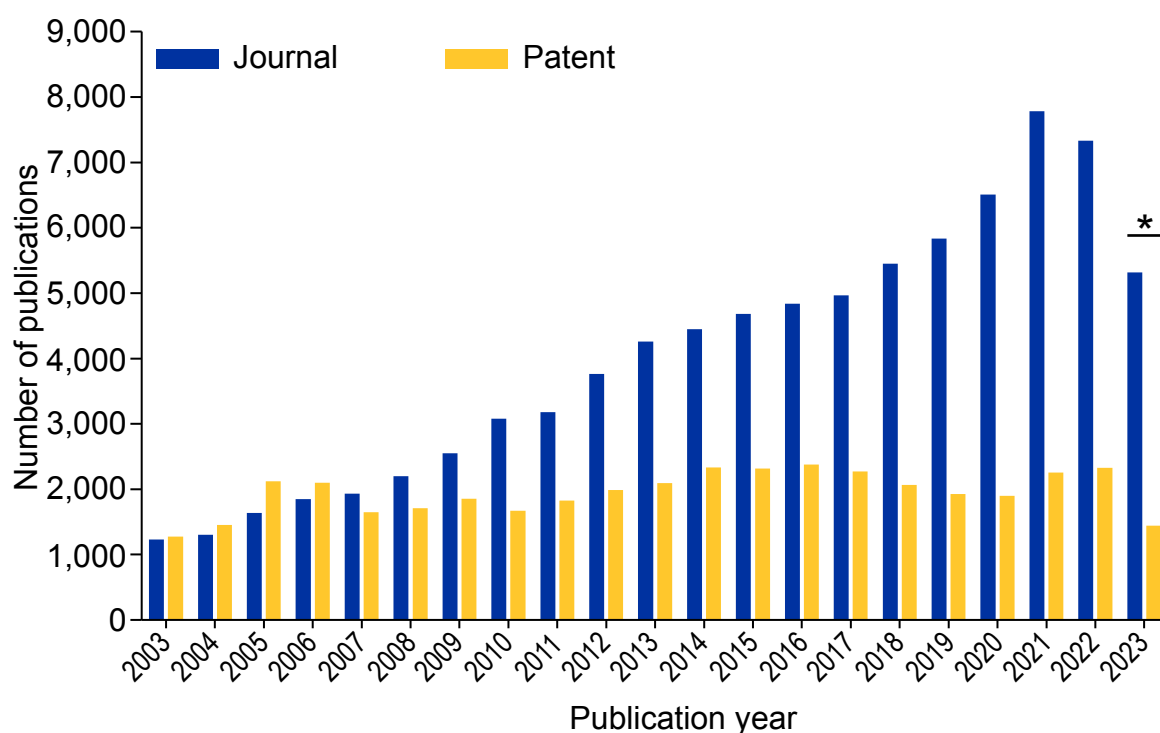


Figure 1. Number of journal and patent publications per year in the field of protein-based materials (shown as blue and yellow bars, respectively) over the period of the last two decades (2003-2023). *The data for 2023 only includes the months from January to August.

Table 1. List of commonly used proteins as materials and their amino acid compositions.

Name of protein	Organism	PDB ID	Abundant amino acids
FISp spidroin	<i>Trichonephila clavipes</i>	7OOM (1.80 Å) ^{14, 33}	Glycine (36%) and Serine (21%)
Intermediate filament proteins keratin 1 (KRT1) and keratin 10 (KRT10)	<i>Homo sapiens</i>	6EC0 (2.98 Å) ^{10, 34}	Human keratin ³⁵ : Serine (13.9%), Glutamine (13.5%), Leucine (12.3 %)
Vimentin Coil 2B fragment	<i>Homo sapiens</i>	1GK4 (2.30 Å) ^{9, 36}	
Serum Albumin	<i>Homo sapiens</i>	1AO6 (2.50 Å) ^{11, 37}	Glutamic acid (14%), Alanine (11%), Leucine (10%), Lysine (10%)
Collagen ³⁸	<i>mammalian source</i>	-	Glycine (33%), Hydroxyproline (22%) Proline (17%)
Elastin ³⁸	<i>mammalian source</i>	-	Glycine (37%), Alanine (~20%), Valine (~17%), Proline (13%)
Silk Fibroin ^{39, 40}	<i>Bombyx mori</i>	-	Glycine (43%), Alanine (30%), Serine (12%), Tyrosine (5%)
Silk Sericin ⁴¹	<i>Bombyx mori</i>	-	Serine (42%), Glycine (10.5%), Threonine (7.9%)
Resilin ⁴²	<i>Drosophila sps.</i>	-	Glycine (27.4%), Serine (11.9%), Alanine (10.4%)

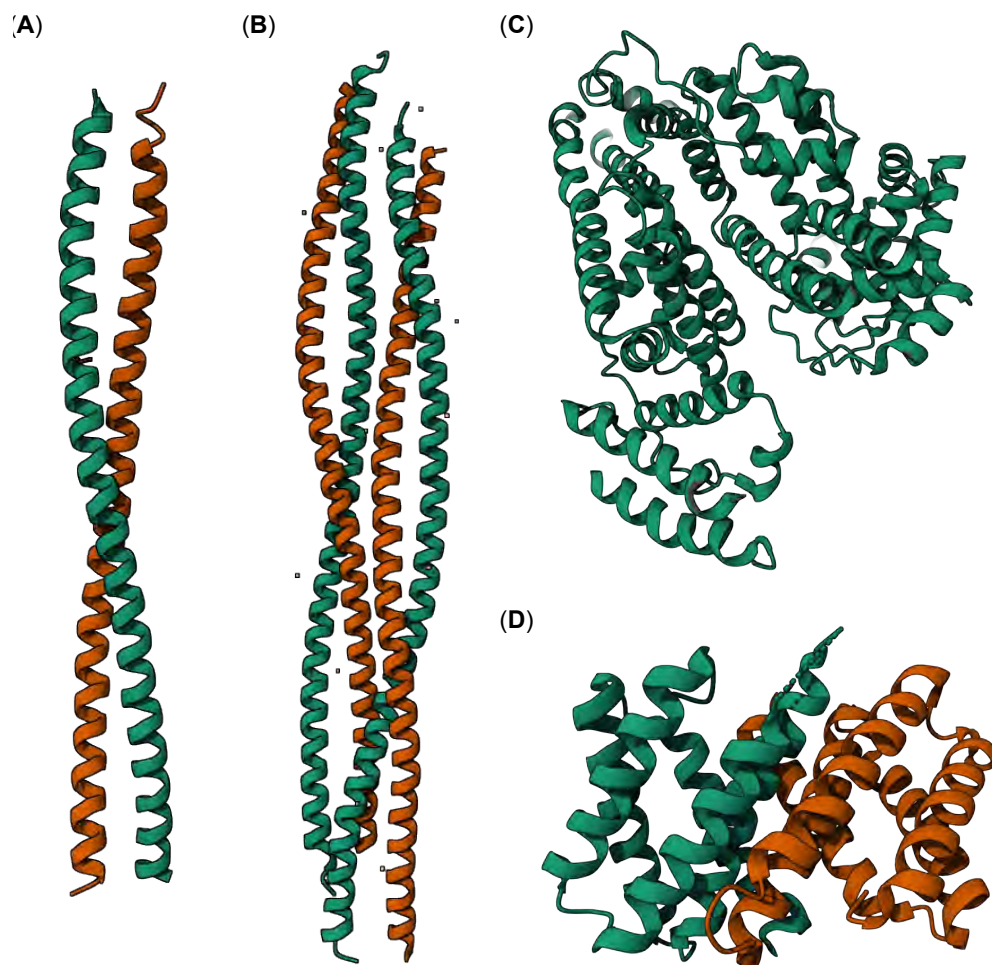


Figure 2. A few representative crystal structures of protein molecules determined using X-ray crystallography: **(A)** human vimentin coil 2B fragment (PDB ID: 1GK4),⁹ **(B)** coil 1b domains of human keratin 1-keratin 10 complex (PDB ID: 6EC0)¹⁰, **(C)** human serum albumin (PDB ID: 1AO6)¹¹ and **(D)** N-terminal domain of FISp spidroin (PDB ID: 7OOM)¹⁴ determined at resolutions of 2.3 Å, 3.0 Å, 2.5 Å and 1.8 Å, respectively.

Journal and patent publication trends

Using the average citation per publication, we shortlisted fifteen among the top 150 institutions (in terms of number of publications) that are leading in research related to protein-based materials (**Figure 3**). China accounts for nearly half (7) of the 15 institutions, followed by 4 and 2 institutions originating in the United States and Singapore, respectively. The remainder is made up by 1 institution each from Canada and the Republic of Korea. The leading institution for research related to protein-based materials appears to be Harvard Medical School with an average citation of ~90 per publication. A few examples of highly cited articles from Harvard Medical School revolve around 3D bioprinting of gelatin methacryloyl (GelMA), a synthetic derivative of gelatin^{43, 44} and the use of collagen in tissue engineering.⁴⁵

Geographical distribution of patent assignees across commercial and non-commercial organizations in the field of protein-based materials shows a high degree of overlap (**Figure 4**). The United States (USA) and China (CHN) lead in terms number of commercial and non-

commercial patent assignees, respectively. Other key countries or regions include Germany (DEU), Republic of Korea (KOR), India (IND), Switzerland (CHE) and Italy (ITA). Japan (JPN) ranks much higher in number of patent commercial assignees as compared to non-commercial ones. In terms of growth in number of patent publications over time, China, India and Korea show an upward trend with the volume being highest for China in general. The USA and Germany show little to no increase or decrease in volume of patent applications staying more or less steady over the two decades. Japan on the other hand shows a slight decline in the number of patents post 2006 which holds steady 2008 onwards.

To determine leading organizations in terms of patent publications, we separated organizations involved in protein-based material research into commercial and non-commercial entities. The geographical distribution of these organizations shows a high degree of overlap although the exact order of leading countries of regions differs between commercial and non-commercial organizations (**Figure 4**). While the USA leads in terms of commercial organizations, followed

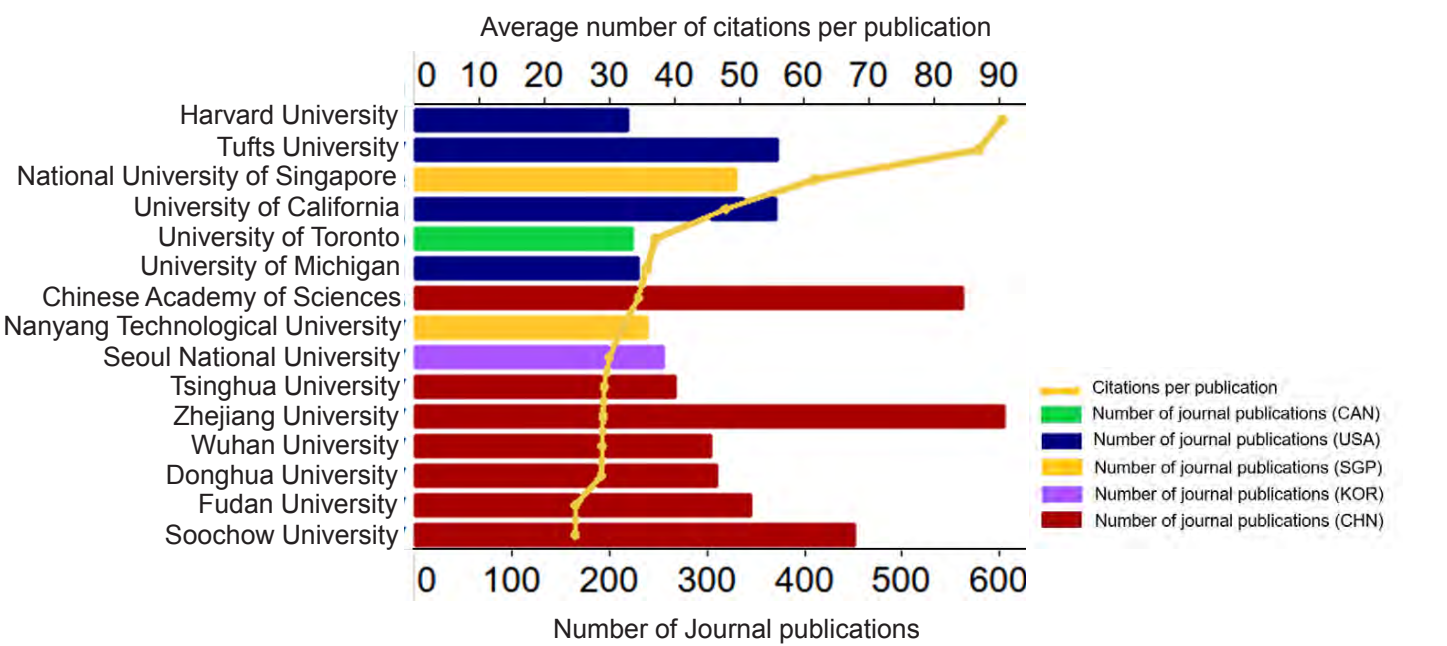


Figure 3. The top 15 institutions in terms of average citation numbers per journal publication and journal publications for the period 2003-2023. The different colors of the bars represent institution’s country/region: blue (USA), red (China), yellow (Singapore), purple (Korea), bright green (Canada); and the yellow line represents the average citation per publication.

by China (CHN) – the order is reversed for non-commercial organizations. In terms of the leading non-commercial organizations, the group is dominated by institutions from China, accounting for nearly 80% of the top 15 with the remaining three members originating from the United States. For the commercial organizations, the distribution is a little more diverse with only 4 and 3 out of the top 15 organizations originating in USA and China, respectively. The remainder of the leading organizations comprised of one organization each from: Switzerland, India, Denmark (DNK), Republic of Korea, Germany,

Japan and France (**Figure 4**). Patent publications from the US based company Allergan, Inc. related to the use of silk fibroin in drug delivery (WO 2019006098 A1⁴⁶), hydrogels (WO 2010123946 A2⁴⁷) and medical devices (US 20150148823 A1⁴⁸). The University of California, the leading non-commercial organization, had patent publications with diverse applications of protein-based materials including tissue engineering (WO 2012002986 A2⁴⁹), drug delivery (WO 2020092229 A1⁵⁰) and hydrogels (US20230158149 A1⁵¹) among others.

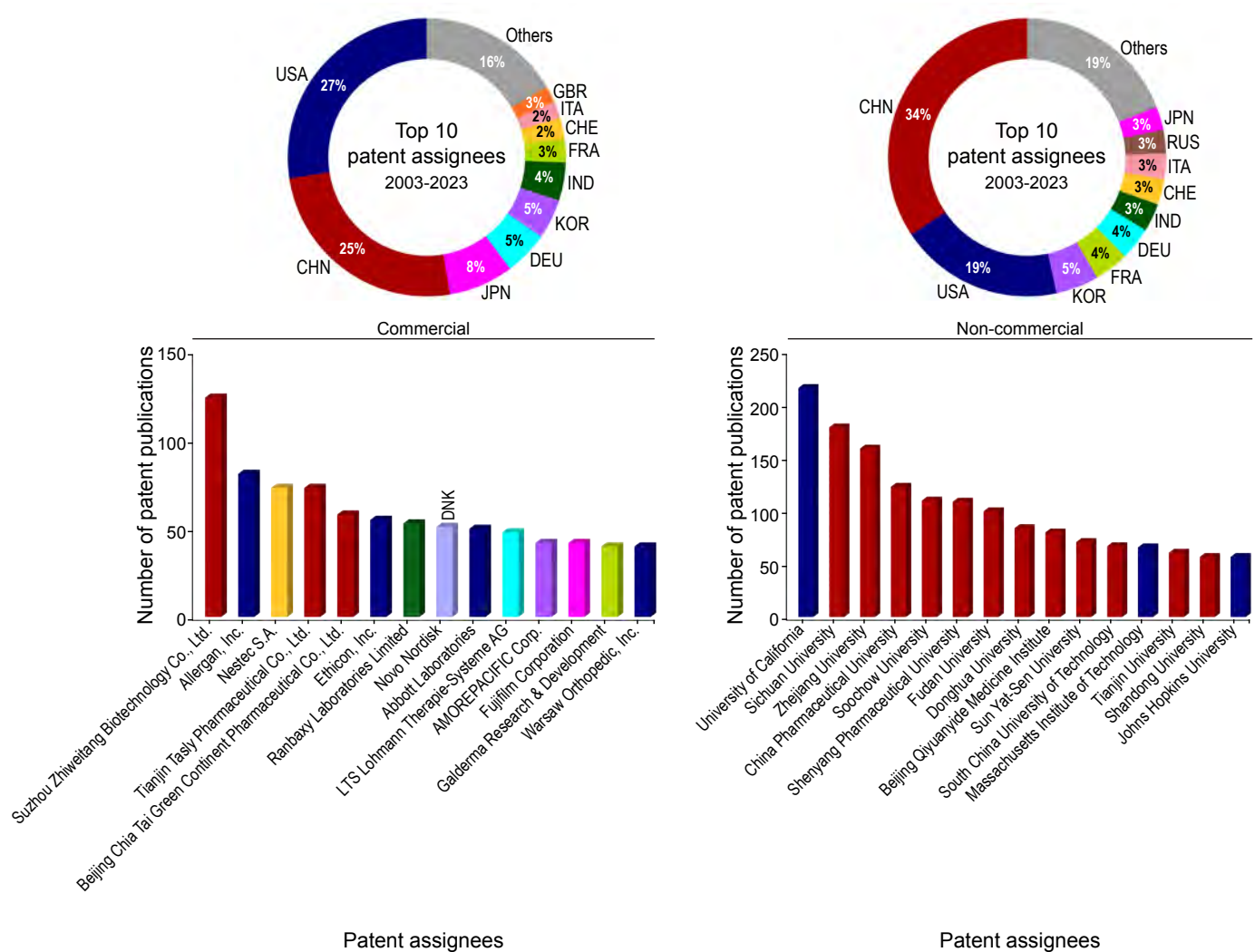


Figure 4. Geographical distribution of patent assignees (top panel – donut charts) and leading patent assignees, presented as commercial and non-commercial, in terms of the number of patent publications (bottom panels – bar charts) from 2003-2023. Bar graph has been color coded by country/region to match color scheme in donut charts. Standard three letter codes used to represent countries/regions.

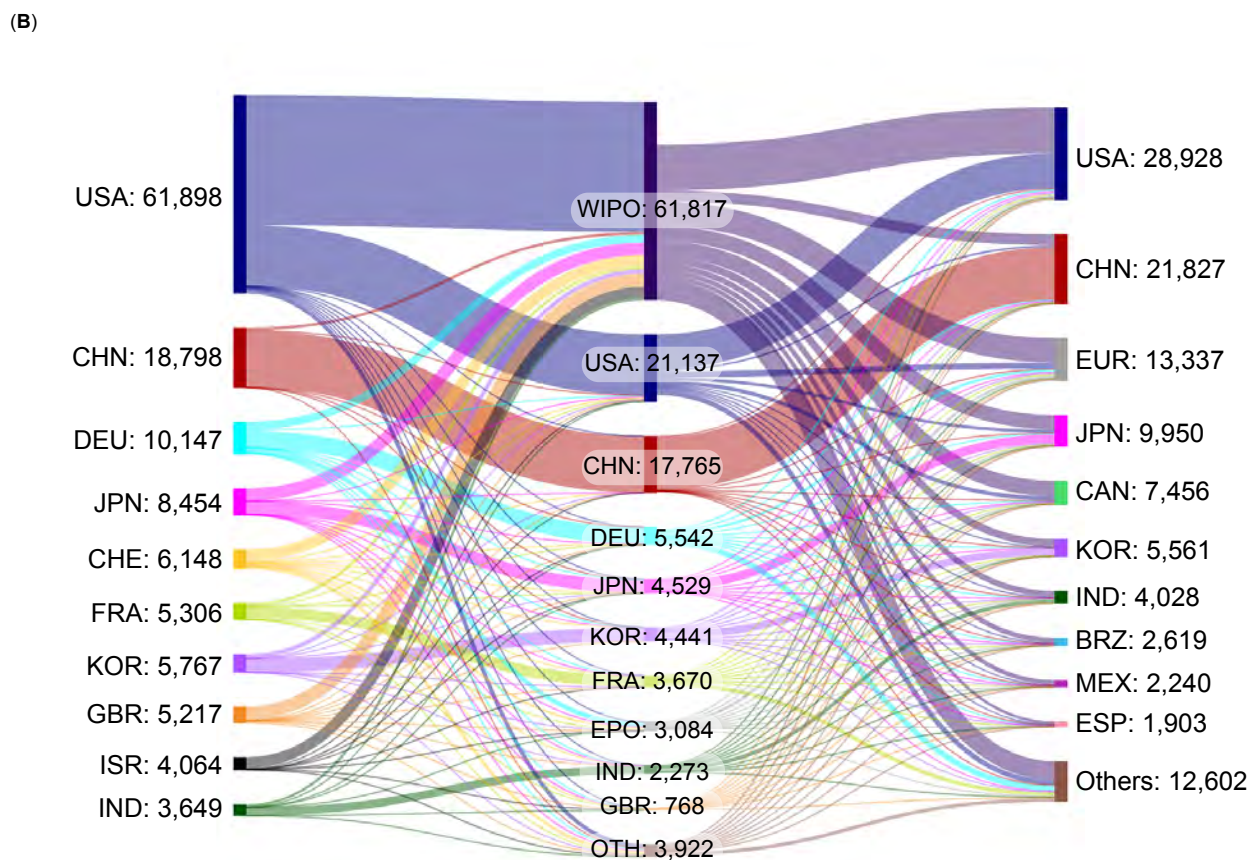
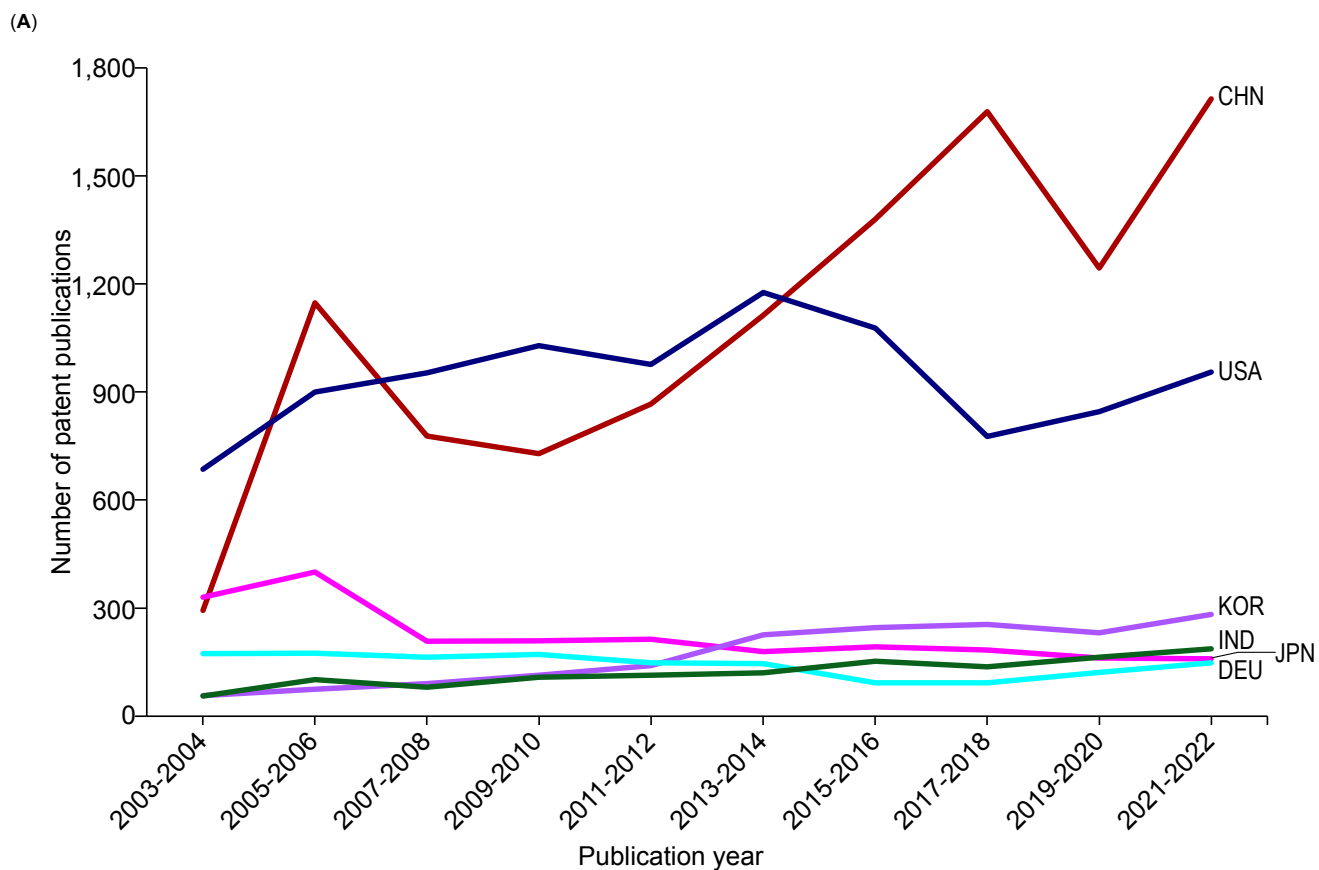


Figure 5. (A) Yearly growth in patents for selected leading countries in terms of patent publications in the field of protein-based materials over 2003-2023 from the CAS Content Collection. **(B)** Sankey graph depicting flow of patent families in the protein-based materials field between assignee countries (left), office where the first application in a family is filed (center) and the office where individual patent publication activities take place (right). Others and OTH includes more than 80 worldwide patent offices.

Key materials and applications

We performed an extensive search across both the document and substance dataset in the CAS Content Collection and identified and categorized protein-based materials into one of the following:

- Structural
- Elastomeric
- Adhesive
- Others

The system of classification was based on the functionality of proteins. One of the biggest classes was structural proteins, comprising of members such as collagen, silk and keratin among others as seen in **Figure 6**. This was followed by elastomeric proteins, elastin, and resilin with the publications related to the former outnumbering those for the latter. The next most abundant group of protein-based materials was adhesive proteins with mussel foot proteins (MFPs) accounting for most of the publications.

Among structural proteins, collagen represents the highest number of publications (**Figure 6**). Publications related to collagen have shown a steady increase over the years with a steeper increase post 2019 (**Figure 7A**). Collagen is one of the most abundantly found proteins in the extracellular matrix (ECM) and collagen-based biomaterials can be derived from the acellular form of collagen. Extracted collagen can be complexed with other biomolecules such as chitosan, elastin, and glycosaminoglycans.⁵² Collagen-based materials can be widely used as tissue scaffolds, in wound dressing, tissue repair, and in drug delivery systems.^{53, 54} Gelatin, a protein derived from collagen hydrolysis, exhibits numerous advantages over collagen such as low immunogenicity, better water solubility, and sol-gel transition.^{53, 55, 56} A closer look at the CAS data shows that gelatin, an important protein for developing gelatin-based materials, has shown a steep increase in the number of publications post 2017. Gelatin-based hydrogels are used for various biomedical applications such as tissue engineering, and medical scaffold preparation. An engineered gelatin-based material, gelatin methacryloyl (GelMA) exhibits crosslinkability making it useful for developing hydrogels for

biomedical applications. In addition GelMA is also widely used for 3D printing and drug delivery.^{57, 58}

Another important category is silk-based materials, which have shown a steady rise in publications since 2003, indicating their wide usage (**Figure 7A**). Recombinantly produced silk protein has shown high versatility and can be made into various forms such as films, coatings, capsules, particles, foams, fiber mats, etc. allowing them to have diverse applications in fields such as tissue engineering and wound dressing.^{59, 60} Recombinant systems have been utilized to obtain silk in large quantities⁶¹⁻⁶³ with the insect *Bombyx mori*^{64, 65} having the most number of publications associated with it in our dataset (**Figure 8A**). This is followed by the prokaryote *Escherichia coli* which has been used to produce spider silk.^{66, 67} Other expression systems that appear to have been used, albeit to a much smaller extent, include plant-based systems such as *Nicotiana tabacum*,⁶⁸ eukaryotic *Pichia pastoris*,⁶⁹⁻⁷¹ animal-based system *Mus musculus*⁷² as well as the prokaryote *Salmonella typhimurium*.⁷³ Silk-based materials are also used in bioelectronic applications such as developing electronic skin (also known as E-skin) (**Figure 8B**).⁷⁴ Silk fibroin can be used to prepare hydrogels either individually or they can be combined with other proteins like elastin to generate silk-elastin-like protein polymer (SELP) hydrogels that can be used for controlled release of molecules such as cytochrome, vitamin B₁₂, DNA, etc.⁷⁵⁻⁷⁸

In addition to structural proteins, adhesive proteins like mussel foot proteins (MFP) (**Figure 6 and 7B**) contain a modified form of tyrosine, 3,4-dihydroxyphenylalanine (Dopa). The presence of Dopa provides attachment ability to MFP, allowing it to bind to solid surfaces, including a wide variety of hydrophilic surfaces such as glass, metals, and hydrophobic surfaces such as plastics. Studies have shown MFP attaches to metal-presenting surfaces (e.g., TiO₂).⁷⁹ and graphene oxide (GO),⁸⁰ forming composite materials that can be used for engineering and antimicrobial applications.⁸¹⁻⁸³ Due to these diverse applications, publications related to MFP have shown a steady increase over the last two decades (**Figure 7B**).

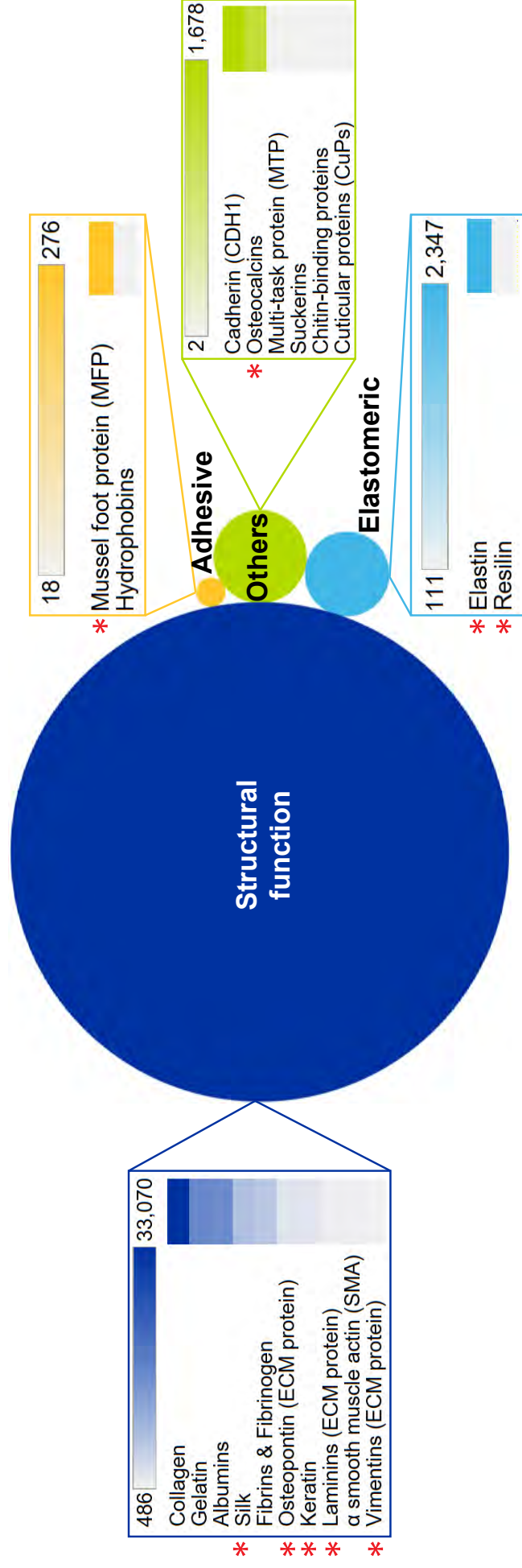


Figure 6. Distribution of protein-based materials based on functionality over two decades (2003 to 2023) from the CAS Content Collection. Size of the circle corresponds to number of publications (journals and patents). Growth of materials marked with an asterisk are shown in Figure 7.

Elastomeric proteins like elastin and resilin have shown a steady increase in the growth of publications related to them. Interestingly, publications related to resilin show a rapid acceleration 2019 onwards (**Figure 7B**). Elastin is an extracellular protein that provides elasticity to tissues and has been used in various forms such as soluble fibers, recombinant tropoelastin (precursor protein of elastin), elastin-like peptides (EPLs), elastin-like recombinamers (ELRs).

Applications of elastin-based materials include use in skin grafts, vascular grafts, heart valves, biomedical devices, drug delivery systems etc.⁸⁴⁻⁸⁶ Resilin is an elastomeric protein which possesses ideal mechanical properties in addition to its self-assembly and ability to undergo phase transition making it ideal/useful for developing smart materials.⁸⁷ Resilin mimetics such as resilin-like polypeptides (RLPs) have sequence rich in hydrophilic amino acids and possess high

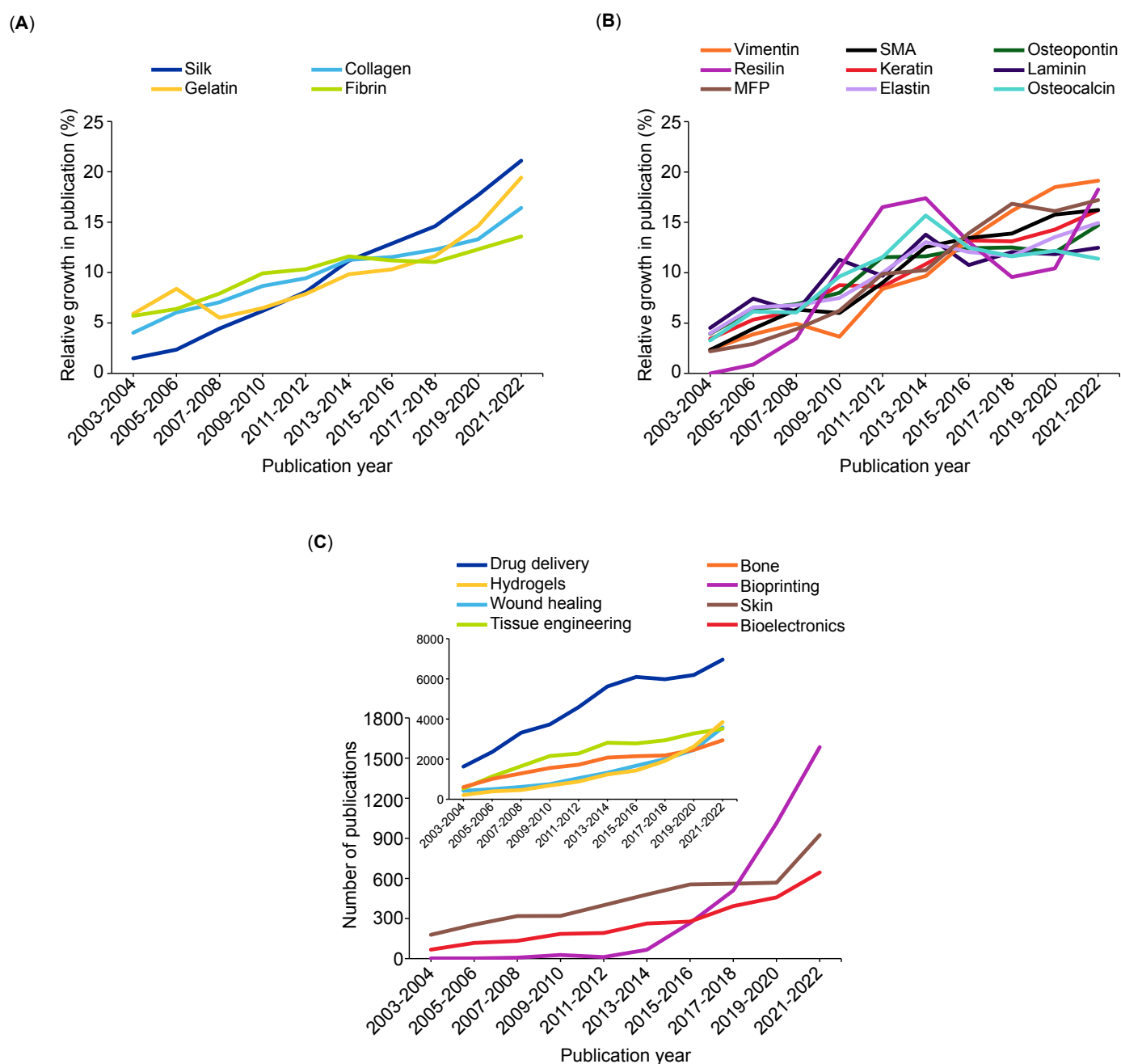


Figure 7. Emerging trends of **(A)** and **(B)** protein-based materials and **(C)** their applications based on data from the CAS Content Collection for 2003-2023.

elastomeric potential expanding the application of resilin in fields such as biosensors, bioelectronics, bioprinting in addition to applications in tissue engineering, biomedical applications and drug delivery.⁸⁷⁻⁸⁹

Extracellular matrix-based biomaterials are used for tissue regeneration, cell growth, drug delivery, and various other biomedical applications. This is made possible due to ECM's ability to act as a natural scaffold for designing various biomaterials owing to their natural biocompatibility and biodegradability.⁹⁰ In addition to major ECM proteins such as elastin, collagen, trace ECM proteins like osteopontins, vimentins and laminins have been used to promote cell growth, adhesion, and maintaining cytoskeletal function.⁹¹⁻⁹⁴ The CAS Content Collection data shows that these proteins show a moderate increase in the last two decades except for osteopontin, which shows a steep increase in the number of publications over

the last four years, indicating the importance of ECM-based biomaterials (**Figure 7B**).

The overall distribution of biomedical applications for protein-based materials are shown in **Figure 8B** in the outer donut chart. The inner pie chart shows the distribution of the same biomedical applications for silk-based materials in particular. Both the overall protein-based and silk-specific applications follow similar trends, the exceptions being that silk-based materials have a relatively higher number of publications associated with their use in tissue engineering,⁹⁵ hydrogels,^{96, 97} and bioelectronics.^{98, 99} Growth in publications over the last two decades indicates an upward trend across the broad with a particularly sharp increase in bioprinting¹⁰⁰⁻¹⁰² and electronic skin^{103, 104} after 2014 and 2020 (**Figure 7C**). On the other hand, wound healing^{105, 106} and hydrogels^{107, 108} are the other applications that show a less sharp but still considerable growth.

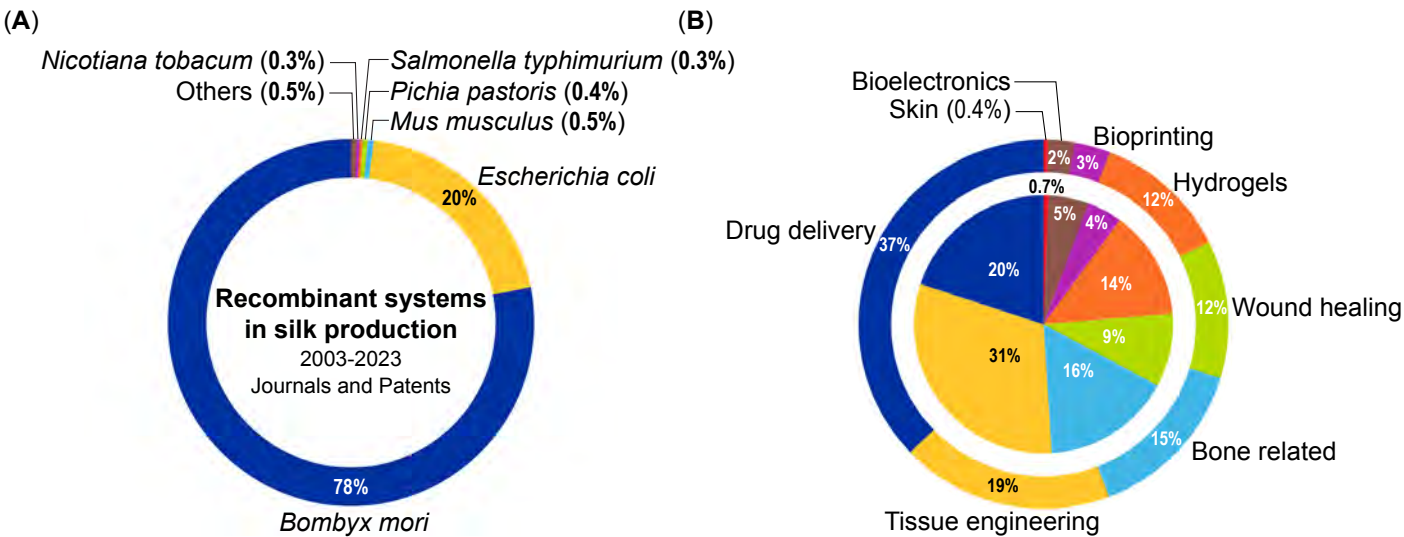


Figure 8. Distribution of (A) recombinant systems used for silk production and (B) applications for protein-based materials overall (outer donut chart) and for silk-based materials (inner pie chart).

Notable journal articles and patents

Table 2 encompasses a set of research articles published from 2020-2023 that represents emerging trends in the field of protein-based materials. These references were selected to provide examples of the materials and applications that appear prominently in our analysis of the protein-based material literature as presented in section III. They were also selected based on other factors, including the impact factor of journal and the number of other articles citing the reference. The listed examples include publications related to silk, gelatin, collagen, elastin, keratin, resilin, MFP, peptides, antibodies, etc.

Notable examples from Table 2 include an article titled “Thermoplastic Molding of Regenerated Silk” which describes a method for transforming solid-state regenerated silk fibroin (derived from *Bombyx mori*) into structural materials. By tuning the processing conditions, these materials can be used to construct biomedical devices such as medical screws for bones, ear plugs etc.¹⁰⁹

Another example is the study titled “Liquid metal-tailored gluten network for protein-based e-skin” by Ye, Shen, et al. at Fudan University, China, which describes the method for the construction of gluten-based electronic skin. Gluten protein is cross-linked using gallium indium alloy (EGaIn), generating a gluten network that can be used to generate electronic skin (e-skin) due to high stretchability, self-healing, biocompatibility, biodegradability.¹¹⁰

In another example, gelatin/gelatin methacryloyl (gelMA) and carboxymethylcellulose (CMC) are used to design dual-network microporous PAM (Protein-based Annealed Microgel) scaffolds via extrusion printing. PAM scaffolds were checked for their strength, biocompatibility, rheological properties, and degradability. Eventually, encapsulation in the scaffolds was tested using recombinant *Escherichia coli* DH5 α to examine cell viability and cell leakage from these scaffolds. Further, *Saccharomyces cerevisiae* encapsulated PAM scaffolds were used for testing ethanol fermentation, indicating that these scaffolds can be functionalized with different microorganisms to carry out various functions.¹¹¹

Furthermore, researchers at Westlake University have developed a green and efficient method with scaling-up potential for modifying native silk fibroin to silk acid with a tunable modification degree. Upon subcutaneous implantation, the silk acid materials with a high carboxylation degree exhibited enhanced degradation, a mild foreign-body response, and pro-angiogenic properties, demonstrating great potential for silk acid as a new implantable biomaterial for tissue regeneration.¹¹²

Table 3 shows notable patents in the field of protein-based materials published from 2018 to 2023. Patents were selected based on relevance, novelty, applicability, and field of study. Most of these involve different proteins in their various forms focusing on their applications in the field as described in section III. For instance, JP6807089B2¹¹³ by Spiber Inc. explains the synthesis of modified silk fibroin with reduced overall glutamine content which reduces the overall hydrophobicity of the protein leading to a reduction in shrinkage of silk fibroin. Modified fibroin fibers, in their various forms like nanofibers, films, and coatings can be used for diverse biomedical applications.

In another example, US20220142936A1¹¹⁴ discusses protein-based nanoparticles that can be used for treating cancer. These nanoparticles could be composed of water-soluble proteins such as albumin, mucin, transferrin, insulin, lysozyme, hemoglobin, collagen, catalase, horseradish peroxidase, glucose oxidase, and/or their combinations in specific ratios and they are synthesized using electrodynamic jetting method. They can contain active nucleic acid as a therapeutic agent and can be functionalized to suit different cancer types.

In a recent example, US11578106B2¹¹⁵ explains the composition of a coating composition based on the use of surfactant adhesive proteins (mostly mussel-derived adhesive proteins) that are versatile and exhibit an excellent affinity to the hydrophilic or lyophilic surfaces. The proteins used in the composition can be modulated to give rise to anticancer, antibacterial, antifungal, or antiviral coating.

Table 2. Notable journal articles in the field of protein-based materials in recent years.

Year	Title	Journal	Research Institute	Application
2020	Cation-induced shape programming and morphing in protein-based hydrogels ¹¹⁶	Science Advances	University of Wisconsin-Milwaukee (UWM)	Human serum albumin-based hydrogels which can undergo temporary shape and morphology changes in response to metal ion stimulus.
2020	A bioinspired and hierarchically structured shape-memory material ¹¹⁷	Nature Materials	Harvard University	A keratin-based system that exhibits hydration-controlled shape memory properties.
2020	Thermoplastic Molding of Regenerated Silk ¹⁰⁹	Nature Materials	Tufts University	Thermal processing method to transform solid-state regenerated natural silk into silk-based bulk material.
2021	Photopatterned biomolecule immobilization to guide three-dimensional cell fate in natural protein-based hydrogels ¹¹⁸	Proceedings of the National Academy of Sciences	University of Washington	Natural hydrogel materials decorated with bioactive proteins which could be used in tissue engineering.
2021	Adhesive protein-based angiogenesis-mimicking spatiotemporal sequential release of angiogenic factors for functional regenerative medicine ¹¹⁹	Biomaterials	Pohang University of Science and Technology	Mussel adhesive protein (MAP) based platform fabricated to spatially separate the release of (vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF).
2021	Nanoengineered Peptide-Based Antimicrobial Conductive Supramolecular Biomaterial for Cardiac Tissue Engineering ¹²⁰	Advanced Materials	Tel Aviv University	A composite hydrogel containing Arg–Gly–Asp (RGD) peptide used for DNA binding and antimicrobial activity.
2021	Elastin-like polypeptide modified silk fibroin porous scaffold promotes osteochondral repair ¹²¹	Bioactive Materials	Northwest University	Porous scaffold made from elastin-like polypeptide (ELP) bound to Silk fibroin (SF) which can mimic 3D cellular microenvironment.
2021	Accelerated polymerization of N-carboxyanhydrides catalyzed by crown ether ¹²²	Nature Communication	University of Illinois	Method for rapid synthesis of polypeptides by accelerated polymerization (catalyzed by crown ethers (CEs)) of N-carboxyanhydrides (NCAs)
2022	Liquid metal-tailored gluten network for protein-based e-skin ¹¹⁰	Nature Communication	Fudan University	Gluten-based electronic skin, which is self-healing, stretchable, and biocompatible.
2023	Silk-based hydrogel incorporated with metal-organic framework nanozymes for enhanced osteochondral regeneration ⁹⁷	Bioactive Materials	Nanjing Medical University	Silk hydrogel with nanozymes which can be used to accelerate Osteochondral defects (OCD) repair
2023	Bioprinting microporous functional living materials from protein-based core-shell microgels ¹¹¹	Nature Communication	University of Cambridge	Gelatin/gelatin methacryloyl (gelMA) and carboxymethylcellulose (CMC) based protein annealed microgel (PAM) for culturing separate microbial consortia simultaneously.
2023	Silk Acid as an Implantable Biomaterial for Tissue Regeneration ¹¹²	Advanced Healthcare Materials	Westlake University	Silk acid materials can be used to fabricate new implantable biomaterials for tissue regeneration.

Table 3. Notable patent publications in the field of protein-based materials in recent years.

Patent number	Publication year	Patent assignee	Title	Description of patented technology
US9925301B2 ¹²²	2018	Trustees of Tufts College, USA	Methods of producing and using silk microfibers	It describes preparation of silk microfiber-reinforced scaffolds which can be used for bone graft applications.
JP6807089B2 ¹²³	2021	Spiber, Inc., Japan	Modified fibroin	It describes method for producing artificially modified fibroin fiber with reduced shrinkage for use in industrial applications.
US11180541B2 ¹²⁴	2021	Geltor, Inc., USA	Recombinant collagen and elastin molecules and uses thereof	It explains the preparation of non-naturally occurring truncated forms of collagen and elastin that can be used for industrial and tissue engineering applications
CN108348577B ¹²⁵	2021	Bengt I Samuelsson Institute of Life Science Co Ltd, China	Mussel mucin product and application thereof in inhibiting skin inflammation	It demonstrates the use of mussel mucin (MAP) known as mussel foot protein (Mefp) as an active ingredient in treating skin inflammation
US11065365B2 ¹²⁶	2021	Allergan Australia Pty Ltd Allergan Pharmaceuticals International Ltd, Ireland	Preparation and/or formulation of proteins cross-linked with polysaccharides	It describes formulations based on Tropoelastin and albumin crosslinked using saccharide-based linker, these could be used for therapeutic purposes.
US20220142936A1 ¹¹⁴	2022	University of Michigan, USA	Therapeutic protein-based nanoparticles for treating cancer	It describes nanoparticles comprising water-soluble proteins. These nanoparticles have a mesh structure encapsulating the inhibitor of the transcription factor and can be used for treating cancer.
CN110951096B ¹²⁷	2022	Guangdong Institute of Medical Instruments, China	GelMA-oxidized glucan double-network hydrogel and preparation method thereof	It describes a method for preparing hydrogel using methacrylate gelatin (GelMA)-oxidized glucan double-network hydrogel which has improved mechanical properties as compared to normal gelatin-based hydrogel.
WO2022178409A2 ¹²⁸	2022	The Regents of the University of Colorado, The University of North Texas Health Science Center, USA	Protein-based therapies for ocular conditions	It demonstrates therapies developed using peptides derived from a heat shock protein, including Hsp20 and/or α B-crystallin which could help in ocular conditions.
CN114748707A ¹²⁹	2022	Sichuan University, China	Degradable anticoagulant and rapid endothelialization coating of occluder and preparation method thereof	It describes the method for preparing degradable, protein-based occluder anticoagulants where proteins like laminin, elastin, gelatin, and RGD peptides are used for promoting endothelial repair.
CN113527895B ¹³⁰	2022	Westlake University	A degradable and super-tough silk protein-based material and its preparation method and application	It describes method of fabricating degradable and super-tough silk protein-based materials.
US20230158149A1 ¹³¹	2022	University of California	Wafer-Scale Protein Patterning of Hydrogel Devices	It describes method of performing extracellular matrix proteins patterning on silicon or glass-based wafer.
US11603393B2 ¹³²	2023	Bondwell Technologies Lp, USA	Self-assembly of protein-based biomaterials with multiple morphologies	It describes the composition of protein-based biomaterial composed of ultrabithorax (Ubx) protein which can be used to form sheets, fibers, films, etc.
US11578106B2 ¹¹⁵	2023	Tme Therapeutics Co Ltd, Korea	Surfactant adhesive composition	It relates to the formation of mussel adhesive protein-based biofunctional adhesive which can be used to develop antibacterial/a antimicrobial films.

Challenges and perspectives

Protein-based biopolymeric materials find application in various realms. Advances in proteomics and next-generation sequencing technologies in the past decade have enabled the identification and characterization of new proteins, thereby accelerating the development of new protein-based materials. Despite these advancements, some challenges still remain:

1. The biggest challenge occurs during the production of proteins using recombinant sources arising from excessive metabolic burden due to the over-expression of certain non-native genes, which directly impacts the yield of the target proteins. Another challenge is the discrepancy in codon usage arising from the use of different expression hosts as compared to natural sources; for instance, bacterial expression systems exhibit a low tolerance for sequence repeats and eliminate such sequences, leading to altered protein sequences. More work is needed for widespread success in this area to overcome host-organism-related challenges encountered during recombinant protein production.¹³⁴⁻¹³⁶
2. Native protein sequences might contain domains with immunogenicity, and it is important to engineer or modify these proteins by removing these domains for efficient use in protein-based materials.¹³⁷
3. Proteins are natural polymers, and can lack sufficient mechanical strength, resorbability, functionality, or access to functionality for their intended use in tissue engineering. Developing new approaches, such as sequence engineering or hybridization of proteins with other synthetic/natural polymers, are needed to increase their usability.¹³⁷
4. Engineered protein-based materials show poor neovascularization - the ability to form new blood vessels. Also, controllable mechanical and low/lack of self-healing properties in engineered protein scaffolds/constructs affect their use in tissue engineering applications.^{110, 137} Efforts are being made to modify these materials or use them as composites, this could help in enhancing the mechanical/physical properties of protein-based materials.
5. Proteins are not completely hydrophobic in nature. They have low water-barrier properties, as compared to synthetic materials like plastics, therefore, structural modifications can help in enhancing protein hydrophobicity.¹³⁸
6. While proteins are being used for tissue engineering applications, they are not an ideal choice for antimicrobial applications due to their susceptibility to protease hydrolysis.¹¹¹ Mapping the protein sequence and linking it to the proteolytic stability profile of the protein can help modulate the sequence to improve its proteolytic stability.

Protein-based materials have advanced in tissue engineering, drug delivery, and regenerative medicine owing to their biocompatibility, cytocompatibility, biodegradability, and bioactivity. However, continued advancements are needed in translating more protein-based materials into various clinical applications.



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VII. Self-healing materials

Introduction

Self-healing materials are defined by their ability to recover from mechanical, thermal, and chemical-induced damage to restore their original properties, without external assistance. For example, a self-healing polymer-based gel can be designed with reversible crosslinks that are broken when it experiences shear forces during injection, allowing it to flow like a liquid through a narrow needle. After the material is at rest inside the body, the crosslinks are re-formed, restoring its gel-like rheological properties.¹

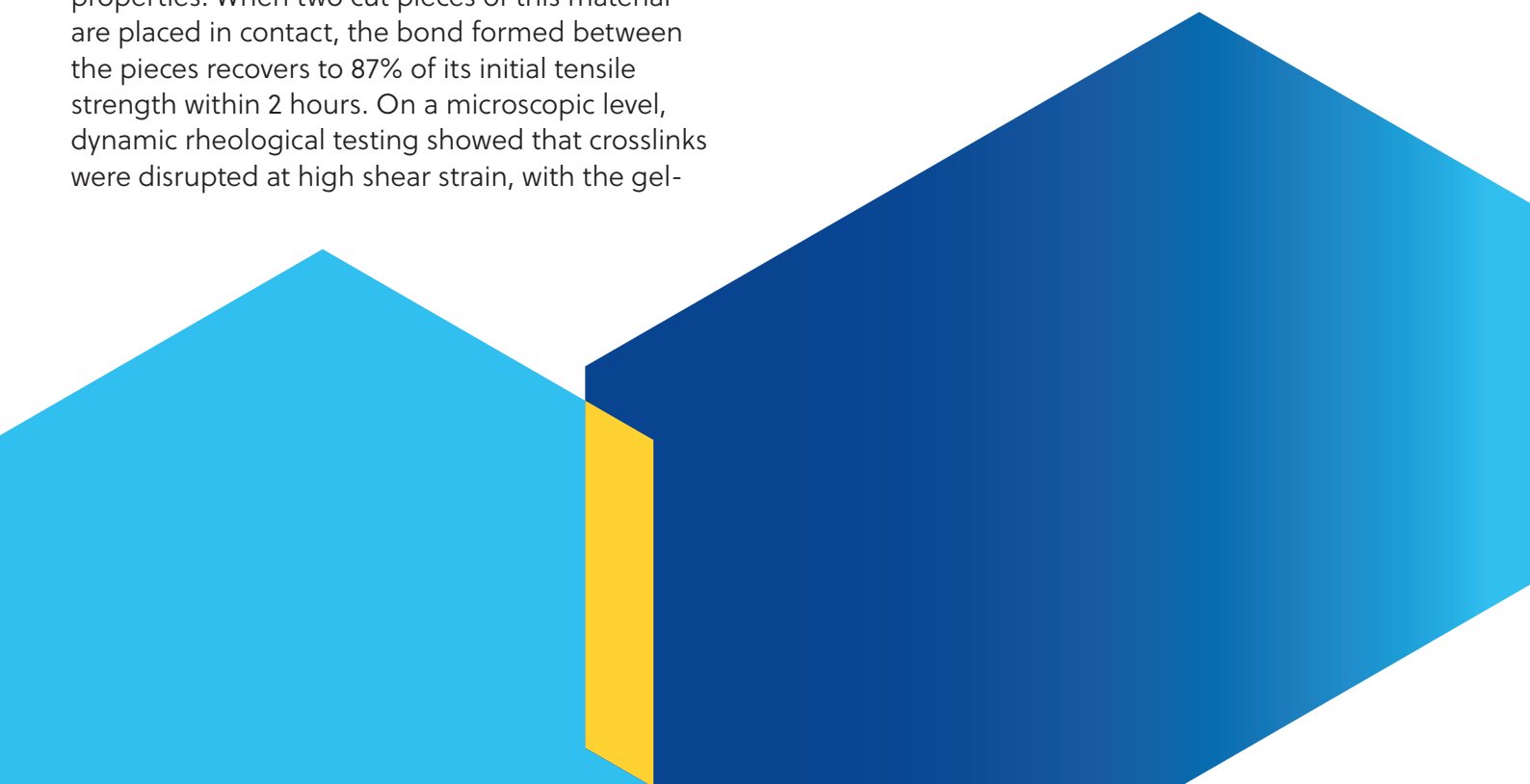
The same approach can be used to repair cracks, cuts, or breaks in a bulk material under static conditions. When two disconnected faces of a self-healing material are placed into contact, reversible bonds can be re-formed, which combined with interdiffusion results in joining of the two faces. In the context of biomedical applications, this can make wound dressings, implanted devices, and scaffolds² more resilient, robust, and reliable, since the damage they can experience due to the dynamic conditions of the body cannot be repaired by natural processes.^{3, 4}

As an example, both types of self-healing are demonstrated by a biocompatible poly(vinyl alcohol) (PVA) based hydrogel containing tannic acid.⁵ This material contains a high density of strong hydrogen bonds between PVA and tannic acid which can be repeatedly broken and re-formed, giving the material self-healing properties. When two cut pieces of this material are placed in contact, the bond formed between the pieces recovers to 87% of its initial tensile strength within 2 hours. On a microscopic level, dynamic rheological testing showed that crosslinks were disrupted at high shear strain, with the gel-

like properties being mostly restored within 70 seconds of removing the high shear strain.

In a broader context, various synthetic self-healing concepts have been developed, based on different physical processes and chemistries. Self-healing has been extensively studied in polymers, polymer composites, ceramics, concrete materials, and metals. Self-healing polymers are the most widely used, primarily because of the ease of chemical functionalization and modification of polymeric systems and the relatively low temperature required to induce the mobility over short length scales required for self-healing.⁶ Polymers are even more heavily represented in biomedical applications due to the biocompatibility of many polymers and the ability to engineer them to have mechanical properties similar to biological tissue.

In this report, we will first examine trends in the frequency of journal and patent publications in the field of self-healing biomaterials from 2003-2023. Next we will discuss the chemical mechanisms that are used to impart self-healing properties to biomaterials, which are closely connected to the specific chemical substances and functionalities used. We will then analyze trends extracted from the CAS Content Collection related to the substances used in this area, and their most prominent applications. Finally, we will highlight a selection of journal and patent publications that represent emerging trends.



Journal and patent publication trends

Figure 1 shows the number of journal and patent publications during the period 2003-2023. There has been a steady growth in the number of journal publications in the past 20 years which appears likely to continue in 2023. The number of patent publications has also shown steady growth, with some deceleration from 2020-2022. Like most other emerging materials, the number of journal publications is significantly higher than the number of patents. The increase in the journal to patent ratio in 2021 and 2022 suggests that research into self-healing materials is focused on early-stage research rather than commercial development.

The institutions with the highest number of journal publications and the average number of citations per publication are presented in **Figure 2**. Overall, the majority of publications in this area originate from research institutions in China, along with one institution each from the United States and Netherlands. The University of Illinois has generated the most citations per publication, followed by Xi'an Jiaotong University and Harbin Institute of Technology.

Figure 3 presents a breakdown of patent publications by country, from commercial and non-commercial assignees. Chinese assignees make up about 80% of the patent publications in both the commercial and non-commercial categories, followed by the US with around 7-8% share of the patents in both the categories. Japan, Korea, and Israel follow the US in the commercial category, while Korea, India, and France are the next highest assignee countries in the non-commercial category.

The trend of patent publications over time broken down by country/region is shown in **Figure 4**. Here again we see the high number of patent publications originating from assignees in China. Patent activity in the area of self-healing materials began to increase in around 2012, with most activity taking place after 2016, and still increasing as of 2023. The other trend we see in this plot is a significant rise in the patent activity from assignees in Korea starting in 2016, leading to Korea originating the second-most patent publications after China from 2016-2023.

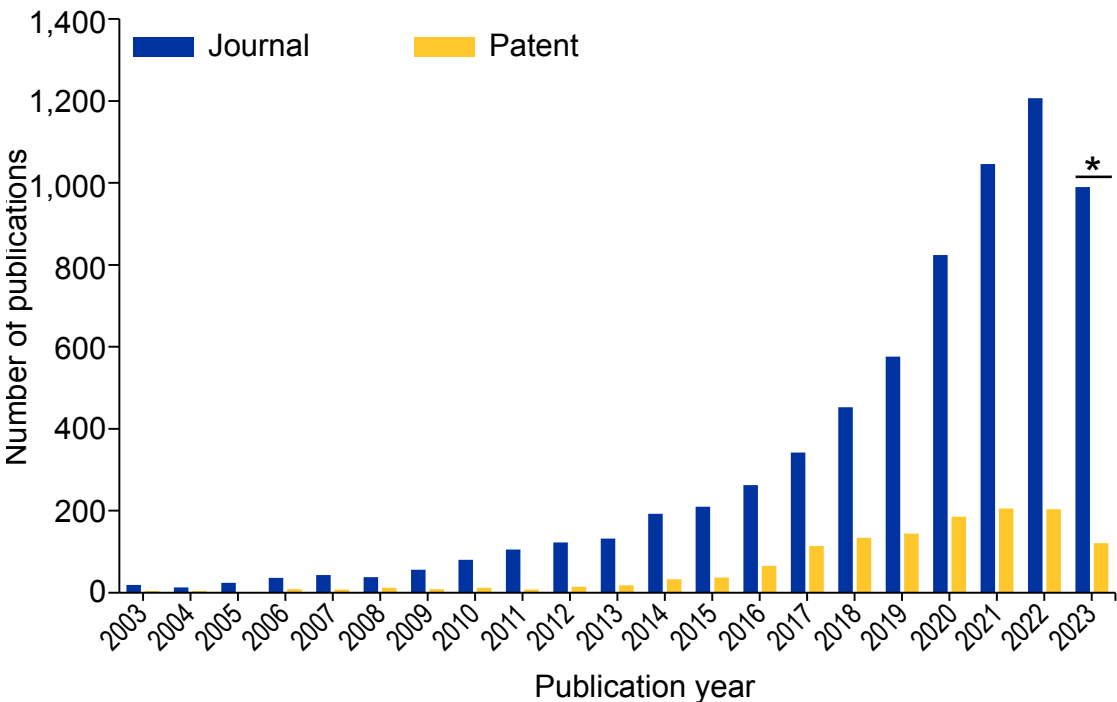


Figure 1. Number of journal and patent publications per year in the self-healing biomaterials field, 2003-2023. * = partial year data for 2023.

Figure 4B shows the flow of patent activities through national patent offices and the Patent Cooperation Treaty (PCT) system. Here, an activity is defined as an event where a patent document, either an application or a granted patent, is published. The left column shows the top ten patent assignee countries/regions in terms of number of patent activities. The right column shows the patent office where the patent activity took place. The center column, connecting the

two, indicates the office where the first patent in the family was filed.

The data in **Figure 4B** indicates that almost all patents filed in China have the first in the family filed in the China national patent office. In the US, first patents in the family also generally are filed in the US, with a smaller portion filed through PCT. This trend is generally observed for assignees in Japan and Korea.

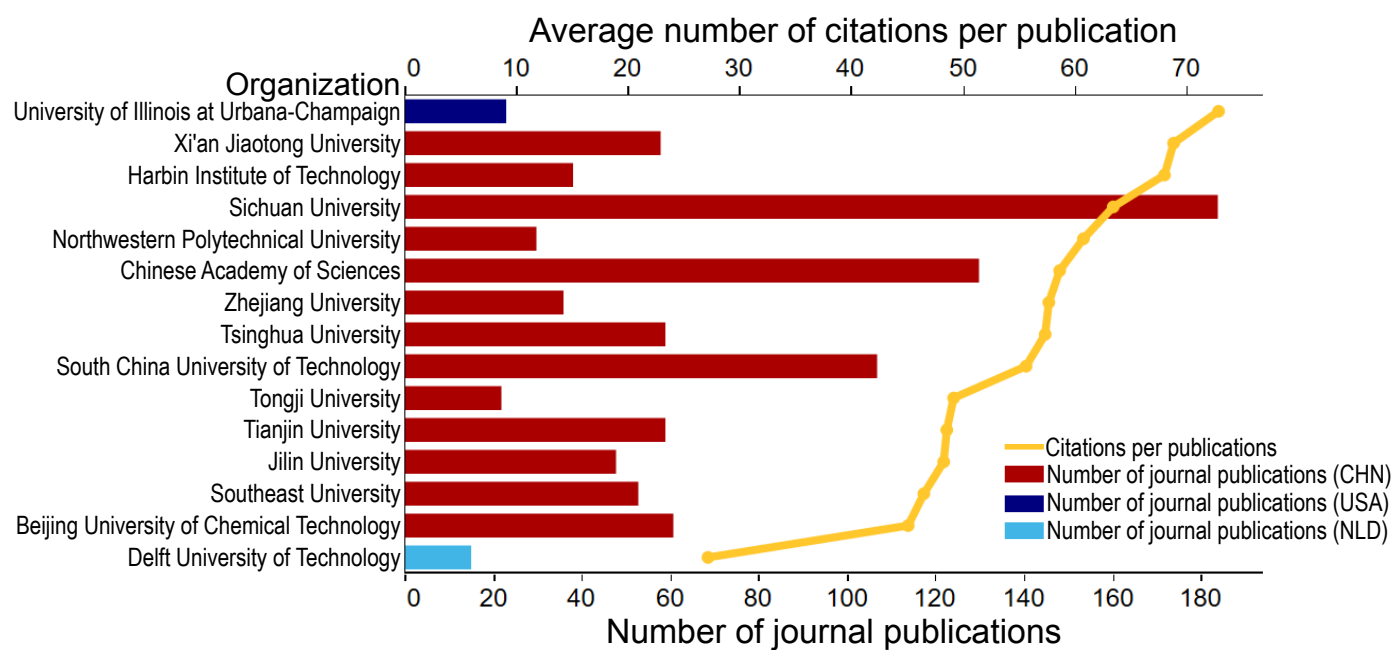


Figure 2. The top 15 research institutions in terms of average citations per publication (yellow line). Total publications from 2003-2023 shown as bars; colors of the bars indicating country/region of the institution.

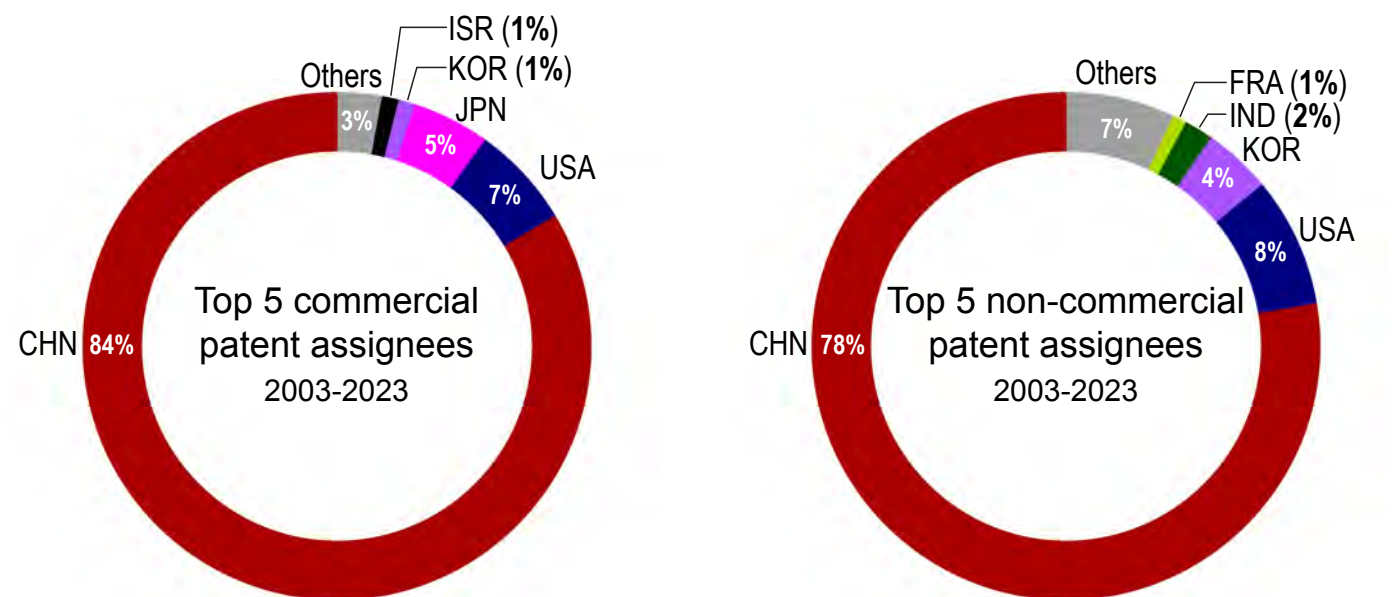


Figure 3. The top countries/regions in terms of number of self-healing biomaterials patent publications between 2003-2023, for commercial (left) and non-commercial (right) entities. (Reduced from the top 10 as shown in other chapters due to the relatively low number of patent publications below the top 5 assignee countries.)

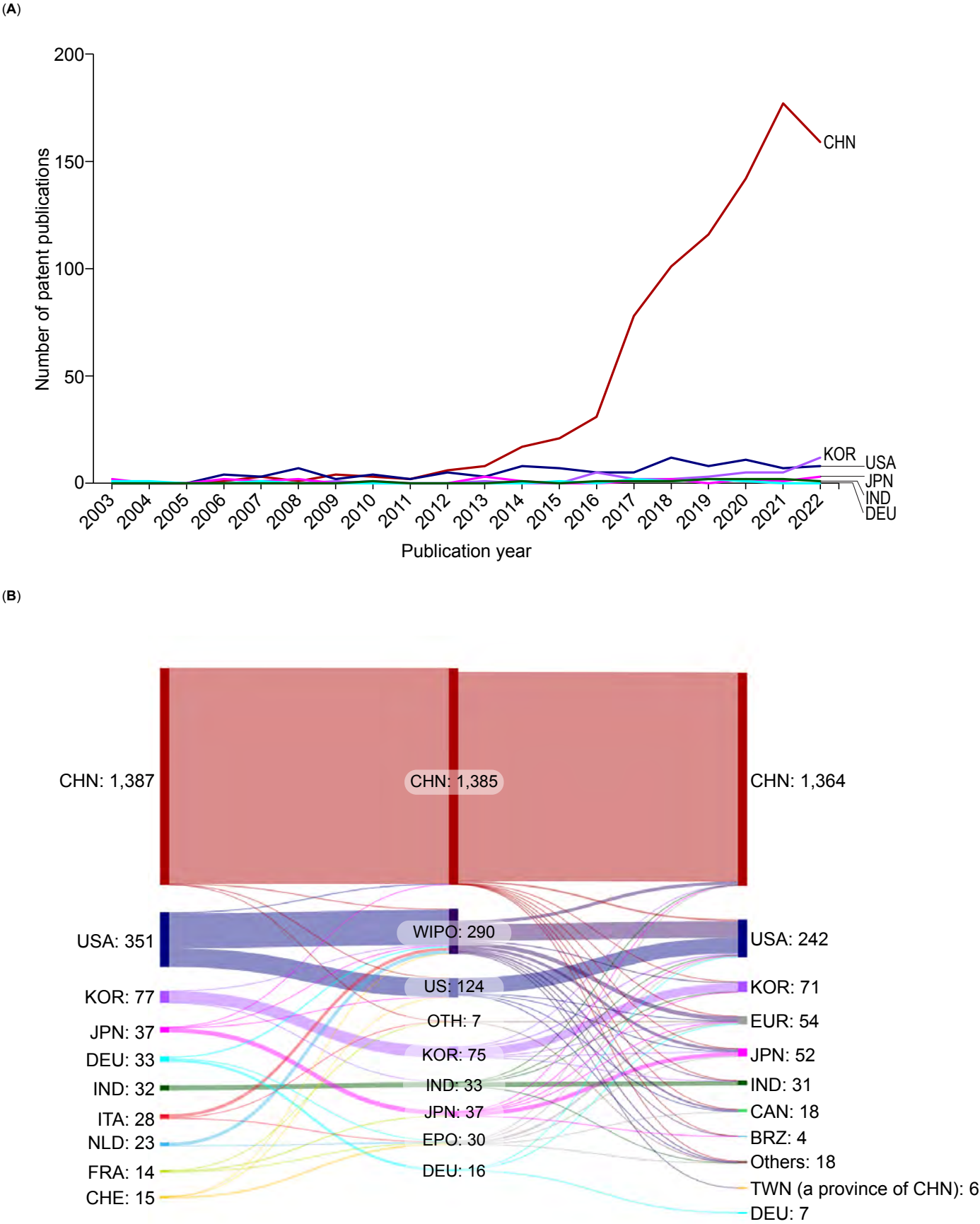


Figure 4. (A) Number of patent publications from the top six patent assignee countries/regions from 2003 to 2022. **(B)** Total patent flow between assignee countries/regions (top ten countries/regions in terms of total patent filings, left), the patent filing office where the first application in the patent family was filed (center) and the destination patent office for individual patent publication activities (right). Standard three letter codes utilized for countries/regions.

Self-healing mechanisms, materials, and applications

Chemical Mechanisms

A variety of chemical interactions can be used to impart self-healing properties to polymers. Hydrogen bonding, as described in the example in Section I, is one type of reversible interaction that is commonly used.^{7,8} Hydrogen bonds are weaker than covalent bonds and so, for this strategy to be effective, there must be a sufficient spatial density of hydrogen bonds. However, hydrogen bonding is a particularly convenient self-healing chemistry since it can be incorporated through several types of chemistry, allowing flexibility in material choice, and because broken hydrogen bonds can be re-formed at room temperature.⁹

Other commonly used non-covalent interactions to provide self-healing properties in polymers include hydrophobic,¹⁰ host-guest,¹¹ electrostatic, π - π stacking,¹² and metal-ligand coordination interactions, notably those between catechols and iron(III) ions.¹³

Dynamic covalent interactions can be used in a similar way to give materials self-healing properties. Within this group, dynamic Schiff base linkages are widely used for biomaterials,¹⁴ with their use growing significantly in the last 5 years. These linkages are based on reactions between a nucleophile and an aldehyde or ketone to form a bond, typically an imine or oxime, which is reversible in the presence of water. An example of this is a self-healing hydrogel based on a mixture of dialdehyde-modified hyaluronic acid and cystamine.¹⁵ Schiff base linkages are well-suited for biomaterial applications because they are easily formed at room temperature with no catalyst, and because the required chemical functionalities can be incorporated into hydrogel-forming polymers. Furthermore, the Schiff reaction is pH-sensitive, which can be used to further control the mechanical properties of gel structures based on their chemical environment, for example, to cause them to release a drug selectively in acidic environments.¹⁶ Self-healing properties can also be engineered

through the use of polymer side chains that participate in thermally induced reversible crosslinking via Diels-Alder reactions^{17,18} and Michael additions.¹⁹ With these mechanisms, higher temperatures (>100 °C) are generally required to induce self-healing, which limits their applications, but also provides an additional route to control their mechanical properties. Disulfide²⁰ and borate ester bonds²¹ are other reversible covalent bonds used in self-healing biomaterials.

A common approach in this field is to use multiple self-healing chemistries in the same material, to cover a range of mechanical properties and self-healing time scales. Recent examples include wound healing hydrogels that achieve self-healing through combinations of catechol-Fe coordination and Schiff base bonds,²² and a combination of Schiff base, hydrogen bonding, and π - π interactions,²³ and a hydrogel for wearable sensor applications that uses a combination of hydrogen bonding and boronic ester bonds.²⁴

Self-healing chemistry can also be synergistically combined with other polymer physics-driven processes to create multifunctional materials. An example of this is a hydrogel based on interpenetrating polyaniline/poly(4-styrenesulfonate) (PANI/PSS) that combines a strain-dependent electrical conductivity with self-healing abilities, and can be used for human motion sensing and other applications.²⁵ Self-healing properties were incorporated into the hydrogel by adding hydrogen bond linkages to the PSS before forming the interpenetrating network, in the form of 2-ureido-4[1H]-pyrimidinone groups.

A second example is a system developed by Bao et al. consisting of alternating layers of immiscible polydimethylsiloxane (PDMS) and polypropylene glycol (PPG), which re-align and heal themselves after being misaligned by cross-layer damage.²⁶ Macroscopic realignment of the 3-15 μ m thick layers is driven by their immiscibility, which causes the layers to minimize interfacial contact between PDMS and PPG and reestablish the PDMS-PPG stratification. Molecular-level self-healing, as well as planar adhesion between the dissimilar layers, is achieved by

adding H-bonding groups to both polymers.

Analysis of the CAS database shows the prevalence of hydrogels in the field of self-healing biomaterials. Hydrogels are employed as scaffolds for tissue regeneration,^{1, 27, 28} as wound dressings,²⁹⁻³² for drug delivery,³³ and several other applications. Hydrogels can be engineered to have other functional properties in addition to being self-healing. For example, Zhang et al.³⁴ fabricated a polymer hydrogel based on the thermo-responsive polymer poly(N-isopropylacrylamide) which swells around 20% in response to a temperature change of 20 °C. The material is also self-healing, based on host-guest orthogonal assembly that takes place in the mixture of star and linear forms of the polymer.

In general, self-healing materials can be classified in two ways: autonomic versus non-autonomic (based on whether an external stimulus is required to initiate healing), and intrinsic versus extrinsic (based on whether the material itself can self-heal, or an additional component is needed to initiate healing).³⁵ In the case of extrinsic self-healing materials, healing can be achieved through the release of material from inside embedded capsules,³⁶ hollow fibers,³⁶ or vascular networks^{37, 38} that rupture under stress. Based on the published literature on this topic, the vast majority of modern self-healing biomaterials use intrinsic mechanisms. Both autonomous and non-autonomous approaches are used, depending on the demands of the application (for example, if thermal or pH-responsiveness is useful to provide additional local control over self-healing).

Materials and Substances

The substances used most commonly in self-healing biomaterials research and development are presented in **Figure 5**. Polymers make up the largest group, with synthetic and natural polymers being used roughly equally. The next major categories are organic and inorganic molecules, followed by the pure elements, which can be further categorized into metals and non-metals. Other categories of substances found in self-healing materials are minerals such as hydroxyapatite, alloys such as stainless steel, and

coordination compounds.

Because hydrogels are a particularly active area of research in the context of self-healing biomaterials, we have also analyzed the subset of materials within our reference set that are used in self-healing hydrogels, shown in **Figure 6**. The top natural polymers used in self-healing hydrogels include chitosan, hyaluronic acid, sodium alginate, and cellulose.³⁹⁻⁴² The existence of multiple functional groups in these molecules, as well as the ability to chemically functionalize or modify them, help them to effectively crosslink, providing gel-like mechanical properties and self-healing ability.⁴³ Notable examples of chemically modified natural polymers are quaternized chitosan, which combines crosslinking sites and antimicrobial activity,⁴⁴ and oxidized hyaluronic acid, which contains aldehyde groups that can form Schiff base linkages.⁴⁵

Similarly, most of the top synthetic polymers in self-healing biomaterials, including polyethylene glycol, poly(vinyl alcohol) and poly(acrylic acid) are also used in hydrogels.⁴⁶⁻⁴⁸ Self-healing biomedical hydrogels can also use a mixture of gel-forming polymers in the same material to optimize performance, for example sodium alginate/PVA,⁴⁹ gelatin/PVA,⁵⁰ gelatin/chondroitin sulfate,⁵¹ and dialdehyde carboxymethyl cellulose/chitosan/poly(acrylic acid).⁵²

Within the non-metallic elements, forms of carbon including carbon fibers, carbon nanotubes,⁵³ graphene, and graphite fillers are used to impart specific mechanical and electrical properties. Silver, in powder form as well as silver nanoparticles, is used in medical dressings due to its antimicrobial properties,^{54, 55} while both materials are used in sensors.⁵⁶

Organic small molecules, including glycerol and acrylic acid, are primarily the starting materials for the polymers used in self-healing hydrogels and other applications.⁵⁷ Silica is the most widely used inorganic material; it can form a gel structure when chemically modified,^{58, 59} or can be used as an encapsulant for drug delivery.⁶⁰ Most other materials in this category are used in synthesis of self-healing materials, with the exception of iron

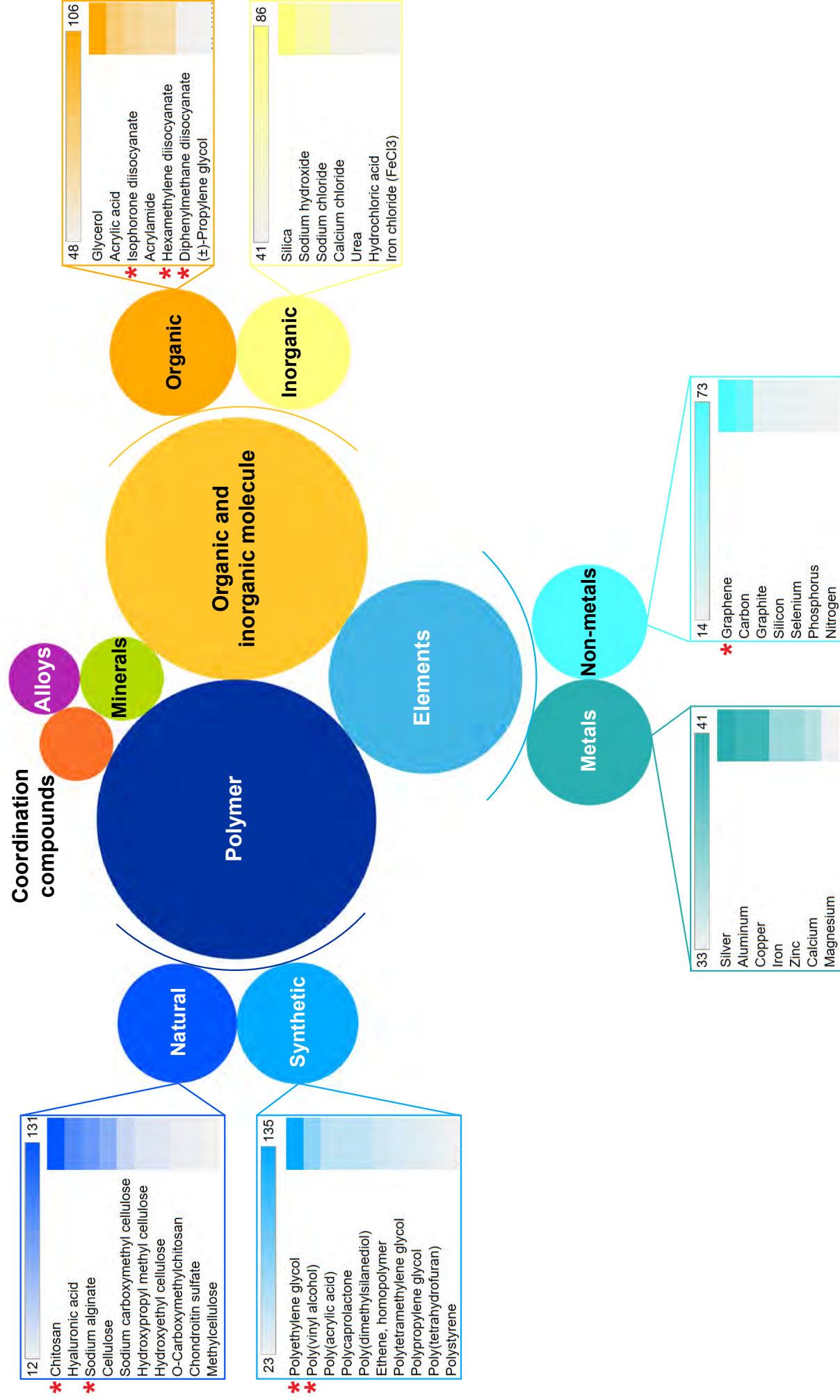


Figure 5. Bubble chart showing distribution of substances used in self-healing biomaterials in terms of number of publications (journals and patents) from 2003–2023. Size of the circles correspond to number of publications.

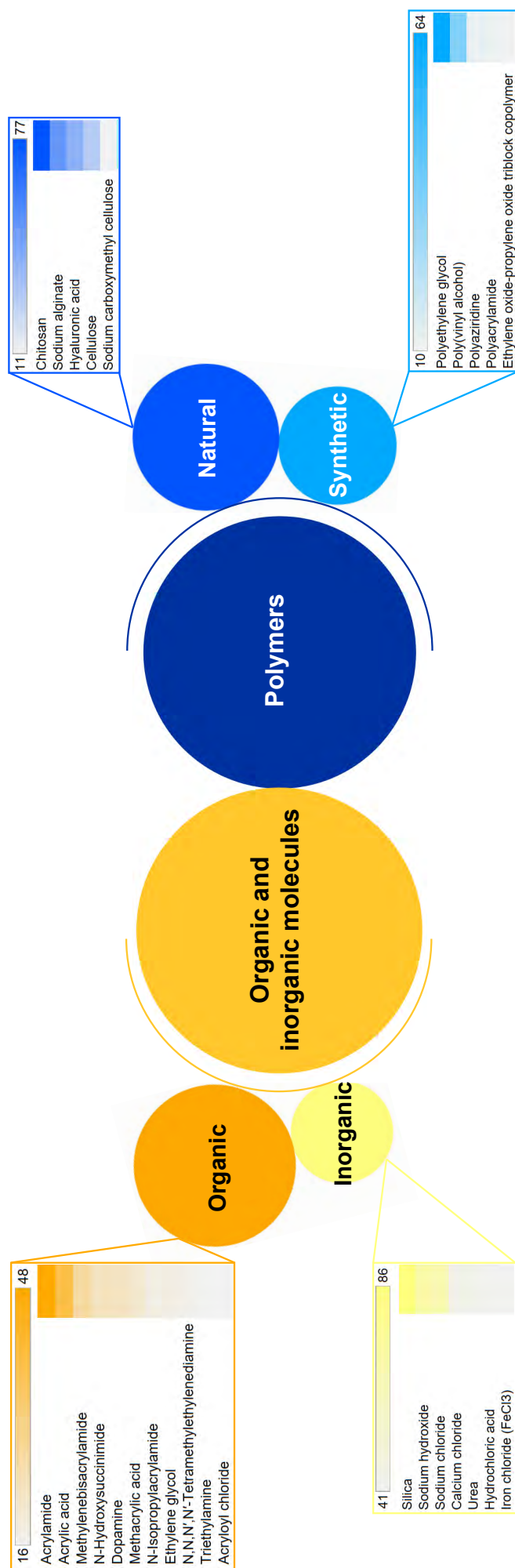


Figure 6. Bubble chart showing distribution of materials used in hydrogels in terms of number of publications (journals and patents) in self-healing materials over two decades (2003-2023). Size of the circles correspond to number of publications.

chloride, which can also be used to form dynamic crosslinks.

Among the minerals, hydroxylapatite is frequently used due to its biocompatibility and is widely used as filler in hydrogel and in bone related applications.⁶¹ The other notable minerals are talc, borax, montmorillonite, and gypsum. Borax, in particular, can be used to generate dynamic crosslinks leading to self-healing behavior in polymer systems.^{62, 63} Stainless steel and titanium-based alloys are the most commonly used alloys due to their inertness and mechanical strength.

In addition, we have also identified substances which showed the highest relative growth in their usage in journal and patent publications the last 5 years, to determine trends in emerging substances, as shown in **Figure 7**. The major category of substances in this list are diisocyanates, followed by alcohols, the natural polymers chitosan and sodium alginate, and graphene.

Diisocyanates are used in the synthesis of polyurethanes, which in turn indicates that polyurethanes are generally an emerging class of substance in the self-healing biomaterials.^{64, 65} Polyurethanes are commonly used as a basis for materials that use hydrogen bonding,⁶⁶ Diels-Alder reactions⁶⁷ and other mechanisms for self-healing. Polyurethanes are well-precedented in polymer chemistry, so their handling, reactivity,

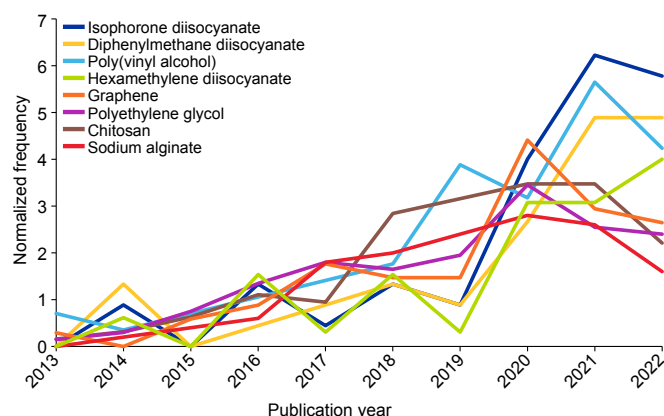


Figure 7. Normalized frequency of representative materials in journal and patent publications from 2013-2022.

and limitations are well-known. The alcohols in this list are commonly used as starting materials for polymers, including polyoxyalkylenes.

Chitosan, sodium alginate, and graphene are common materials in self-healing hydrogels. Overall, these emerging substances suggest that polymers, primarily polyurethanes, and hydrogels are the most actively researched in self-healing biomaterial applications.

In a similar way, we can identify self-healing mechanisms that are increasingly being used in biomedical applications.^{1, 6, 68, 69} As discussed earlier in this section, there are a variety of chemical mechanisms used for self-healing, which can involve non-covalent or reversible covalent interactions.

The plot in **Figure 8** shows how frequently different self-healing mechanisms have been referenced in journal and patent publications over time, from 2013-2023. From this analysis, we see that the most frequently mentioned mechanisms involve hydrogen bonding, Schiff base formation, and metal coordination bonding.

Applications

The development of self-healing materials has significantly contributed to the advancement of several biomedical applications. Specifically, they have found applications in medical devices, drug delivery systems, and tissue engineering,

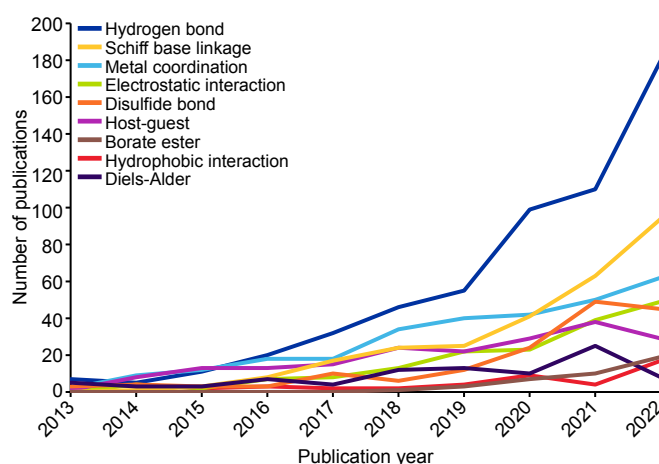


Figure 8. Count of journal and patent publications referencing self-healing mechanisms from 2013-2022.

eventually improving patient outcomes and enhancing the quality of life. These applications, and the substances most commonly associated with them, are shown in **Figure 9** as a heat map.

One prominent application area for self-healing coatings and polymers is tissue regeneration and wound care.^{30, 70} Self-healing coatings and polymers are not only injectable, but can also be engineered to have antibacterial properties based on photothermal response,¹³ or through the incorporation of antibacterial materials such as quaternized chitosan,⁷¹ moxifloxacin,⁷² or Mxenes.⁷³ Through these combined effects, self-healing wound dressings reduce patient suffering, speed up the healing process, and lower the chance of infection.

An example of the use of self-healing materials for wound healing is a hydrogel developed by Zhang et al. that can be injected into irregular deep burn wound beds.⁷⁴ This hydrogel is fabricated from carboxymethyl chitosan (CMC) and dialdehyde-modified cellulose nanocrystals (DACNC), which

are derived from the naturally occurring polymers chitosan and cellulose. Dynamic Schiff base linkages between the amine groups of CMC and the DACNC allows this material to immediately self-heal after injection to form an integrated hydrogel that completely fills the wound and protects it from the external environment.

In a second example, Luo et al. developed a series of N-carboxyethyl chitosan- and sodium alginate-based injectable self-healing antibacterial hydrogels containing CuS nanoparticles.⁷⁵ The physical properties of this material could be further tuned by adjusting the oxidized sodium alginate (OA) content, with the storage modulus increasing at higher OA content due to the higher density of imines. Conductive, self-healing gels for wound treatment have also been demonstrated. For example, Jiang et al. reported an injectable, biocompatible, self-healable, and conductive material made from poly(3,4-ethylenedioxythiophene):poly(styrenesulfonate) (PEDOT:PSS) and guar slime for healing wounds in parts of the body that undergo stretching such as knees and elbows.⁷⁶

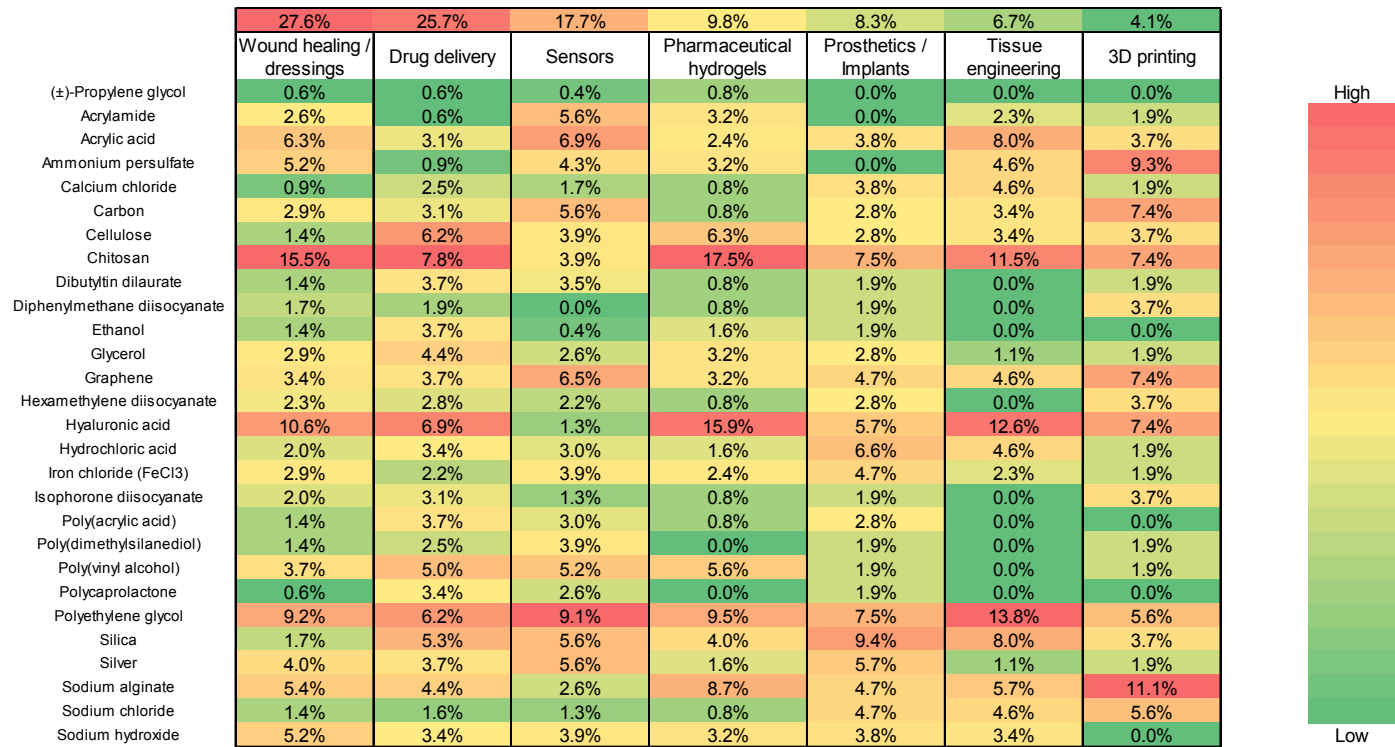


Figure 9. Heat map of the relationship between the most commonly used substances in self-healing materials and the most common material applications. Relative frequencies of each substance have been calculated within each application category.

Since 2015, biomedical hydrogels with self-healing properties have gained attention as promising options for tissue engineering and regenerative medicine. Self-healing scaffolds that can repair themselves after damage are being investigated in regenerative medicine to promote the development of tissues and organs *in vitro* and *in vivo*.^{77, 78}

Hwang et al. developed a mechanically compliant interpenetrating polymer network (IPN) hydrogel using polyacrylamide (PAAM) and gelatin. The PAAM/gelatin hydrogel matched with the native vocal fold tissue in physical and chemical properties, and thus, functioned as an adhesive artificial tissue implant for voice recovery.⁷⁹

The development of medical implants and devices is another use of self-healing materials in biomedicine. In recent years, injectable self-healing hydrogels have shown promise as part of minimally invasive surgical approaches to treating issues in the brain and nervous system.^{80,}

⁸¹ For example, Hsu et al. developed a semi-interpenetrating network polymer composed of hyaluronan and chitosan to make an injectable, self-healing hydrogel to deliver neural stem cells as a treatment for traumatic brain injury.⁸²

Implants such as vascular stents, prosthetic joints, and pacemakers undergo constant wear in the body. The longevity of these devices can be increased by using materials and coatings which can self-heal microscale damage from corrosion or mechanical forces. This improves the reliability and safety of these devices while reducing the need for frequent replacements.^{83, 84}

Using injectable self-healing materials for drug delivery is an interesting new direction of research and application. Self-healing materials can be loaded with drugs, for example via microcapsules, and designed to release them gradually, in targeted locations, or in response to an external stimulus. Here, self-healing properties aid in controlling the properties of the drug-releasing medium after injection, improving therapeutic efficacy.^{85, 86} One common example is pH-

responsive injectable drug delivery gels, which have been designed to break down in acidic environments, allowing for targeted local delivery for cancer and infection treatment.⁵⁸ In these applications, the self-healing property of the gel allows it to recover its rheological properties after injection, and to repair itself macroscopically if it breaks apart.

Mooney et al. developed an alternate drug release strategy which uses ultrasound to disrupt ionically crosslinked hydrogels.⁸⁷ In this study, the chemotherapy drug mitoxantrone was selectively released from a self-healing injected alginate hydrogel *in vivo* using an ultrasonic horn. The researchers also demonstrated similar ultrasonically-driven drug release with other molecules, proteins, and condensed oligonucleotides using alginate and chitosan-based gels. In 2019, Ji et al. reported a structure-switchable coating based on poly(ϵ -caprolactone)-poly(ethylene glycol)-poly(ϵ -caprolactone) triblock copolymer network.⁸⁸ After absorbing water and freeze-drying, this coating adopted a microporous morphology. However, on mild heating ($\sim 40^\circ\text{C}$), it switched back to a pore-free structure within as little as 5 seconds.

Self-healing materials can also be used in biomedical sensing applications.^{89, 90} In 2020, You et al. reported autonomously ultrafast self-healing poly(sebacoyl 1,6-hexamethylenedicarbamate diglyceride) (PSeHCD) elastomers for bioelectronics⁹¹ that could also be re-processed into different shapes. Similar to the naturally occurring peptidoglycan structure, PSeHCD was designed with repeating units that contained both ester and urethane groups. The ester groups conferred biodegradability, while the urethane groups enabled the formation of extensive and uniformly distributed hydrogen bonds, which gave the elastomers the ability to rapidly self-heal. The material was also easily reprocessed into different shapes by placing it in a mold at elevated temperatures. This reprocessability was possible due to the high density of H-bonds in the polymer network, which controlled the structure but could be dissociated on heating.

Notable journal articles and patents

Table 1 is a set of research articles published from 2020–2023 that represents emerging trends in the field of self-healing biomaterials. These articles were selected to represent the range of materials and applications being studied today, in combination with other factors including journal impact factor and number of citations.

Notable examples from the table include a quaternized chitosan-based self-healing hydrogel that possesses protocatechualdehyde–ferric iron as a crosslinker to enhance the reversibility of pH-responsive aldehyde–Fe bond and Schiff base bond formation developed by Guo et al.²² This hydrogel demonstrates injectability, biocompatibility, reversible adhesion, and effective wound healing in a rat model. The adhesive strength of the hydrogel in the presence and absence of deferoxamine mesylate (a chelating agent) provides evidence for the reversibility of adhesion. The antimicrobial property of this chitosan-based hydrogel is also significant, and is based on a photothermal effect. This dual cross-linked chitosan-based hydrogel sealant has potentials to be broadly applied to infected wound healing.

Earlier in 2023, Fu et al.⁹² described a composite material based on a soft self-healing polyurea (SSPU) coupled with the gallium–indium–tin eutectic alloy Galinstan. SSPU was obtained from the reaction of bis(3-aminopropyl)-terminated poly(dimethylsiloxane) (PDMS, $M_n=3000$), trimethyl hexamethylene diisocyanate (THI), and 3,3'-dimethyl-4,4'-biphenylene diisocyanate (DBI). The self-healing activity is driven by the dynamic hydrogen bonding between THI and DBI, while Galinstan increases the fracture toughness to prevent mechanical failure without softness loss. This approach can effectively prevent the materials from crack propagation. This material could be further used in capacitive strain-sensors in human-machine interfaces, bioelectronics, and even soft robotics for applications of biomimicry.

Maxillofacial hard tissue regeneration such as dentin and bone is challenging because of material expense, the risks of autologous or allogeneic transplantation, and the ineffectiveness of mineral materials alone. To resolve this issue,

Guo et al. synthesized a mineralized hydrogel, polyacrylic acid (PAA)-carboxymethyl chitosan (CMC)-treated dentin matrix (TDM), which is self-repairable and injectable.⁹³ This hydrogel composite contains amorphous calcium phosphate forming reversible coordination bonds between CMC and PAA, followed by dynamic ionic and hydrogen bonds formation within the stabilized TDM structure. This study showed that this PAA-CMC-TDM hydrogel retains its bioactivity and promotes the regeneration of dentin/bone hard tissue.

Table 2 lists notable patent documents (granted patents and applications) in the field of self-healing biomaterials published from 2018 to 2023. Patents were selected based on relevance, novelty, applicability, and field of study.

Notable examples include CN114246982A, assigned to Nanjing Drum Tower Hospital. This patent application discloses an injectable hydrogel based on a mix of a 4-arm benzaldehyde-terminated PEG with carboxymethyl chitosan to improve the delivery of mesenchymal stem cells to specific parts of the body

CN111068107A (Shanghai Jiaotong University) describes a fiber-hydrogel composite scaffold for use in regeneration of tissues such as muscle. The fiber is electrospun from a mixture of graphene, melatonin, and a biocompatible polymer such as polylactic acid or polycaprolactone, while a hyaluronic acid derivative is used as the hydrogel matrix.

In WO2023084521A1 (Technion Research and Development Foundation Limited), a self-healing (disulfide based) wound dressing is described that also contains embedded sensors for measuring glucose level, pH, and temperature. The prevalence of hydrogel-based self-healing materials in these patent examples is a reflection of the growing use of hydrogels in this area. However, CN116284671B provides a recent example of a non-hydrogel based self-healing biomaterial. This patent describes the synthesis of a heparin-functionalized polyurethane, which has self-healing properties based on hydrogen bonding and disulfide bonds. This material is intended for use in medical implants.

Table 1. Notable journal publications in self-healing biomaterials in recent years.

Year	Title	Journal	Research Institute	Summary
2020	Muscle-Inspired Self-Healing Hydrogels for Strain and Temperature Sensor ⁹⁴	ACS Nano	Nanjing Tech University	Polyaniline nanofibers (PANI NFs) are incorporated into a poly(acrylic acid) (PAA) hydrogel to fully mimic the microstructures and multifunctionalities of human muscle
2020	Physical Double-Network Hydrogel Adhesives with Rapid Shape Adaptability, Fast Self-Healing, Antioxidant and NIR/pH Stimulus-Responsiveness for Multidrug-Resistant Bacterial Infection and Removable Wound Dressing ¹³	Advanced Functional Materials	Xi'an Jiaotong University	A hydrogel adhesive made up of catechol-Fe ³⁺ coordination cross-linked poly(glycerol sebacate)-co-poly(ethylene glycol)-g-catechol and quadruple hydrogen bonding cross-linked ureido-pyrimidinone modified gelatin
2020	Resilient yet entirely degradable gelatin-based biogels for soft robots and electronics ⁹⁵	Nature Materials	Johannes Kepler University Linz	A versatile self-adhering gelatin-based biogel derived entirely from natural and food-safe constituents
2021	Dual-Dynamic-Bond Cross-Linked Antibacterial Adhesive Hydrogel Sealants with On-Demand Removability for Post-Wound-Closure and Infected Wound Healing ²²	ACS Nano	Xi'an Jiaotong University	A series of adhesive antioxidant antibacterial self-healing hydrogels fabricated through dual-dynamic-bond cross-linking among ferric iron (Fe), protocatechualdehyde (PA) containing catechol and aldehyde groups and quaternized chitosan (QCS)
2022	Molecular Design and Preparation of Protein-Based Soft Ionic Conductors with Tunable Properties ⁹⁶	ACS Applied Materials & Interfaces	Westlake University	Silk-based soft ionic conductors fabricated using silk proteins and calcium chloride
2023	Bioactive self-healing hydrogel based on tannic acid modified gold nano-crosslinker as an injectable brain implant for treating Parkinson's disease ⁹⁷	Biomaterials Research	National Taiwan University	A bioactive self-healing hydrogel comprising chitosan crosslinked by the oxidized tannic acid-modified gold nano-crosslinker
2023	Biomimetic mineralization-inspired mineralized hydrogel promotes the repair and regeneration of dentin/bone hard tissue ⁹³	NPJ Regenerative Medicine	Sichuan University	A composite mineral matrix hydrogel PAA-CMC-TDM containing amorphous calcium phosphates (ACPs), polyacrylic acid (PAA), carboxymethyl chitosan (CMC) and dentin matrix (TDM)
2023	A self-healing electrically conductive organogel composite ⁹⁸	Nature Electronics	Carnegie Mellon University	A poly(vinyl alcohol)-sodium borate-based organogel composite embedded with silver microflakes and gallium-based liquid metal microdroplets
2023	Vascular smooth muscle-inspired architecture enables soft yet tough self-healing materials for durable capacitive strain-sensor ⁹²	Nature Communications	Nanjing University of Science and Technology	A class of core-shell structured liquid droplets, i.e., gallium-indium-tin eutectic alloys (Galinstan) wrapped with thin oxide layer introduced into a soft self-healing polyurea (SSPU) through robust interfacial coordination interactions, forming a synthetic structure similar to that of vascular smooth muscles
2023	Ultrarobust subzero healable materials enabled by polyphenol nano-assemblies ⁹⁹	Nature Communications	Sichuan University	An ultrarobust subzero healable glassy polymer fabricated by incorporating polyphenol nano-assemblies with numerous end groups into polymerizable deep eutectic solvent (PDES) elastomers

Table 2. Notable patent documents in self-healing biomaterials in recent years.

Patent or Publication number	Publication year	Patent assignee	Title	Description of patented technology
CN114479124B ¹⁰⁰	2023	Chinese Academy of Medical Sciences and Peking Union Medical College	Preparation of self-healing hydrogel with good antibacterial activity for preparing wound dressing	Self-healing, antibiotic, non-cytotoxic hydrogel based on quaternized chitosan and glucomannan used for wound healing
CN114246982A ¹⁰¹	2022	Nanjing Drum Tower Hospital	Injectable self-healing hydrogel loaded with mesenchymal stem cells (MSCs), its preparation method and application	Injectable hydrogel consisting of a mixture of 4-arm benzaldehyde-terminated PEG with carboxymethyl chitosan, intended to improve the delivery of mesenchymal stem cells to specific parts of the body
CN113583262B ¹⁰²	2022	Sichuan University	Near-infrared response hyaluronic acid hydrogel for articular cartilage repair and preparation method thereof	Hydrogel used for cartilage repair, based on a mixture of azobenzene-modified hyaluronic acid and cyclodextrin-modified hyaluronic acid. The non-covalent crosslinking density of the gel is reduced by exposure to near-infrared light, causing it to change its mechanical properties and friction coefficient.
CN113384754B ¹⁰³	2022	First Affiliated Hospital of Jinan University	Preparation method of injectable self-healing hydrogel for promoting regeneration of periodontal tissues	Mixed aldehyde-modified hyaluronic acid / hydroxyethyl chitosan hydrogel used to fill defects and promote periodontal tissue regeneration. The hydrogel releases drugs and converts from a gel to a solution slowly over time.
WO2023084521A1 ¹⁰⁴	2023	Technion Research and Development Foundation Limited	Biocompatible self-healing polymers and uses thereof	"Smart", self-healing wound dressing material based on an aliphatic disulfide-containing polyurethane containing embedded sensor for measuring glucose, pH, or temperature.
CN111068107A ¹⁰⁵	2020	Shanghai Jiaotong University	Three-dimensional bionic self-healing hydrogel fiber scaffold composition and preparation method and application thereof	A fiber-hydrogel composite scaffold where the fiber is electrospun from a mixture graphene, melatonin, and a biocompatible polymer (polylactic acid, polycaprolactone given as examples), and the hydrogel is a hyaluronic acid derivative.
WO2023009830A1 ¹⁰⁶	2023	Becton, Dickinson and Company	Self-healing thermoplastic elastomer composition	A membrane containing a styrenic block copolymer that prevents leaks and re-seals when punctured with a needle for medical applications.
CN116284671B ¹⁰⁷	2023	Suzhou Xinrui Medical Technology Co., Ltd.	Production of heparin-like polyurethanes with self-repairing property using polyether polyols	Synthesis of a heparin-functionalized polyurethane with self-healing properties based on hydrogen bonding and disulfide bonds
CN116440066A ¹⁰⁸	2023	Zhengzhou University	Strong antioxidant and rapid antibacterial wound repair self healing pharmaceutical hydrogels with strong adhesion and promoting blood vessels	Gel containing PVA, oligomeric procyanidine, borax, and Fe ³⁺ . Self-healing properties are based on hydrogen bonds, B-O bonds, and Fe ³⁺ coordination complexes.
US20190298852A1 ¹⁰⁹	2019	Industry-University Cooperation Foundation Hanyang University	Glycol chitosan-based hydrogel capable of exhibiting self-healing behavior in the presence of iron oxide nanoparticles without the use of toxic crosslinkers, and use in drug delivery	Hydrogel consisting of only natural polysaccharides (glycol chitosan and oxidized hyaluronate) and iron oxide nanoparticles, with no crosslinkers. The self-healing mechanism in this material can be controlled using a magnetic field through the nanoparticles.

Challenges and perspectives

Self-healing materials have emerged as a promising class of materials with applications in several aspects of biomedicine, and significant attention has been focused on the development and characterization of these materials with a view toward these applications.

One of the applications where self-healing materials have shown significant potential is wound healing. While several types of wound dressings with self-healing properties have already been developed, obstacles remain to developing smart wound dressings.⁴

According to our analysis, as shown in **Figure 9**, in the natural polymer category, cellulose-based materials are used in wound healing research at a relatively lower level compared to chitosan, hyaluronic acid, and alginate. Cellulose and its derivatives have received research attention in other fields because of its widespread availability, low cost, and mechanical strength. However, the mechanical properties of cellulose, including its Young's modulus ranging from 20 to 355 GPa,¹¹⁰ may impede its application in wound healing as a soft and injectable material without further modification. The stiffness of cellulose makes it unsuitable for soft tissues/organs like skin and other parts of the body that are frequently in motion.

Instead, in recent years cellulose has been utilized as a reinforcing agent to modify the stiffness of self-healing base materials such as chitosan,^{74, 111, 112} poly(vinyl alcohol),¹¹³ and poly(vinyl alcohol)-borax (PB).^{114, 115} Nanocrystalline cellulose, cellulose nanofibers, and their modified species increases the stretchability of self-healing composite hydrogels significantly. Recently, injectable, self-healing cellulose-containing hydrogels have been reported for wound healing applications.^{116, 117} These examples suggest that, while the use of cellulose in wound healing materials is challenging, it has the potential to become one of the primary natural materials in this field, as a reinforcing agent or a base material.

Due to their use in highly dynamic environments, flexible biosensors can benefit from the incorporation of self-healing materials^{94, 118} (this is reflected by the prominence of sensor applications as shown in **Figure 9**). Materials used in flexible biosensors have several other key requirements, including stretchability, conductivity, durability, softness, and biocompatibility.¹¹⁹⁻¹²¹ The analysis presented in Section III indicates that the use of natural polymers in sensors remains challenging, likely due to poor conductivity and stretchability.¹²² For this reason, natural polymers like chitosan have been combined with synthetic polymers and ionic compounds to form self-healing composite hydrogels with metal coordination bonds and hydrogen bonds that results in electroconductive, durable, stretchable, and sufficiently soft materials for biosensor use.^{122, 123} These examples indicate the potential of using natural polymers with novel modifications to achieve multifunctional biosensors and other biomedical devices, in addition to incorporating self-healing properties.¹²⁰

Another potential future research direction is the development of self-healing wound dressings that are also stimulus-responsive, making them capable of responding to changing conditions such as temperature and pH. While new self-healing materials and novel mechanisms have been introduced into wound dressings¹²⁴ the safety and toxicity of the materials needs to be thoroughly investigated.⁴

The use of self-healing hydrogels in many applications (as shown in **Figure 9**) has driven research into their rheological properties and their responsiveness to external stimuli such as pH, temperature, and stress, and into theoretical models of their properties.^{1125, 126} The use of machine learning to develop more detailed models of polymer dynamics, including their non-covalent bond interactions, has been reported recently.¹²⁷⁻¹²⁹ In this area, more extensive use of computational tools to predict the properties of multifunctional composites should reduce the experimental costs of developing self-healing materials.

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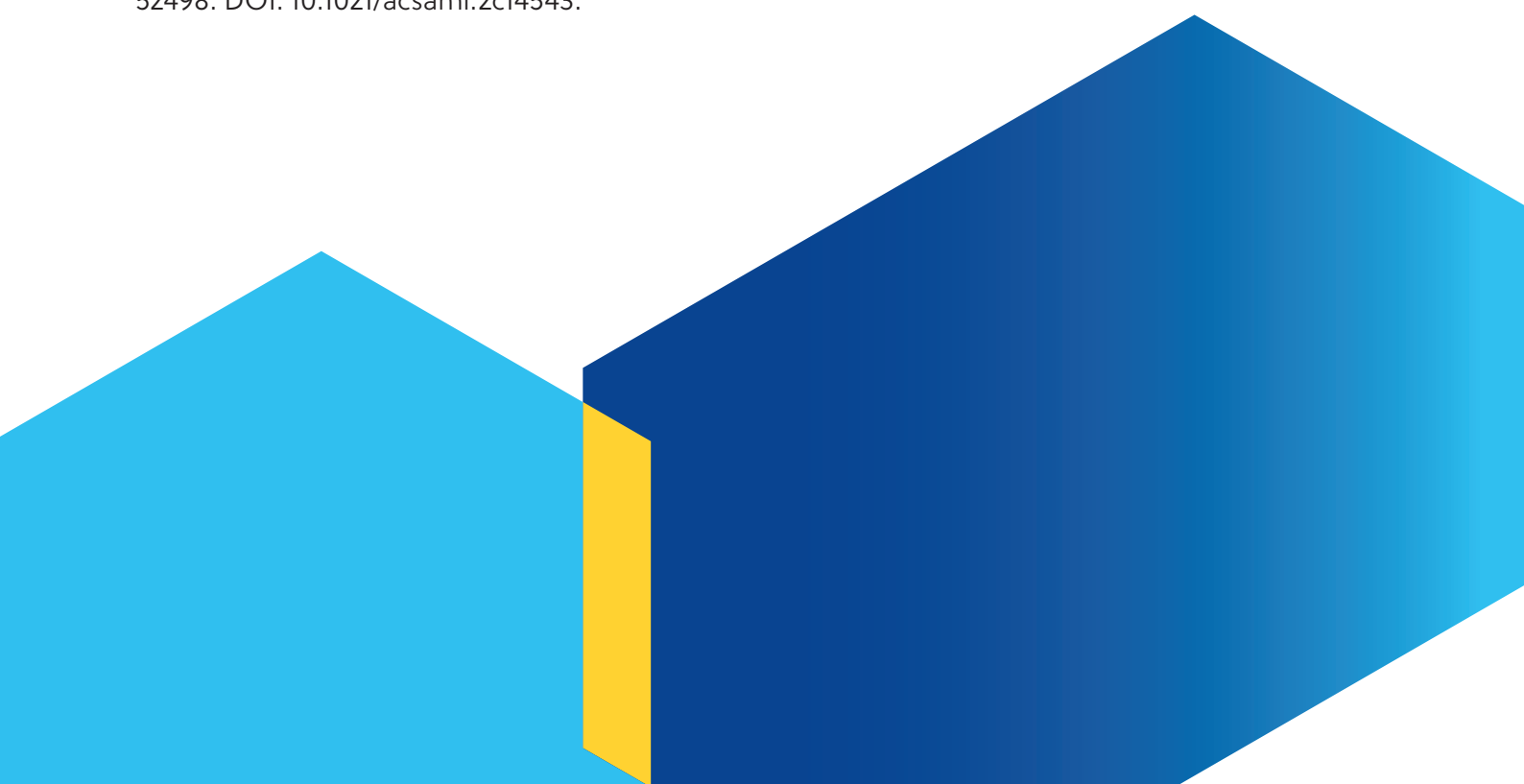
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VIII. Bioelectronic materials

Introduction

Bioelectronics is an interdisciplinary field in which electronic devices are integrated into biological systems, including the human body.¹⁻⁵ Integration can take the form of implantation or attachment to the skin. The emergence of bioelectronics as an active research topic has led to a new realm of possibilities that bridge the gap between micro- and nano-electronics and living organisms.

Bioelectronics involves the development of new devices, often using novel materials and methodologies, that allow electronic systems to interface with biological components at the molecular, cellular, and organ levels. This approach capitalizes on the intrinsic ability of living organisms to sense, process, and respond to external stimuli, in combination with the precision and speed of modern electronic components. This combination has unlocked a diverse range of applications that hold significant promise across various sectors, such as real-time monitoring of brain activity or heart rate, delivering therapeutic electrical signals or drugs, chemical sensing, and new prosthetic devices.

Bioelectronics heavily relies on an array of specialized materials that enable effective integration with biological tissue. One example is organic electronics,⁶⁻⁸ including organic semiconductors and conductive polymers. These materials can offer advantages such as flexibility and biocompatibility, making them ideal for creating interfaces that seamlessly interact with biological tissues. Biodegradable materials which can be resorbed by the body and used to make transient bioelectronic devices, are a second important class of materials which appear prominently in the literature.^{4, 9, 10}

The materials used in bioelectronic devices are engineered to have specific, application-dependent properties that are critical to their performance. Examples of these properties include:

- a. Softness and stretchability
- b. Adhesion to biological tissues
- c. Biocompatibility, non-toxicity, resistance to fouling, and reduced inflammatory response
- d. Bioresorbability
- e. Mechanical durability
- f. Large response to physical stimuli (piezoelectric response, for example)
- g. Large electrical response to chemical environment
- h. Electrical and ionic conductivity
- i. Effective ionic-electronic transduction

The requirements for these properties are often beyond what is typically found in other applications. For example, since electrical signals are usually carried by ions in biological systems, materials that form the interface between electronics and living tissue must effectively convert from electron- to ion-based signaling.¹¹⁻¹³ In addition, these materials must simultaneously have mechanical properties that are well matched to the biological material they are in contact with, so that they can move with the body and maintain physical comfort. For example, a low Young's modulus may be needed for a bioelectronic material that is used at an organ interface.¹⁴ Any materials implanted in the body must also be biocompatible, and resist biofouling over time.¹⁵

In this report, we will analyze substance, function, and application data from approximately 50,000 journal and patent publications from 2003-2023 to examine trends and connections in these areas. In addition, we will focus on identifying emerging trends and materials.

Journal and patent publication trends

The number of bioelectronics-related journal and patent publications between 2003 and 2023 is shown in **Figure 1**. Two notable trends are observed in this data. First, we see a substantial increase in the number of journal publications from 2017 to 2022. Second, the ratio of journal to patent publications also increased during this period. This trend suggests an increase in the amount of academic research in the last five years which has not yet resulted in commercialization.

Among the top 100 research institutions in terms of number of journal publication, the top 15 based on the average number of citations per publication are shown in **Figure 2**. This statistic provides a measure of the average impact per publication. Most of the top institutions based on this ranking are in the US or China, with the top institutions in terms of average number of citations and total number of publications being Massachusetts Institute of Technology and the Chinese Academy of Sciences, respectively.

Figures 3 and 4 summarize patent activity in

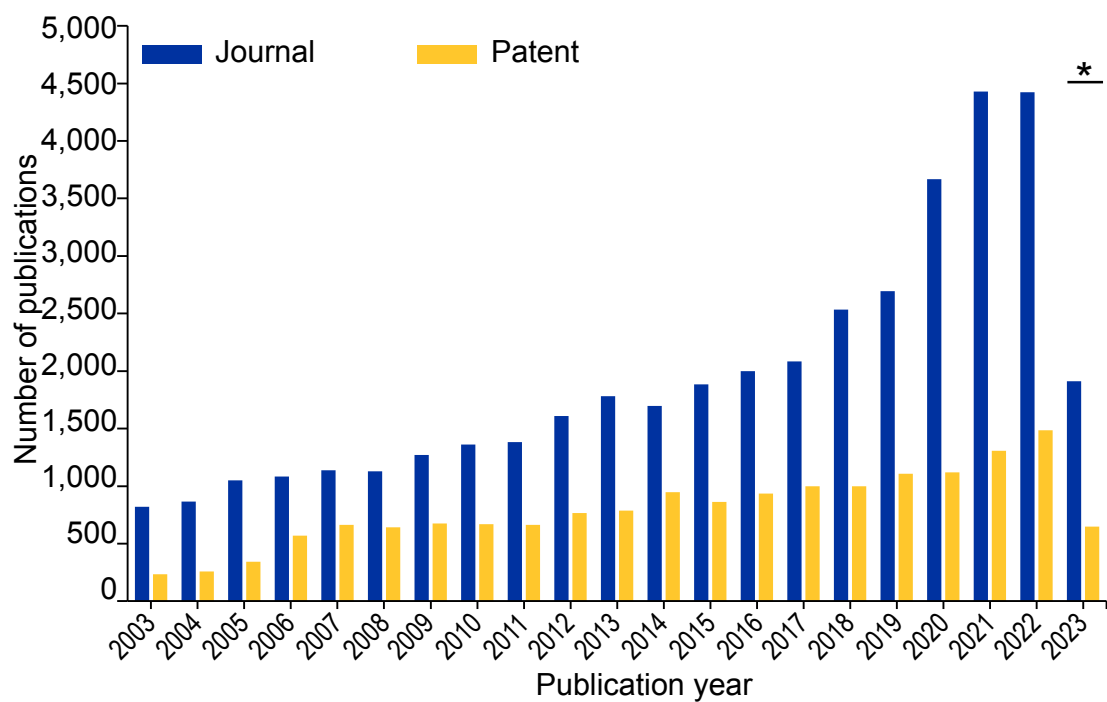


Figure 1. Number of journal and patent publications per year in the bioelectronics field from 2003 to 2023 (journals: blue bars, patents: yellow bars). * The data for 2023 only include months from Jan to Aug.

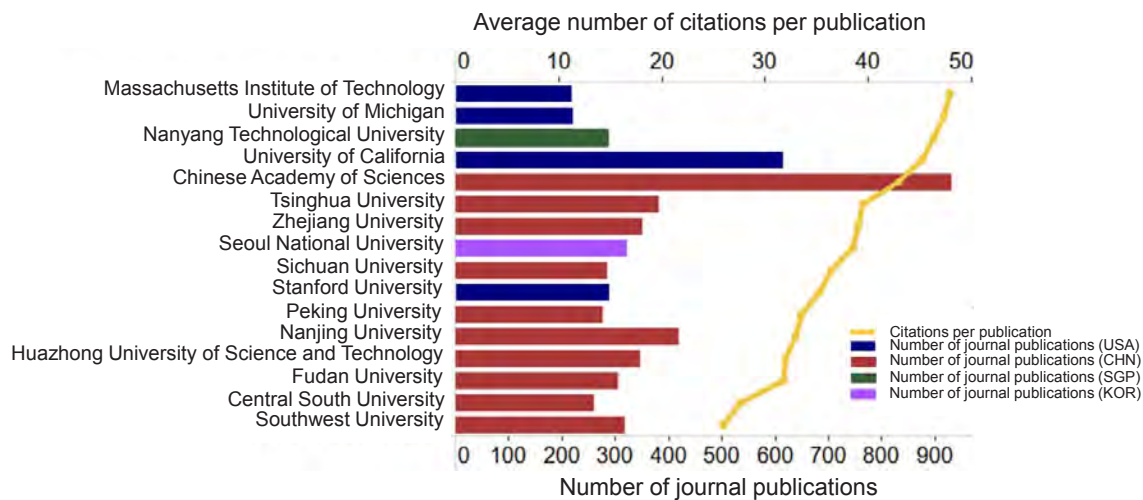


Figure 2. The top 15 research institutions in terms of average citations per publication (yellow line). Total publications from 2003-2023 shown as bars; colors of the bars indicating country/region location (blue: USA, red: China, dark green: Singapore, purple: Korea).

the area of bioelectronic materials. In **Figure 3**, the top patent assignees are separated into commercial and non-commercial entities. This analysis shows that the most commercial patent activity has been generated by companies in the US, in terms of number of patent families generated, while non-commercial patent activity is driven more by institutions in China. A notable exception to this is the University of California, which has been listed as the assignee on more patent publications than any other research institution. Part of the reason for this is that University of California is an assembly of 10 separate public universities.

The trend of patent publications over time shown in **Figure 4A** indicates that patent activity has

grown more significantly in China compared to the US, particularly since 2017. The relative amount of patent publications has also grown significantly in Korea in the last 10 years.

Figure 4B shows the flow of patent activities through national patent offices and the Patent Cooperation Treaty (PCT) system. Here, an activity is defined as an event where a patent document, either an application or a granted patent, is published. The left column shows the top ten patent assignee countries/regions in terms of number of patent activities. The right column shows the patent office where the patent activity took place. The center column, connecting the two, indicates the office where the first patent in the family was filed.

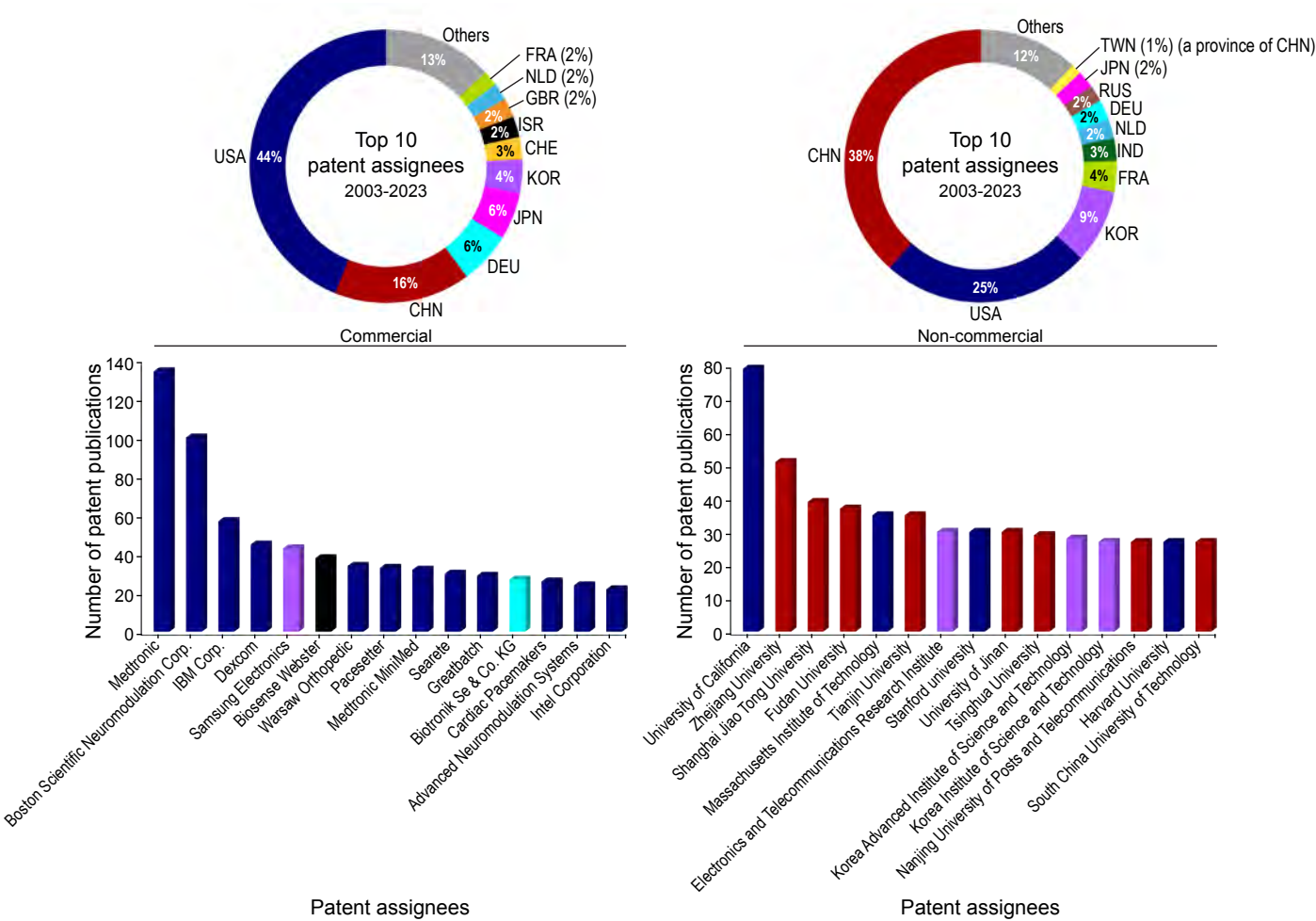


Figure 3. Top panel: The top 10 countries/regions in terms of number of patents published between 2003-2023. Lower panel: The top 15 patent assignees in the field of bioelectronics in the same time period. Both panels are divided into commercial and non-commercial entities. Bar graph has been color coded by country/region to match color scheme in donut charts.

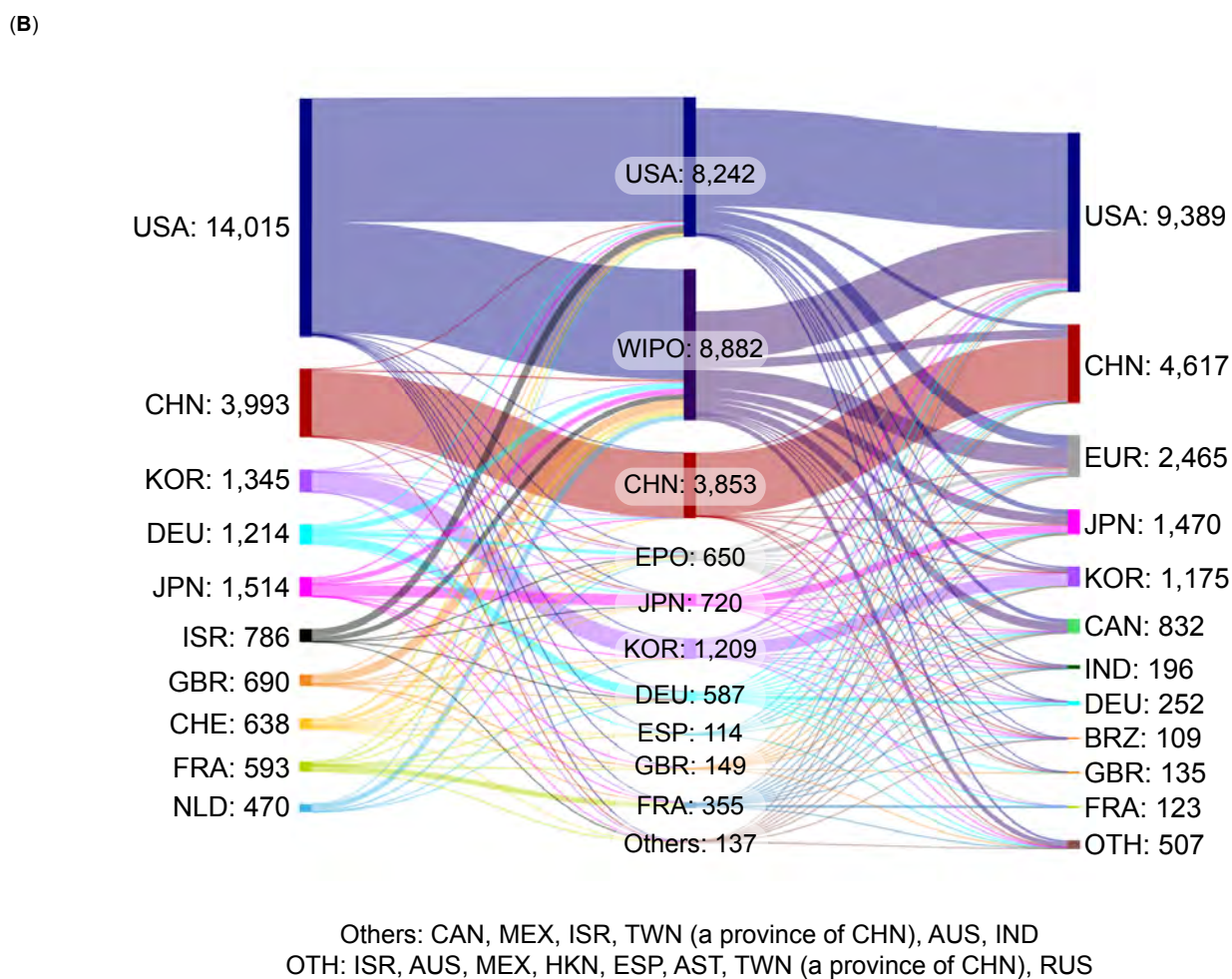
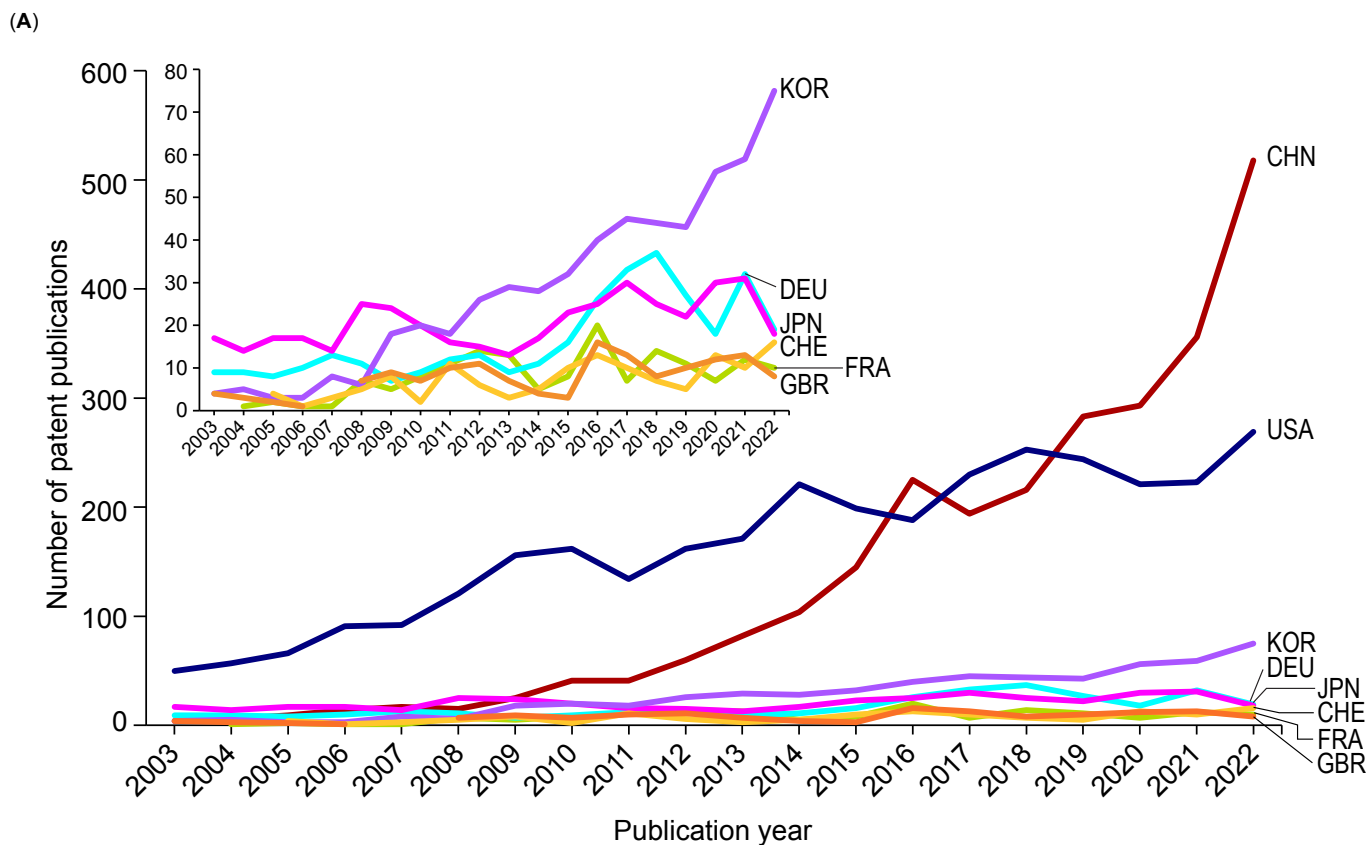


Figure 4. (A) Number of patent family publications per year between 2003-2022 for the top 8 most prolific countries/ regions. **(B)** Total patent flow between assignee countries/regions (top ten countries/regions in terms of total patent filings, left), the patent filing office where the first application in the patent family was filed (center) and the patent office where individual patent publication activities took place (right). Standard three letter codes utilized for countries/regions.

For example, a patent application filed by a US-based assignee in the Japan national patent office might first have been filed as a PCT/WIPO application. In this diagram, that patent activity would flow from the United States, to WIPO, then to JP.

From this figure, we see that in the US, France, and Switzerland, the initial filings for a given family are roughly split evenly between PCT and the home country/region patent office. For assignees in Germany, Korea, and Japan, a significant fraction of initial filings are done in the USPTO. UK-based companies more heavily favor PCT applications, while China-based companies file the majority of first applications in the Chinese national patent office.

Figure 5A depicts the locations within the human body that bioelectronic devices are used, as discussed in journals and patents published from 2003 to 2023. Analysis was performed by counting the total number of publications that referenced specific organs or regions of the body, including synonyms, then normalizing by the total publication count.

Devices targeted at the facial region constitute roughly 37% of total applications. In some cases, this research has progressed to the point of commercialization, for example the Argus II Retinal Prosthesis System, which in 2013 became the first retinal implant approved by the FDA.¹⁶ ¹⁷ This device uses platinum electrodes, titanium, and niobium, with many of the components encased in polydimethylsiloxane (PDMS).¹⁸ Later research on retinal implants investigated replacing platinum in the electrode with materials that have a higher charge injection limit (the amount of charge that can be delivered without exceeding voltage that leads to irreversible and possibly damaging chemical reactions, primarily water electrolysis), such as conductive polymers and nanocomposites.¹⁹ A recent example is a retinal implant based on iridium oxide, insulated with SiC and SiO₂.²⁰

The brain and nervous system closely follow, making up 30% of applications. Applications in this area include deep brain stimulation (DBS), which can significantly improve the quality of life for Parkinson's disease patients by delivering precise electrical pulses to mitigate motor

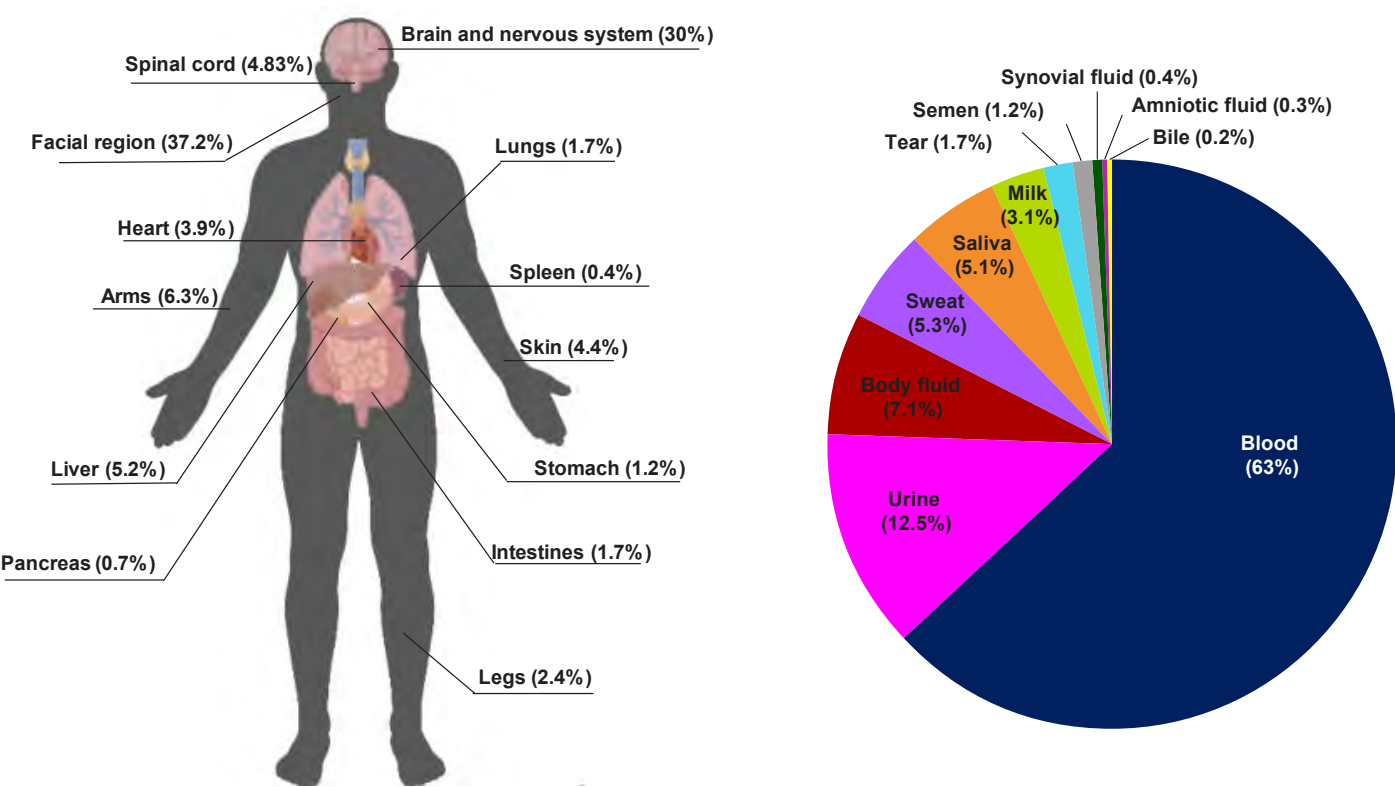


Figure 5. (A) Human silhouette illustrating the distribution of publications (2003-2023) concerning bioelectronic devices in different regions of the body(illustrations sourced from Biorender-www.biorender.com). **(B)** Pie chart displaying the distribution of various biofluids in publications related to bioelectronic applications.

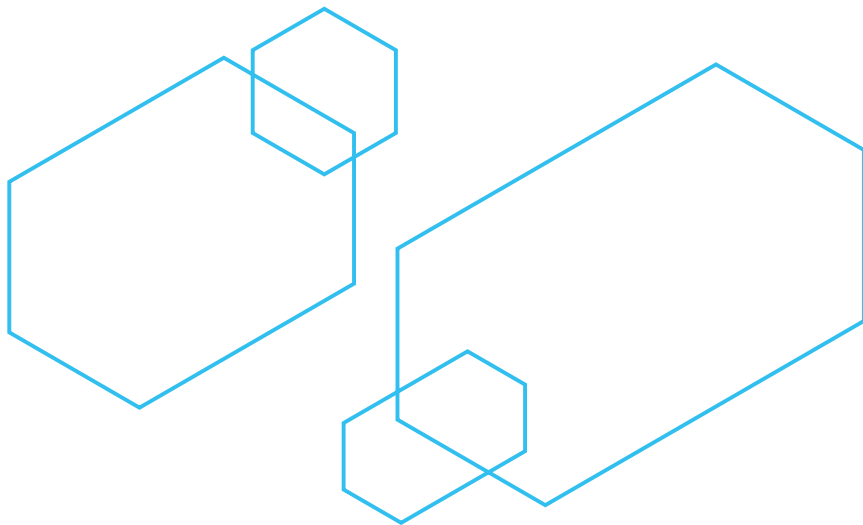
symptoms.²¹⁻²³ The materials used in commercial DBS devices include Pt-Ir electrodes with polyurethane or PDMS encapsulation.^{24, 25} In addition, devices to deliver electrical stimulation to the spinal cord, for example as a treatment for chronic pain, have been on the US market since 2015.

Devices and materials which replicate components of the nervous system, such as neuromorphic devices and artificial nerves, are notable as having increased research activity recently. These include materials based on conductive hydrogels that can be used to repair peripheral nerves,²⁶ neuromorphic devices that interface with the brain, which have been made using a variety of materials,²⁷ and a sensor that can replicate tactile and other senses using poly(3-hexylthiophene)/polyethylene glycol nanowires printed on soft silicone.²⁸

In the heart, bioelectronic devices have been used to monitor and deliver electrical signals, or even replace cardiac tissue.²⁹ Other major application areas include myoelectric limb prosthetics, where bioelectronic devices enable amputees to control artificial limbs with residual muscle signals,³⁰ and sensors used for continuous monitoring inside the body, for example in the liver,³¹ or skin, which represents a particularly emerging area of development.^{32, 33}

Figure 5B shows an overview of the various biofluids that are referenced in combination with bioelectronic devices, using an analysis similar to that described for **figure 5A**.

Blood and urine account for roughly 75% of these references, in applications that include real-time glucose level tracking,^{34, 35} and implanted or prosthetic devices to monitor and control urine.³⁶ The other 25% of references include biofluid,³⁷ sweat,³⁸ saliva,³⁹ and milk.⁴⁰



Key material substances, forms, and functions

There are several possible methods to classify biomaterials when analyzing research trends. In this report, we will classify them in three ways:

- **Chemical Substance.** For this classification, we can leverage the indexing of chemical substances by name and CAS Registry Number, which is done for all journal and patent publications in the CAS Content Collection. Examples of this classification include gold, graphene, and poly(3,4-ethylenedioxythiophene) (PEDOT).
- **Form.** This can be considered as a related, but orthogonal method to chemical substance classification. Examples are hydrogels, nanoparticles, and composites.
- **Function.** Most bioelectronic devices are hybrids, composed of several materials with different properties and functions. Breaking bioelectronic materials down by function will allow us to examine the materials used in each individual component of a device. Examples of functions are electrodes, sensor materials, and encapsulation materials.

Figures 6-9 are focused on classifying and identifying trends in bioelectronic materials by their chemical substance. The first group of chemical substances, metals and inorganic compounds (**Figure 6**) were found to be the most frequently mentioned type of substances in bioelectronic material literature from 2003-2023.

Included within this class are several important sub-classifications. The first is noble metals, which include gold, silver, platinum group metals, and their alloys. These materials are used primarily for their high electronic conductivity, chemical stability, and the ability to form them into functional nanomaterials using well-developed methods.^{41, 42}

The next are transition metals, primarily iron, titanium, copper, and nickel, as well as their alloys, including stainless steel and nitinol. Several of these materials are used in part due to their known biocompatibility, particularly titanium,⁴³ while other metals are encapsulated using inert polymers or other materials to prevent degradation by the body.^{44, 45}

In general, the use of noble and transition metals has not increased significantly relative to other materials discussed here, and as such are indicated by gray circles in **Figure 6**.

Biodegradable and bioresorbable metals, which include zinc, magnesium, and molybdenum, are of unique interest for bioelectronic applications that involve temporary placement of an electronic device.⁹ These materials combine the electrical properties of a metal with the ability to be safely broken down and absorbed by the body over time. Full transient bioelectronic devices have been constructed by combining these metals with biodegradable encapsulating polymers, for example an electronic nerve stimulator electrode and power receiver antenna consisting of Mo encapsulated in a biodegradable polyurethane.⁴⁶

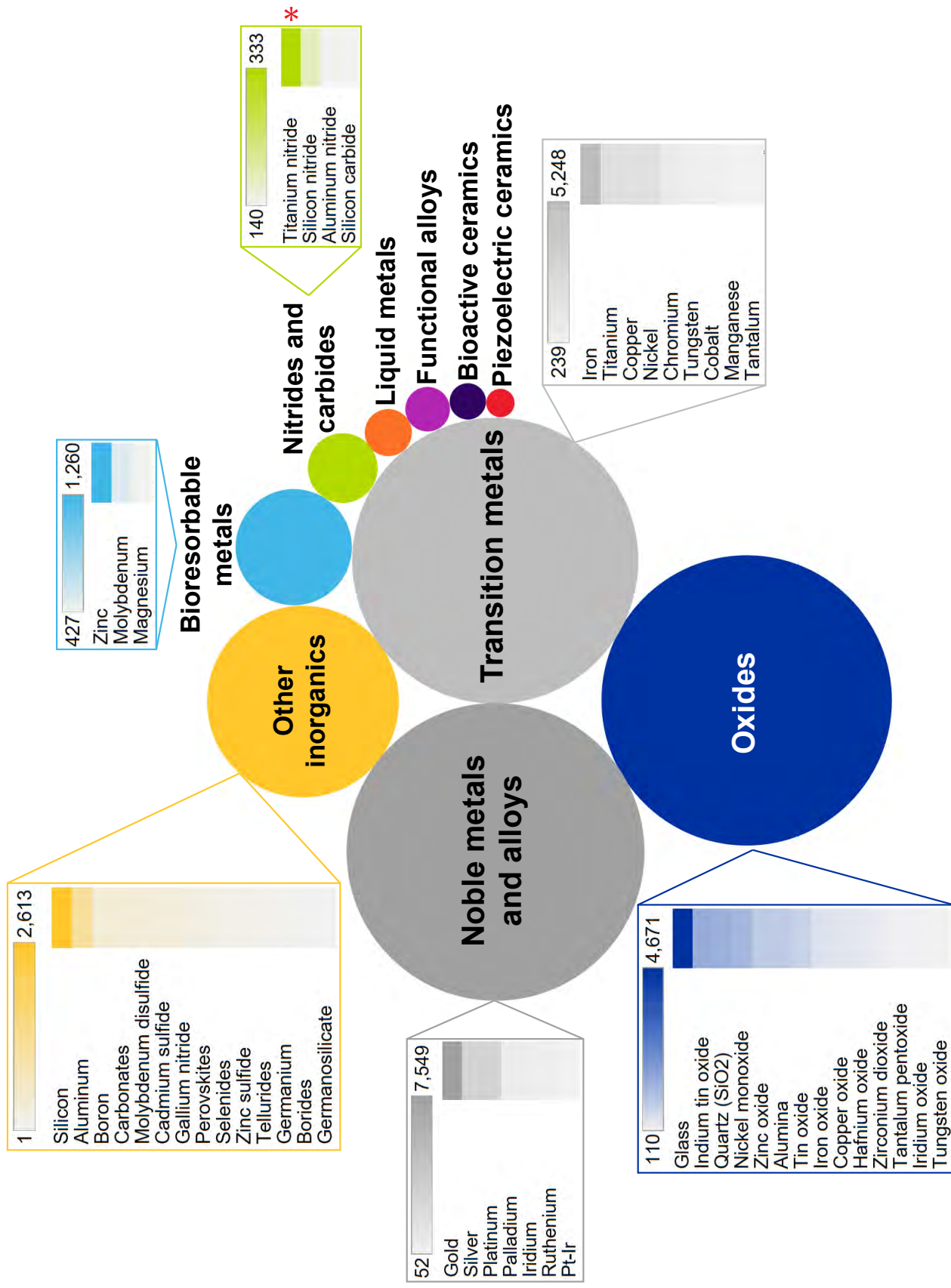


Figure 6. Bubble chart and heat maps showing frequency of the use of metals and inorganic compounds in the field of bioelectronics. Bubble size corresponds to the number of bioelectronics-related publications mentioning the material type (both patents and journals) between 2003-2023. The asterisk indicates emerging materials (see Fig. 9).

Metal oxides are a broad class of material that can serve several functions, from insulating layers for electrical isolation or semiconductor device purposes (SiO_2 , TiO_2 , and HfO_2 for example), or as charge conductors (SnO_2 , ITO, IrO_x). Of these, IrO_x , or “SIROF” (sputtered iridium oxide film), a mixture of iridium and iridium oxides, is commonly used as a bioelectronic electrode interface material due to its low impedance, relatively high charge injection limit, and durability.^{20, 47} Among the nitrides found in bioelectronic devices, TiN stands out as being a highly studied material for brain interface multi-electrode arrays (MEAs).⁴⁸

Another notable material in this category is hydroxyapatite, which is included in the bioactive ceramics group, and can be used as a scaffolding material for integrating bioelectronics into human bone.⁴⁹

As shown in **Figure 7**, polymers make up a second class of bioelectronic materials, and also serve a variety of functions. The most commonly referenced functional polymers are conductive, notably PEDOT, polypyrrole, and polyaniline. PEDOT:PSS is the most commonly used conductive polymer material in bioelectronics research.¹ In our analysis, we found that PEDOT appears in journal and patent publications at roughly double the frequency of the other common conductive polymers polypyrrole and polyaniline. This may be due to concerns over the long-term stability and potential toxicity of these two materials in the body, respectively.^{50, 51} The second and third most referenced classes of functional polymers are those that are used to form hydrogels, notably poly(lactic acid), polyethylene glycol, and poly(vinyl alcohol), and biodegradable polymers including polycaprolactone and poly(glycolic acid). As discussed in other sections of this report,

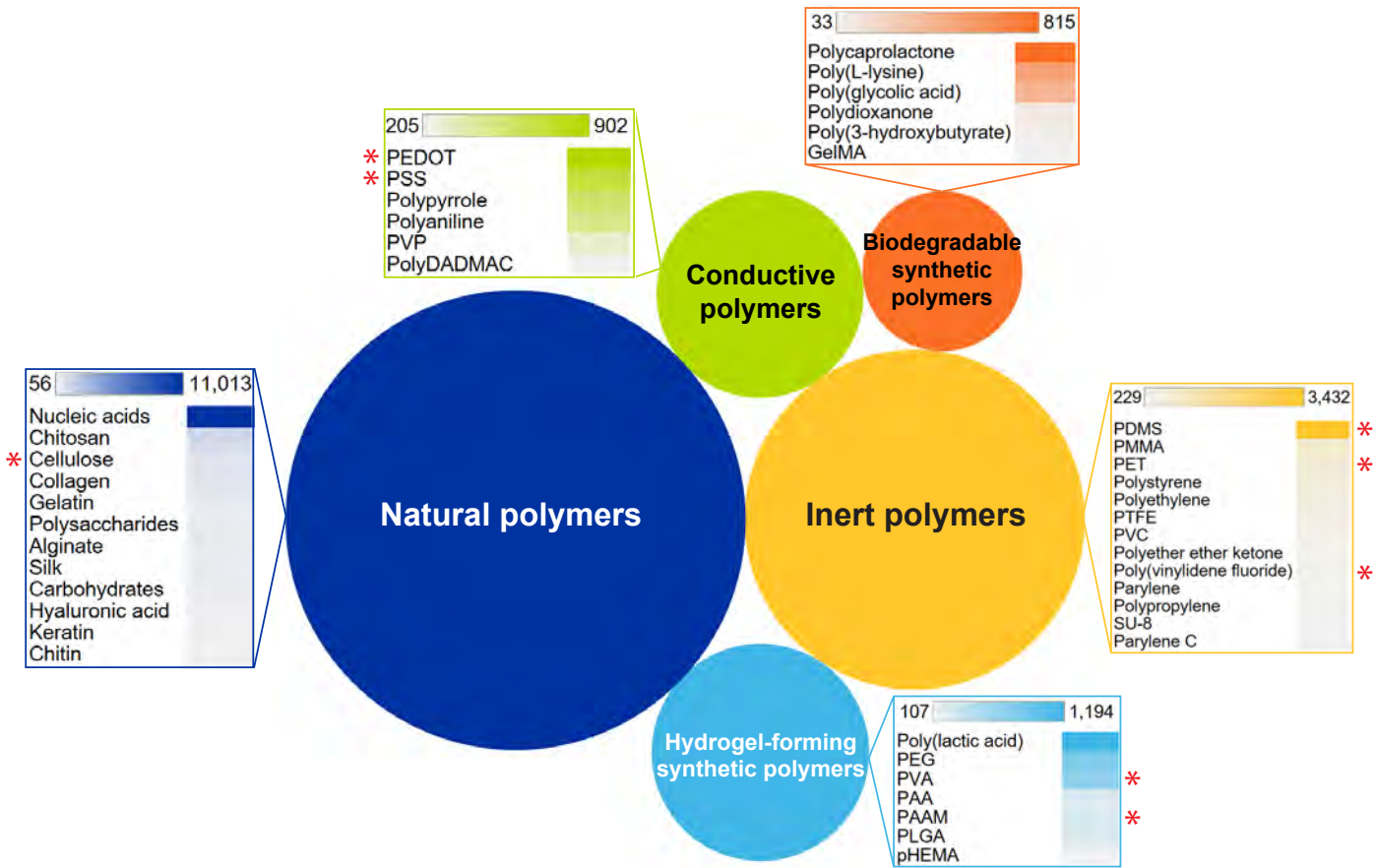


Figure 7. Bubble chart and heat maps showing frequency of the use of various polymers in the field of bioelectronics. Bubble size corresponds to the number of bioelectronics-related publications mentioning the material type (both patents and journals) between 2003-2023. Asterisks indicate emerging materials (See **Figure 9**).

hydrogels are heavily used in bioelectronic applications due to their physical similarity to biological tissues.⁵² Polycaprolactone and poly(glycolic acid) are safely resorbed into the body and used in other biomedical applications,⁵³ so they have advantages as encapsulation materials for bioelectronic devices that are meant for only temporary use.

Another notable class of polymers are those that are derived from natural sources including cellulose, chitosan, and alginate.⁵⁴ These polymers have attracted significant research attention due to their biocompatibility and resorbability. A recent example is the combination of biodegradable MoO_x and sodium alginate gel to make a resorbable supercapacitor to power transiently implanted bioelectronic devices.⁵⁵

Silk-based materials are particularly notable due to their versatility, biocompatibility, and mechanical strength.^{4,56} A recent example is the use of silk to encode encrypted data in an implanted device.⁵⁷ In this case, the tunable electrical and biodegradation properties of silk were used to encode electronic and optical-based data simultaneously on a single device which degraded over time in a rat model. Parallel efforts are underway to generate spider silk from alternate sources, for example transgenic silkworms,⁵⁸ and to synthesize artificial materials inspired by the structure of spider silk.⁵⁹

The class of polymers that appear most frequently in bioelectronics references are inert or passive, and are used for encapsulation, as substrates, or as a matrix material in functional composites. In

this area, poly(dimethyl siloxane) (PDMS) is the most commonly used material.

PDMS has several advantageous properties that explain its widespread use in bioelectronics. First, its tunable flexibility and elasticity enables the creation of flexible and stretchable electronic devices that can mechanically integrate with biological tissues. PDMS-based substrates are commonly used for the fabrication of flexible electrodes,^{60, 61} sensors,⁶² and wearable devices.⁶³ Moreover, PDMS is optically transparent in visible and near-infrared wavelengths, making it suitable for optical applications, enabling real-time monitoring and imaging of biological processes.

The biocompatibility of PDMS is also important for bioelectronic implants. PDMS-sheathed neural interfaces, for instance, can be implanted into the brain or peripheral nervous system to record neural activity or deliver electrical stimulation without causing significant tissue damage or immune response.^{64, 65} Additionally, PDMS is relatively easy to process and fabricate into complex structures using techniques such as soft lithography and replica molding, which allows for rapid prototyping, customization, and potential for high-volume manufacturing.

The unique properties of carbon nanomaterials, shown in **Figure 8**, makes them particularly useful for bioelectronic materials. Carbon nanotubes (CNTs), including single-walled (SWCNTs) and multi-walled (MWCNTs), are used to improve electrical and mechanical properties of bioelectronic composites,^{66, 67} and as sensor components.⁶⁸ Similarly, graphene can be used as a conductive filler,⁶⁹ or in tissue engineering, by

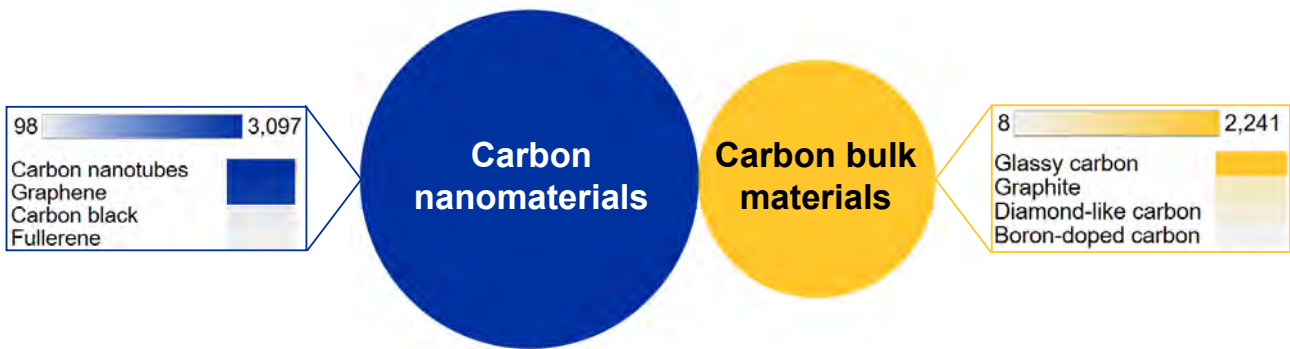


Figure 8. Bubble chart and heat maps showing frequency of the use of carbon and its allotropes in the field of bioelectronics. Bubble size corresponds to number of publications (both patents and journals) between 2003-2023.

serving as the basis for biocompatible scaffolds for regenerating bone,⁷⁰ and neural tissue.⁷¹ Graphene oxide (GO), a water-dispersible graphene derivative, can also be used for drug delivery,⁷² acting as a carrier for targeted therapeutic agent delivery.

The data shown in Figures 6-8 are aggregated from 2003-2023, and therefore represent a time-averaged view of the substances used over that time. To identify substances that that have been used more frequently in recent years (emerging substances), we counted the number of times an individual substance was mentioned each year from 2013-2022, then normalized these counts by the average number of times the substance was referenced per year between 2013-2018. This allowed us to identify substances that are growing in use over the last 5 years.

The plot in **Figure 9** shows the substances with the highest normalized growth rate in terms of mentions over the last 5 years, limited to

materials mentioned in at least 20 publications in 2022. Gold and silicon are shown as a basis for comparison, and their use has not increased significantly over this time. This analysis shows that the highest growth rates are in:

- Hydrogel-forming polymers: polyacrylamide, poly(vinyl alcohol) and cellulose
- Inert polymers: poly(vinylidene fluoride), poly(dimethyl siloxane), poly(ethylene terephthalate)
- Conductive polymers: poly(3,4-ethylenedioxythiophene) and poly(styrenesulfonic acid)
- Titanium nitride

Beyond their chemical composition, we can also classify bioelectronic materials by their physical form, as shown in **Figure 10**. Here, we see that the materials used in bioelectronic applications are roughly split between gels (mainly hydrogels), nano-scale materials, macromolecules, thin films/coatings, and composites (note that there is

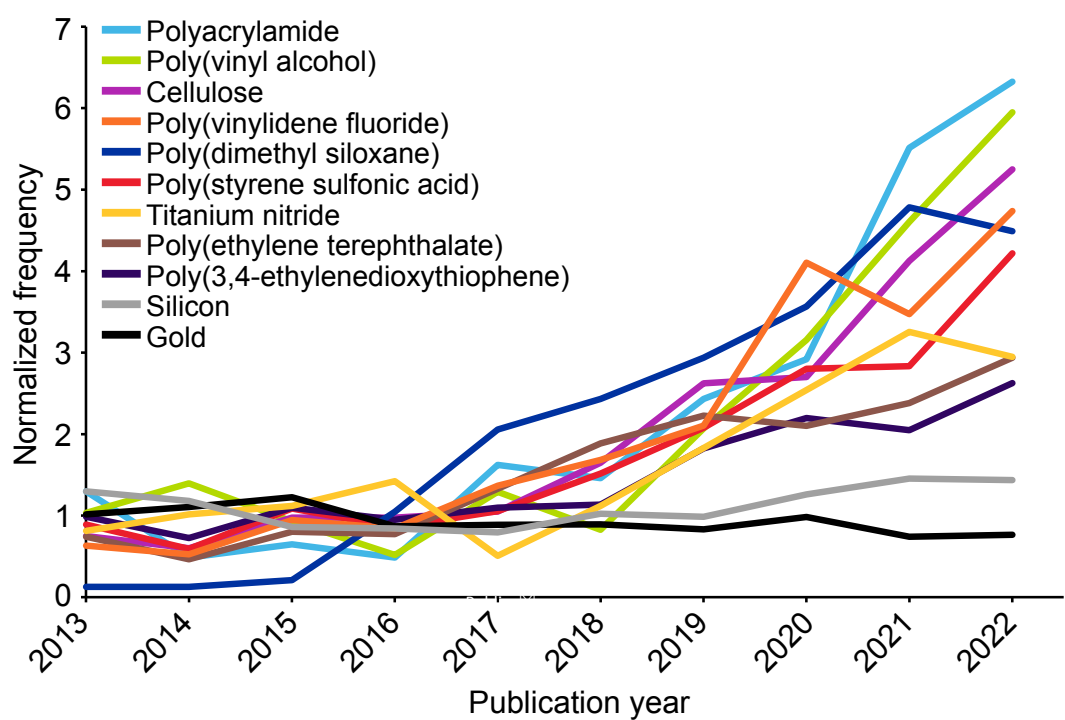


Figure 9. Normalized frequency of representative materials in journal and patent publications from 2013-2022.

significant overlap between some of these forms in single devices or materials).

The data shown in **Figure 9** indicates that hydrogel-forming polymers are a particularly emerging class of substances, which is also reflected in the forms classification shown in **Figure 10** Furthermore, combining hydrogels with nanoscale materials can be particularly useful. This approach takes advantage of the biological tissue compatibility of hydrogels and the unique electrical and mechanical properties, potential for functionalization, and high surface area of nanoscale materials.

The forms in **Figure 10** that have a particularly high ratio of mentions in patent publications compared to journal articles, suggesting that these materials have progressed further towards commercialization, are highlighted in color. The final method to classify bioelectronic materials

is by their function in a device, shown as a heat map in **Figure 11**. Here, individual material functions are shown in the top row, and the top materials associated with these functions are listed in the left column. This figure indicates that the primary function of individual bioelectronic materials are active sensor components, interface materials between electronic components and biological tissues (including electrical sensing/ mapping/stimulation applications), optoelectronic materials, signal processing components, and mechanical sensors. In general, the heat map reflects the frequent use of noble metals, as well as ITO, graphene, titanium, and the polymers PDMS, PEDOT, PET, and PMMA.

A major function of biomaterials is to form a physical and electrical interface between an electrical device and biological tissue. This can take the form of an electrode, electrode coating, bioadhesive, or combination of these things.

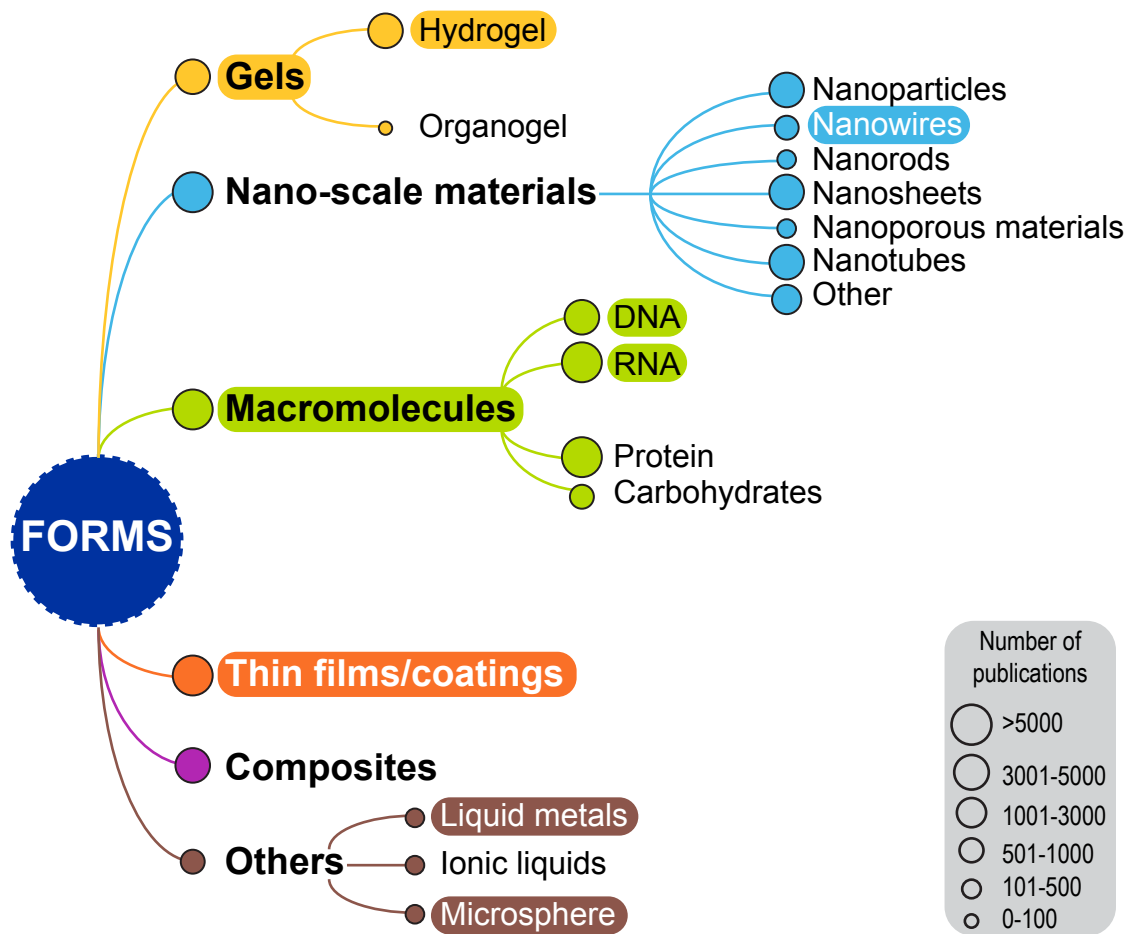


Figure 10. Trend map showing distribution of various forms in the field of bioelectronics. The size of colored circle corresponds to number of publications (journal and patent) over 2003-2023. Topics with high patent-to-journal ratio are highlighted using colored rounded rectangles.

The primary function of these components is to maintain low-impedance electrical contact for electrical sensing and/or stimulation, while maintaining a compliant and durable attachment to tissue.

This combination of properties is often achieved in modern bioelectronic devices using composites where one component provides the desired mechanical characteristics, and the other provides the desired electron and/or ion conductivity. Notable examples include percolated silver / polyacrylamide-alginate hydrogel,⁷³ graphene oxide / PVA hydrogel,⁷⁴ carbon nanotube / PDMS bottlebrush elastomers,⁶⁶ PEDOT:PSS mixed with a supramolecular solvent,⁷⁵ bicontinuous PEDOT:PSS / polyurethane hydrogel,⁷⁶ and PEDOT/functionalized graphene oxide/ polyacrylamide hydrogel.⁷⁷

A conformal, well-adhered interface between bioelectronic materials and biological tissues is important for stable and reliable functioning of bioelectronic devices. However, this can be challenging to realize in soft, wet, dynamic bio-interfaces. To this end, Zhao et al. developed an electrical bioadhesive interface by a graphene-PVA nanocomposite material, demonstrating superior biocompatibility, applicability, mechanical and electrical stability, as well as the ability to trigger detachment of the material.⁷⁴ In another example, an ionic-conductive

dopamine-containing polymer film based on copolymerization of dopamine methacrylamide (DMA), acrylic acid (AA), and methoxyethyl acrylate (MEA), p(DMA-co-AA-co-MEA), was integrated with Au/PDMS bilayer films to create water-resistant electrodes, which could be used for monitoring electrocardiography (ECG) signals underwater as they could maintain conductivity and firm adhesion to skin.⁷⁸ In this material, the DMA component provided the water-resistant adhesive properties. Recently, a bioelectronic patch was developed for precise cardiac monitoring, which used an ionically conductive catechol-conjugated alginate (Alg-CA) hydrogel to provide instantaneous adhesion to the dynamic cardiac tissues. This material was used to demonstrate measurement of ECG signals in live rat models for up to 4 weeks.⁷⁹

Bioelectronic materials are also incorporated into biomedical sensor devices,^{2, 11} where they are designed for applications such as detecting, chemical environments⁸⁰ or sensing pressure.⁸¹ For example, Lee et al.,⁶⁸ developed a sensor based on single-walled carbon nanotubes modified with a human olfactory receptor protein, which could detect the presence of an odorant at concentrations as low as 1 femtomolar with high sensitivity. Doped carbon nanomaterials, such as nitrogen-doped graphene, are used as electrochemical biosensors for molecules including DNA, proteins, glucose, and hydrogen peroxide.⁸²⁻⁸⁴

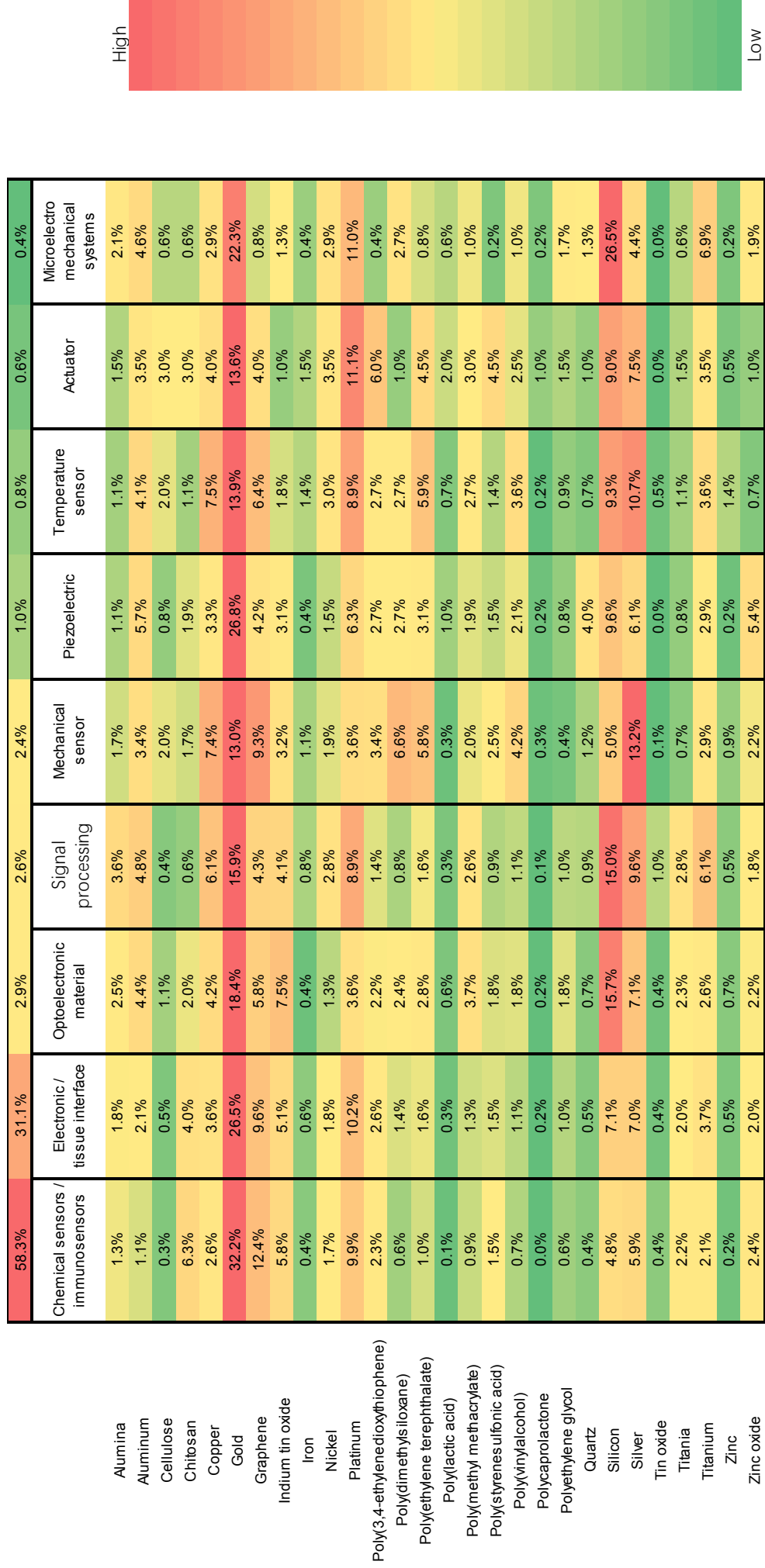


Figure 11. Heat map of the relationship between the most commonly used substances in bioelectronic materials (left) and the most common material applications (top). Relative frequencies of each substance have been calculated within each application category. Note that the electronic/tissue interface category also includes electrical sensing and stimulation.

Notable journal articles and patents

Table 1 is a set of research articles published from 2020-2023 that represents emerging trends in the field of bioelectronics. These references were selected to provide examples of the materials and applications which appear prominently in our analysis of the bioelectronics literature as presented in Section III. They were also selected based on other factors including journal impact factor and the number of other articles citing the reference. The examples include the use of IrO_x , PEDOT:PSS, PEG, silk-based materials, carbon nanotubes, hydrogels, and PDMS, for applications including retinal implants, micro-electrocorticography, wearable devices, tissue/electrode interfaces, and neural interfaces.

Notable examples from **Table 1** include a photovoltaic-based subretinal implant that achieved a visual resolution of 28 microns, matching the limiting visual resolution in rats. In this system, images are projected using near-infrared light onto a photovoltaic array implanted in the eye, which directly transmits electrical signals to the retinal neural network. The array consists of silicon-based photovoltaic pixels, using IrO_x / Ti / Pt stack electrodes, with SiO_2 and SiC as encapsulating materials. In this application, use of IrO_x , in the form of sputtered iridium oxide film or SIROF, is important due to its high charge injection capacity relative to other electrode materials.

In a second example, Jiang et al.⁸⁶ developed and optimized a mixture of PEDOT:PSS and a functionalized polyrotaxane for use as a stretchable, patternable conductive material. The key structure to optimize in this material is the polyrotaxane, which consisted of a PEG backbone with encircling cyclodextrin. The primary function of the cyclodextrin was to prevent crystallization of the PEG, a process that would degrade the mechanical properties of the mixed material. In addition, a fraction of the cyclodextrins were functionalized with PEG and

methacrylate groups, to control water solubility and enable photopatterning of the material. They also demonstrated the use of this optimized material on human and octopus skin for surface electromyography, and as an electrode array for stimulating and mapping the rat brain. Pokorski et al. have also developed a method for 3D printing PEDOT:PSS using direct ink writing (DIW), and used it to print a flexible, cortex-wide micro-electrocorticography array for stimulating and calcium imaging a mouse brain.⁸⁷

Chen et al.⁸⁸ reported a silk-based electrode for advanced wearable devices and on-skin sensors that utilizes an electrospun silk fiber mat coated with PEDOT:PSS, featuring high stretchability and comfort against sweat on the skin. The electrode material can be stretched more than 250%, has low evaporative resistance (10 times lower than commercially available gel electrodes) and high water-vapor transmission (2 times higher than the rate of water loss from the skin). This electrode also demonstrates no apparent disturbance during data collection under sweaty conditions.

Another recent example of composite materials in bioelectronic devices is a mixture of single-wall carbon nanotubes (SWCNTs) with PDMS-based bottlebrush elastomers (PDMS BBEs).⁶⁶ The PDMS BBEs can be made ultra-soft by optimizing the polymer side chain length, grafting density and network strand length, making them suitable for applications in cardiac muscle and the brain. SWCNTs (incorporated at 0.4–0.6 wt%) provide conductivity.

A soft interlayer in an electric thin film can make a high modulus thin film more stretchable on a low modulus substrate. This approach leads to more applications of the existing stretchable electronic materials to tissue-like modulus devices, such as sensors on cardiac muscle. Wang et al. reported a polystyrene-ethylene-butylene-styrene (SEBS) as the interlayer that acts as an adhesive for electronic materials and low modulus

substrates.¹⁴ The design of SEBS interlayer on the polyacrylamide (PAAm) hydrogel is ultra-soft, around two orders of magnitude lower than polydimethylsiloxane (PDMS) and SEBS. This design is further utilized for PEDOT:PSS-based electrodes, with mechanical tests demonstrating increased stretchability and softness of the interlayer-inserted electrode.

Table 2 shows notable patents in the field of bioelectronics published from 2018 to 2023. Patents were selected based on relevance, novelty, applicability, and field of study. Most of these involve implantable devices for organ stimulation, pain management, monitoring, and/or analysis of bioelectronic data.

For instance, US 10898718B2, 'Sensor-based pain management systems and methods' (Boston Scientific Neuromodulation Corp, USA) describes a system for measuring and managing pain. The system first collects data from the patient, for example a galvanic skin response, electrodermal activity, electromyogram, electroencephalogram, blood pressure, heart sounds, or saliva production

rate, then uses this data to generate a quantitative pain score. This can then be reported to a clinician or used to control an automated pain control system. This invention can be helpful for patients who do not have the ability to communicate a subjective pain score, or do not have immediate access to medical care.

In recent years, hydrogels, natural polymers and conductive polymers such PEDOT: PSS have been cited in patents in the bioelectronic field. US 11633589B2 (QV Bioelectronics Ltd.) describes an injectable electrode material consisting of a mixture of solid PEDOT:PSS particles dispersed in a PEDOT:PSS-containing gel or liquid phase. This material can be injected into a tumor resection cavity, then used to deliver electrotherapy treatments targeting residual cancer cells left at the edge of the cavity after surgery. The biphasic material allows the electrode to conform to the edges of the cavity, which can move due to swelling, while generating electric fields close to the tumor site at lower voltages compared to externally mounted electrodes.



Table 1. Notable journal publications in bioelectronic materials in recent years.

Year	Title	Journal	Research Institute	Summary
2020	Muscle-Inspired Self-Healing Hydrogels for Strain and Temperature Sensor ⁸⁹	ACS Nano	Nanjing Tech University	Self-healing sensor based on a poly(acrylic acid) hydrogel with polyaniline nanofibers
2020	Functionalized helical fibre bundles of carbon nanotubes as electrochemical sensors for long-term <i>in vivo</i> monitoring of multiple disease biomarkers ⁹⁰	Nature Biomed Eng.	Fudan University	CNTs modified with different materials (Pt nanoparticles, glucose oxidase, ZnO, PEDOT:PSS) for sensing H ₂ O ₂ , glucose, and ions; CNTs were insulated using PDMS
2020	Enhancement-mode ion-based transistor as a comprehensive interface and real-time processing unit for <i>in vivo</i> electrophysiology ⁹¹	Nature Materials	Columbia University	PEDOT:PSS/polyethyleneimine mixture as the active channel in an ion-gated electrochemical transistor for <i>in vivo</i> electrophysiological sensor
2021	Electrical bioadhesive interface for bioelectronics ⁷⁴	Nature Materials	Southern University of Science and Technology	Electrically conductive bioadhesive using a PVA hydrogel with reduced graphene oxide filler, and poly(acrylic acid) modified with N-hydroxysuccinimide ester for adhesion
2021	An electrically conductive silver–polyacrylamide–alginate hydrogel composite for soft electronics ⁷³	Nature Electronics	Carnegie Mellon University	Polyacrylamide–alginate hydrogel with percolated silver to make a soft, conductive electrode
2021	Permeable superelastic liquid-metal fibre mat enables biocompatible and monolithic stretchable electronics ⁹²	Nature Materials	Hong Kong Polytechnic University	Poly(styrene-block-butadiene-block-styrene) fiber mixed with eutectic gallium-indium alloy (EGaIn) as a conductive, stretchable material
2022	A transient, closed-loop network of wireless, body-integrated devices for autonomous electrotherapy ¹⁰	Science	Northwestern University, USA	Bioresorbable, temporary wireless cardiac implant made of dynamic covalent polyurethane, Mo, and Si
2022	A double-layer carbon nanotubes/polyvinyl alcohol hydrogel with high stretchability and compressibility for human motion detection ⁶⁷	Engineered Science	Beijing University of Posts and Telecommunications	Flexible strain sensor based on a carbon nanotube/PVA hydrogel mixture
2022	Topological supramolecular network enabled high-conductivity, stretchable organic bioelectronics ⁸⁶	Science	Stanford University, Tianjin University	Mix of PEDOT:PSS and a PEG/MA-functionalized PEG-backbone polyrotaxane as a stretchable, photo-patternable conductive material
2022	Electronic photoreceptors enable prosthetic visual acuity matching the natural resolution in rats ²⁰	Nature Comm.	Stanford University	Subretinal implant using IrO _x electrodes with SiO ₂ and SiC encapsulation
2022	Three-dimensional printing of soft hydrogel electronics ⁹³	Nature Electronics	University of Adelaide, Westlake University	3D printing of conductive Ag-based networks inside of an alginate–polyacrylamide hydrogel matrix; rheological properties of the matrix are engineered to allow printing, followed by curing to form a stretchable, covalently bound structure
2023	3D printable high-performance conducting polymer hydrogel for all-hydrogel bioelectronic interfaces ⁷⁶	Nature Materials	Massachusetts Institute of Technology, Jiangxi Science and Technology Normal Univ.	Use of a bicontinuous PEDOT:PSS/hydrophilic polyurethane structure to optimize the combination of electrical and mechanical properties of a hydrogel; material can be formed by 3D printing, electrospinning, spin coating, or micro-molding
2023	Zinc hybrid sintering for printed transient sensors and wireless electronics ⁹	Npj Flexible Electronics	Ecole Polytechnique fédérale de Lausanne	Zn particle ink printed onto polyimide, paper, PLA, as bioresorbable pressure sensors and wireless power receivers
2023	Conductive and elastic bottlebrush elastomers for ultrasoft electronics ⁶⁶	Nature Communications.	University of Toronto	Soft electrode based on PDMS bottlebrush/single wall carbon nanotube mixture
2023	Achieving tissue-level softness on stretchable electronics through a generalizable soft interlayer design ¹⁴	Nature Communications.	University of Chicago	Use of a polystyrene-ethylene-butylene-styrene adhesion interlayer with PAAm hydrogel/PEDOT:PSS
2023	Graphene and Poly(3,4-ethylenedioxythiophene)-Polystyrene Sulfonate Hybrid Nanostructures for Input/Output Bioelectronics ⁹⁴	ACS Applied Nano Materials	Carnegie Mellon University	High surface area PEDOT:PSS formed on graphene/Si nanowire composite as electrode material

Table 2. Notable patent publications in bioelectronic materials in recent years.

Patent or publication number	Publication year	Patent assignee	Title	Description of patented technology
US 10065036B2 ⁹⁵	2018	Second Sight Medical Products, Inc., USA	Method for measuring stable and reproducible electrode-tissue impedance	A system to pre-condition and measure the impedance of electrode-tissue interfaces for an implanted visual prosthesis
US 10668290B2 ⁹⁶	2020	Medtronic Inc., USA	Delivery of pacing therapy by a cardiac pacing device	Implantable medical device to deliver pacing signals (pacemaker, defibrillator for example) combined with ECG sensors for closed-loop cardiac resynchronization therapy.
CN 111363097 A ⁹⁷	2020	Wenzhou Research Institute of Chinese Academy Of Sciences, Wenzhou Institute Of Biomaterials And Engineering, China	Preparation method of bioelectronic hydrogel, product, and application thereof	A bioelectronic hydrogel made by photopolymerizing a mixture of carboxylic acid monomers (acrylic and methacrylic acid), calcium nitrate, PVA, gold nanorods, distilled water, and a photoinitiator. IR irradiation heats the nanorods to kill bacteria on the surface of the gel.
US 11517238B2 ⁹⁸	2022	University of Illinois, Northwestern University, USA	Encapsulated flexible electronics for long-term implantation	Processes for optimizing the encapsulation of implantable electronic devices, including bendable, stretchable, or flexible devices. Cited encapsulation and coating materials include SiO ₂ , diamond, SiC, Al ₂ O ₃ , HfO ₂ , parylene, PDMS, polyimide, SU-8, and PMMA.
US 10898718B2 ⁹⁹	2021	Boston Scientific Neuromodulation Corporation, USA	Sensor-based pain management systems and methods	Sensors use physiological signals from patients (galvanic skin response, electrodermal activity, electromyogram, electroencephalogram, blood pressure, heart sounds, or saliva production) to generate pain scores and deliver treatment.
CN 214175051U ¹⁰⁰	2021	Huashan Hospital of Fudan University, China	Movement intention identification system of exoskeleton glove equipment based on brain plasticity	A human-computer interaction device to identify intended movements using myoelectric signals for a prosthetic glove.
US 11633589B2 ¹⁰¹	2023	QV Bioelectronics Ltd., UK	Biphasic injectable electrode	A biphasic injectable electrode material consisting of solid particles of PEDOT: PSS in a PEDOT:PSS-containing liquid or gel phase, used for delivering electrical treatments to the edges of a surgical tumor resection cavity.
WO2023154259A2 ¹⁰²	2023	Cz Biohub Sf, LLC, The Regents Of The University Of California, USA	Woven fabric bioelectronic device	Implantable devices consisting of two or more types of threads woven together, to be used for tissue repair. Threads can be made from polymer fiber (polypropylene, PVC, polyethylene, PEEK, polycarbonate, polyetherimide (PEI), polysulfone, polyurethane, cellulose, chitosan), metal wire, or permeable tubing, in conjunction with other components.
WO2023038703A1 ¹⁰³	2023	Obsidio, Inc., USA	Piezoelectric shear-thinning material compositions and methods for use	Shear-thinning hydrogels containing piezoelectric nanoparticles (laponite, bentonite, kaolinite, or montmorillonite-smectite nanoclay, quartz, ZnO, or AlN). These materials can be injected into the body and used to stimulate cells/tissues using wireless impulses (ultrasound, RF, or microwave). Polymers in the hydrogels include gelatin, collagen, chitosan, silk, poly(lactic acid), cellulose, alginate, agarose, starch, PVDF, PEG, lignin, keratin, PVA, and PTFE.
WO2023075689A2 ¹⁰⁴	2023	Nanyang Technological University, Singapore	Bioinspired water shrink film for shape-adaptive bioelectronics	A thin film which contracts by more than 50% of its original length upon exposure to water. The film contains crystalline inclusion complex domains formed from poly(pseudo)rotaxanes or a-cyclodextrin/PEG polyrotaxanes, crosslinked with polyethylene oxide, with electrically conductive layers (gold, silver, copper, IrO _x , or TiN) and passive insulating layers (PDMS, self-healing styrene-ethylene/butylene-styrene given as examples). The conductive layers can be formed on the thin film in its dry, rigid state, then the film transforms to a soft, stretchable state after implantation.

Challenges and perspectives

As discussed in this report, the field of bioelectronics has seen a surge in scientific papers introducing advanced materials and devices, particularly in the last five years. The focus of much of this work has been combining highly engineered materials into hybrid and composite devices, mainly to impart these devices with the unique properties needed for bioelectronics applications. These properties, such as softness, electrical conductivity, biodegradability, and piezoelectricity, are highly diverse and not found together in conventional materials used in other applications.

While this approach has resulted in remarkable advances in this area, it has also introduced several new challenges.^{1-3, 5, 52, 105} Based on a survey of recent bioelectronics literature, the most significant current challenges in this field are:

- Biocompatibility / toxicity / immune response of materials used in bioelectronics materials, including nano-scale materials and composites whose properties vary with synthesis and other processing conditions. Device materials interacting with skin can cause skin contamination, irritation, and infection. When a bioelectronic device is implanted inside the body, a foreign body reaction can be activated by the immune system, which might lead to the formation of a fibrotic capsule covering the implanted device. This can isolate it from the surrounding tissues, causing it to become inactive.¹⁰⁶
- Long-term chemical and physical stability of materials in the dynamic environment of the body, including adhesion to and compliance with biological tissue, is also a challenge.¹
- Difficulties with converting electron to ion current at the interface between electrodes and biological tissue while avoiding irreversible chemical reactions.^{12, 107}
- Matching the physical characteristics of existing electronic device materials, which are generally planar and rigid, having elastic modulus approximately >1GPa, with curvilinear, soft, low elastic modulus <100 kPa tissues.¹⁰⁸ This mechanical mismatch between the skin and device can cause injury.¹⁰⁹
- The performance of the implanted device can degrade owing due to physical deterioration, such as mechanical damage to the electrode components or probe.^{110, 111}
- Poor adhesion and abrupt mechanical stresses can also result in cracking and delamination of devices. The most common outcome in these cases is the damage to the insulating layer, leading to the exposure of metallic interconnections. Thus, parasitic current pathways can be set up between the tissue and any electronic processing system, resulting in unintended cross-talks.¹¹²

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IX. Sustainable materials for biomedical applications

Introduction

Sustainability is defined by the United Nations Brundtland Commission as “meeting the needs of the present without compromising the ability of future generations to meet their own needs”.¹ Sustainability is a multi-faceted topic, with environmental, economic, and social aspects. In materials science, the environmental and economic aspects are most relevant, and include pollution prevention, use of renewable resources, cost saving, and energy efficiency.²

Increasing the use of sustainable materials in biomedical applications can significantly contribute to enhancing the sustainability of the overall global economy.^{3, 4} In the context of biomedical applications, sustainability involves using materials that have one or more of the following characteristics:

- Biodegradable or compostable—they degrade in natural conditions without human intervention
- Made from bio-based, naturally abundant, or renewable raw material sources
- More environmentally benign than the materials they replace

Bio-based substances are either obtained directly or are derived from biological systems such as plants or agricultural waste. Bio-based polymers are considered sustainable since they can be obtained from renewable bio-resources, though not all bio-based polymers are biodegradable.

Examples of sustainable materials used in biomedical applications include various types of personal protective equipment (PPE),^{5, 6} medical packaging,⁷⁻⁹ textiles,^{10, 11} and other single-use, disposable lab or clinic supplies used in health and life science settings.¹²

In general, the desired properties of these materials include biocompatibility, non-toxicity, mechanical and thermal stability, processability, as well as other application-specific functionality.^{13, 14} A major theme in this area is adapting, modifying, or combining intrinsically sustainable materials (such as biodegradable polymers and naturally-derived materials) with other substances to give them these required properties.

In recent years, sustainability has become more important due to the limited availability of fossil fuels from which some synthetic polymers are made, and growing concern about the impact of non-biodegradable waste on the environment.¹² One recent example is the environmental impact of PPE made from non-biodegradable plastics during the COVID-19 pandemic,¹⁵⁻¹⁸ which highlighted the importance of biodegradable plastics in health care and motivated research in this area.^{19, 20} The use of sustainable materials for face masks has been widely studied due to their ubiquity during the COVID-19 pandemic and because sustainable nanoscale fibers are available and can substitute for the traditional materials in face mask filters.⁵

Single-use biomedical packaging materials have stringent requirements, such as durability, strength, resistance to various environments, and low weight. To meet these requirements, conventional packaging is made from fossil fuel-based polymers that are not easily biodegradable. Overall, packaging accounts for nearly 40% of all plastics produced.²¹ For these reasons, research attention has been directed towards developing sustainable packaging for biomedical applications.⁷

In this chapter, we describe the publishing trends, most prominent and emerging materials, and applications of sustainable materials in biomedical settings. Polymers represent the majority of these materials, and include natural polymers,^{22, 23} and synthetic polymers which can be further categorized as bio-based, biodegradable, or both, with polylactic acid as a key example.^{24, 25} In addition to developing new materials to meet required specifications, there are other significant challenges involved in the growth of this area. These include matching existing materials with appropriate applications (often displacing existing, less expensive non-sustainable materials), supply chain establishment, and obtaining regulatory approvals. To illustrate how these challenges can be overcome, we will also provide examples of sustainable biomedical materials that have been commercialized for a range of applications.

Journal and patent publication trends

The time trend of journal and patent publications in the area of sustainable materials is shown in **Figure 1**. Journal publication frequency has shown a steady increase from 2003, with a particularly high growth after 2017. Patent publication activity has also generally increased since 2003, but not as steadily or quickly. However, a rise in patent activity from 2019 to 2021 was observed. Comparing these trends with the journal and patent publication trends in the other chapters, the overall number of journal and patent publications is lower, but growing quickly since 2015.

Figure 2 shows the top 10 institutions in terms of publication count in the area of sustainable materials, ranked by the average number of citations per publication. Based on this analysis, there is significant research interest in this area

in China. Among the institutions with the most publications, Sichuan University has the highest average citations, and the Chinese Academy of Sciences has the highest number of total publications.

Figure 3 shows a geographical distribution of patent publication assignees. China has the highest share of patent publications from commercial entities, followed by almost equal share from the United States and Japan. For non-commercial assignees, China has roughly 49%, followed by the United States, Korea, and Japan.

Figure 4 shows the patent publication frequency time for the 5 countries which have generated the most patent publications overall. Besides China, patent activity has been relatively flat, indicating that organizations in China are largely driving patent activity in this area.

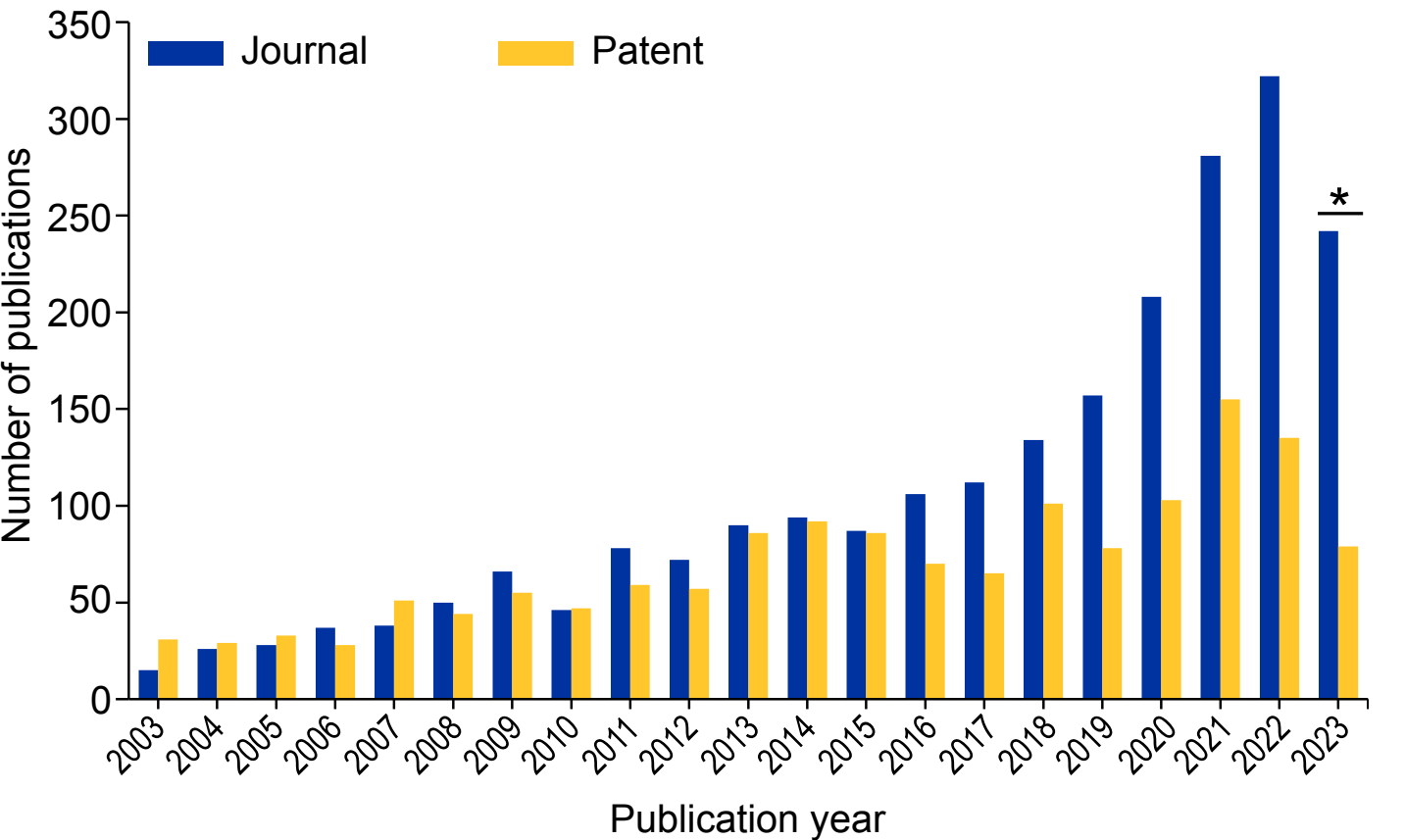


Figure 1. Number of journal and patent publications per year in the sustainable biomedical materials field from 2003 to 2023 (journals: blue bars, patents: yellow bars). * The data for 2023 only include months from Jan to Aug.

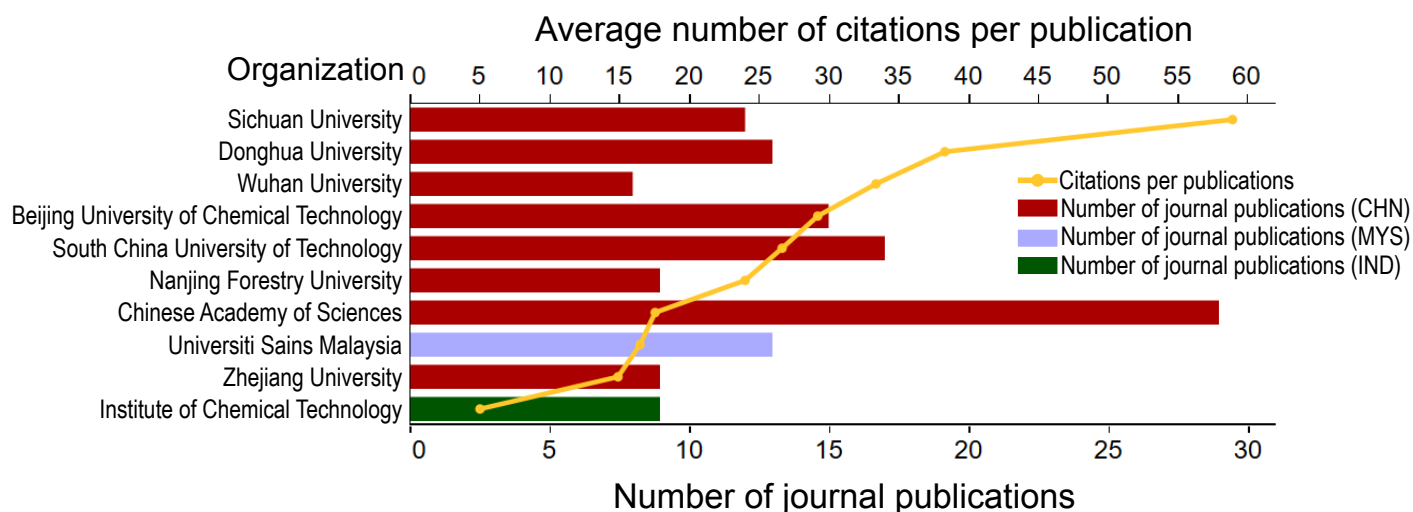


Figure 2. The top 10 research institutions in terms of average citations per publication (yellow line). Total publications from 2003-2023 shown as bars; colors of the bars indicating country/region location.

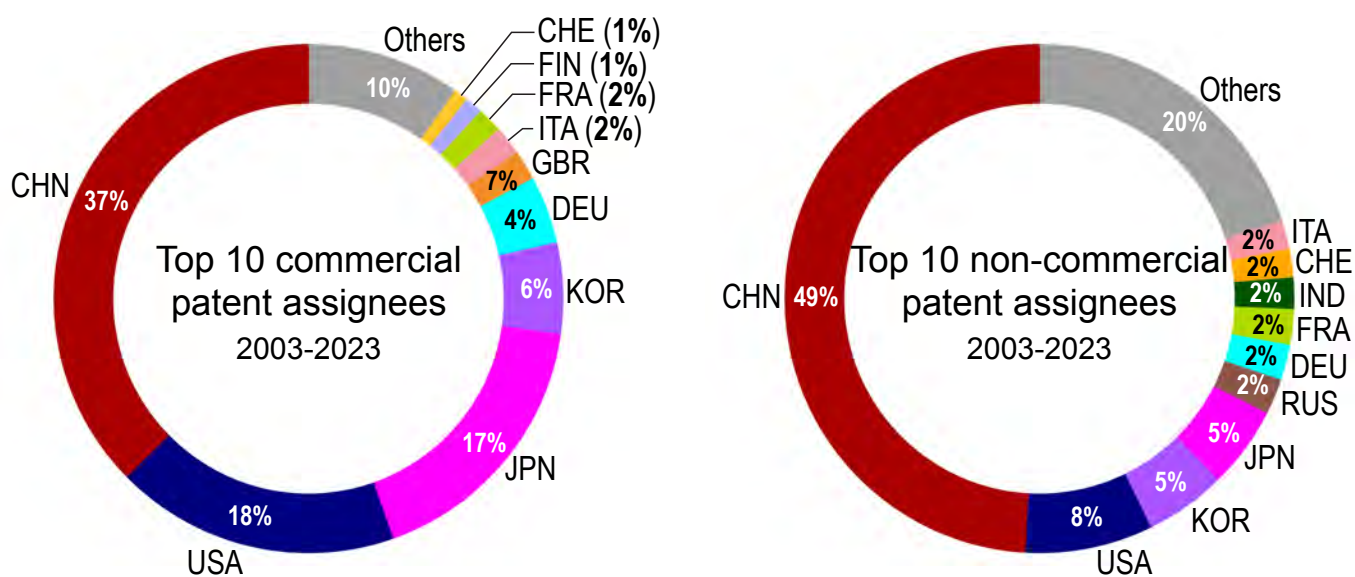


Figure 3. Geographical distribution of 2003-2023 patent publication assignees for commercial (left) and non-commercial (right) entities.

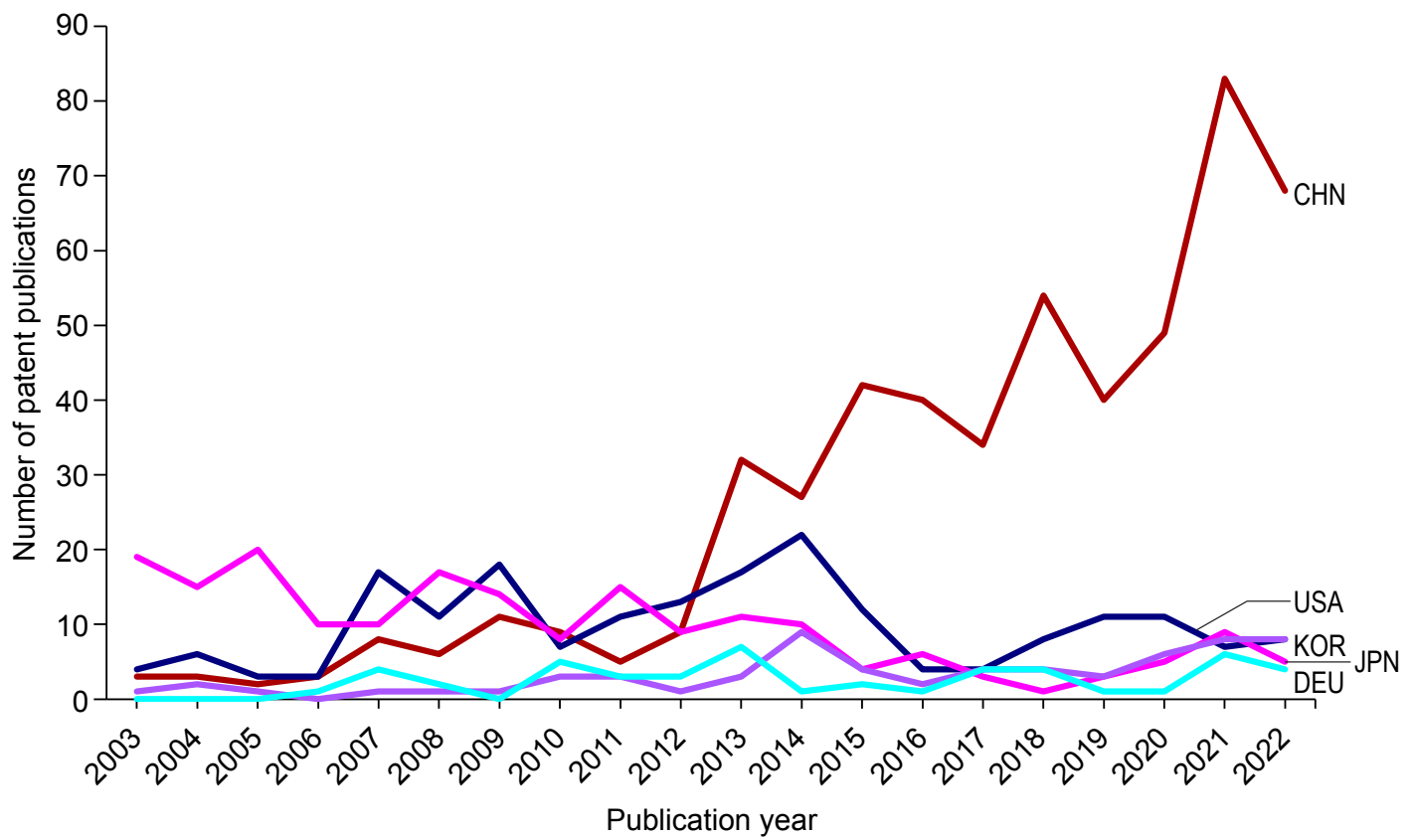
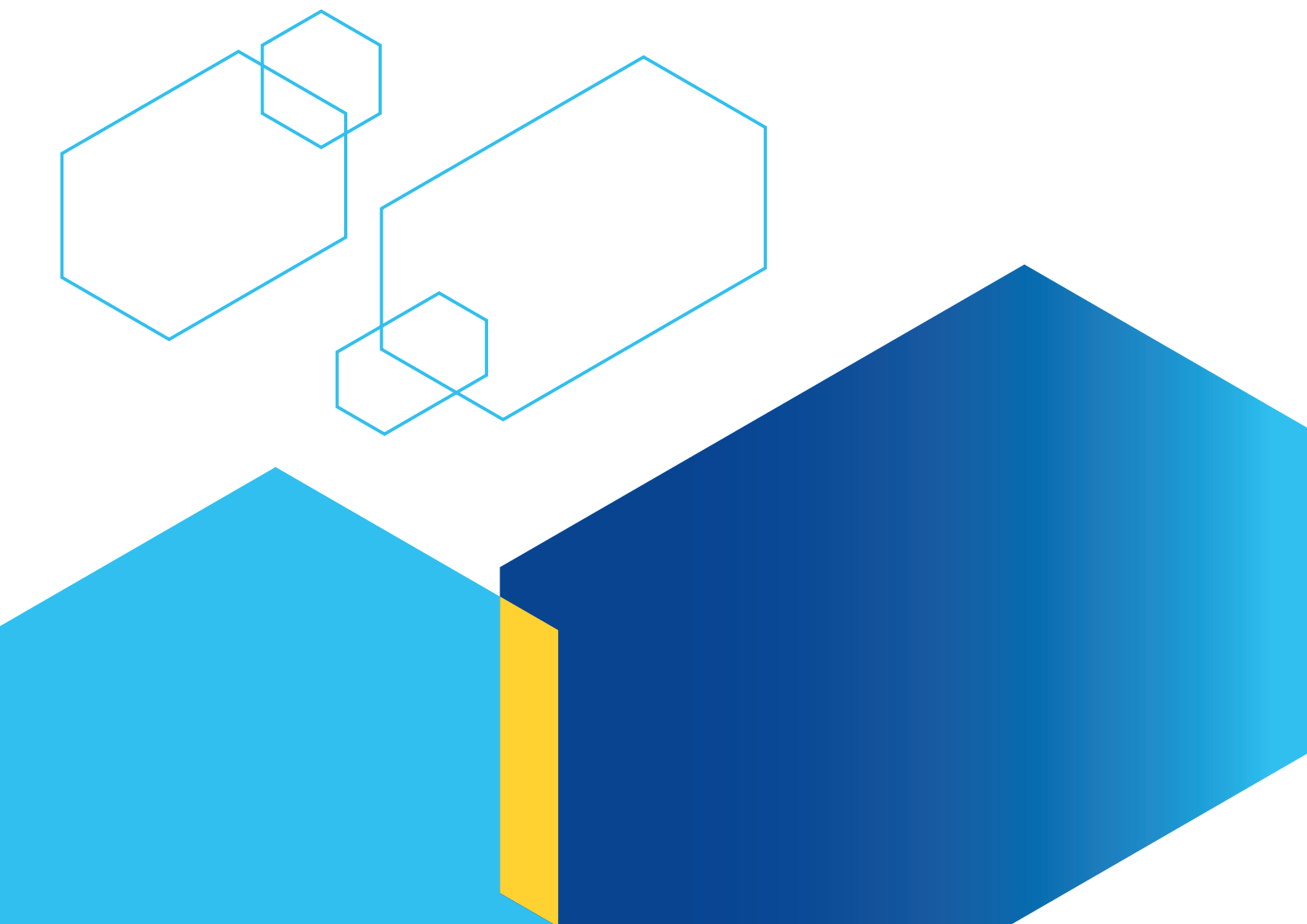


Figure 4. Number of patent family publications per year between 2003-2022 for the top five most prolific countries/ regions.



Key material substances, forms, and applications

The substances that appear most frequently in sustainable materials-related publications are shown in **Figure 5**, grouped as polymers (natural and synthetic), inorganic and organic small molecules, salts, elements (metals and nonmetals), alloys, minerals, and coordination compounds.

Natural polymers, primarily cellulose, starch, and chitosan, appear prominently in this data set. Cellulose, a highly abundant and renewable biopolymer, is present in plant and algae cell walls, as well as in bacterial biofilms. Cellulose has been identified in several of the preceding chapters as being used in various types of emerging biomaterial applications.

In addition to those applications, cellulose has also been studied as a replacement for nonrenewable synthetic polymers such as polypropylene for medical supplies.²⁶ These medical applications can also benefit from the inclusion of antimicrobial components, such as embedded copper²⁷ or silver²⁸ nanoparticles, naturally derived antimicrobials (for example, *Murraya koenigii* extract²⁹) or covalently grafted antimicrobial polymers and drugs.³⁰ It is important to note that, for many of these applications, chemical modification of cellulose to further enhance or otherwise modify its properties is required. To this end, a wide array of possible chemical modifications have been developed, with new environmentally benign, non-toxic or “green” techniques being an active area of research.³¹

A strong trend identified in the data set is the use of cellulose nanomaterials^{7, 32, 33} (cellulose nanofibers, cellulose nanocrystals, and bacterial nanocellulose) and fibrillated cellulose³⁴ in biomedical applications and packaging. These emerging materials have multiple, abundant sources, including biomass and cellulose-containing waste,^{35, 36} and are significantly lower cost options compared to alternatives such as carbon nanotubes, petroleum-based materials, ceramics, and others.

For this reason, cellulose nanomaterials have widely been used as fillers to improve the barrier

and mechanical properties of other polymers,^{37, 38} including poly(lactic acid) and polycaprolactone, which are also frequently used sustainable materials. Notably, cellulose nanocrystals have been demonstrated to reduce the oxygen and water permeability of poly(lactic acid) composites, which is important in their use as packaging materials.³⁹ The macroscopic properties of these composites are strongly dependent on coupling between the cellulose nanomaterials and the matrix, which can be controlled by chemically modifying the cellulose surface.⁴⁰ Conversely, materials such as lignin,⁴¹ PEG,²⁹ and graphene⁴² have been incorporated into cellulose-based materials to further enhance their mechanical and barrier properties.

Starch, a plant-derived polysaccharide, is also a fully biodegradable, nontoxic, and low-cost resource for sustainable biomedical materials.^{43, 44} Limitations of starch-based films related to moisture sensitivity and mechanical properties can be addressed through the inclusion of fillers such as zinc oxide,⁴⁵ copper oxide,⁴⁶ montmorillonite,⁴⁷ and silver nanoparticle-immobilized cellulose nanofibrils.⁴⁸ As with cellulose, antibacterial additives such as silver⁴⁹ or chemically grafted biocides⁴⁹ can also be incorporated into starch. Chitosan is another abundant natural polysaccharide that has generated significant interest in the field of sustainable biomedical materials because of its high biodegradability and biocompatibility.^{50, 51} For example, chitosan has been chemically modified and combined with other naturally derived materials to make strong, self-healing materials with antibiotic effects.⁵²

Poly(lactic acid) (PLA) is the most frequently used polymer in this field, because it can be synthesized from a variety of naturally abundant sources, and is both biocompatible and biodegradable.^{24, 53} However, along with these major advantages, PLA has a number of weaknesses related to its processability and material properties.

These weaknesses can largely be addressed through physical blending with other polymers or naturally derived substances (such as cardanol),⁵⁴ chemical modification, nanomaterial fillers (including silica⁵⁵ and graphene⁵⁶), and even CO₂ treatments.⁵⁷ Alternate synthesis methods

for PLA, for example in situ self-nucleating polymerization,⁵⁸ can also provide routes to improving manufacturability and physical properties. A subset of these additives has been studied for their ability to confer antimicrobial properties to PLA.⁵⁹

Similarly, polycaprolactone (PCL) is also a commonly used biodegradable polymer that is frequently referenced in publications on sustainable biomedical materials. In addition to biocompatibility, PCL-based materials have also been engineered to have shape-memory (as PCL-polyurethane-chitosan composite⁶⁰) and photocurable properties (as polycaprolactone diacrylate⁶¹), enabling them to be formed using stereolithography and 3D printing via digital light processing.

Other notable materials that appear in **Figure 5** are graphene,^{62, 63} silica,^{64, 65} zinc oxide (ZnO),^{66, 67} and silver,⁶⁸ which are used as fillers to improve functional properties and, in the case of ZnO and silver, to confer antibacterial properties. These materials are often used in the biodegradable polymers discussed here.

In **Figure 6**, we have identified several emerging materials, the use of which has increased significantly since 2018. These include materials that have been discussed above, including graphene, ZnO, starch, and cellulose. A notable additional material is the biodegradable polyester, adipic acid-1,4-butanediol-terephthalic acid copolymer (also known as polybutylene adipate terephthalate or PBAT). Examples of its use include blending PBAT with PLA and reinforcing fillers to make medical equipment,⁶⁹ combining PBAT nanofibrils with PLA to improve barrier properties for medical packaging,⁷⁰ and melt-blending PBAT with used coffee grounds containing lignocellulosic material as a reinforcement in a biodegradable composite.⁷¹

From this document data set, the prevalent biomedical applications of sustainable materials can be broken into three major areas:

- Disposable medical clinic and laboratory supplies, such as face masks, gloves, surgical gowns, bandages, and labware
- Packaging used in medical settings
- Materials used for a variety of medical purposes, manufactured using alternative or novel methods which are environmentally benign compared to traditional methods

In the first category, there are several examples of new materials and methods for making personal protective equipment, particularly face masks, motivated by the increase in the use of these masks during the COVID-19 pandemic.^{15,72} Materials for these applications include PLA,^{73, 74} poly(butylene succinate),⁷⁵ cellulose,²⁶ and chitosan.⁷⁶ For mask filter applications, electrospinning is a prominent technique for forming nanoscale fibers from these materials,^{5, 77, 78} which can be used to make fine particle filters. In some cases, these biodegradable, electrospun fiber-based filters have comparable or better particle removal characteristics compared to traditional N95 masks, which are typically made using melt-blown polypropylene fibers. The performance of these materials can be further enhanced by embedding antimicrobials,⁷⁹ or through the incorporation of polar functionality in the filter, for example by adding chitosan.⁷⁴

Beyond personal protective equipment, sustainable materials such as algae-derived starch, PLA, and lignin have been used to make medical packaging materials^{44, 70, 80} and single-use medical diagnostic equipment.^{81, 82}

Examples of the third category include environmentally benign or “green” methods to synthesize materials used in biomedical applications, including gold,⁸³ silver, platinum,⁸⁴ and ZnO⁸⁵⁻⁸⁷ nanoparticles, MXenes,⁸⁸ and polyesters (through the use of lipase catalysts).⁸⁹

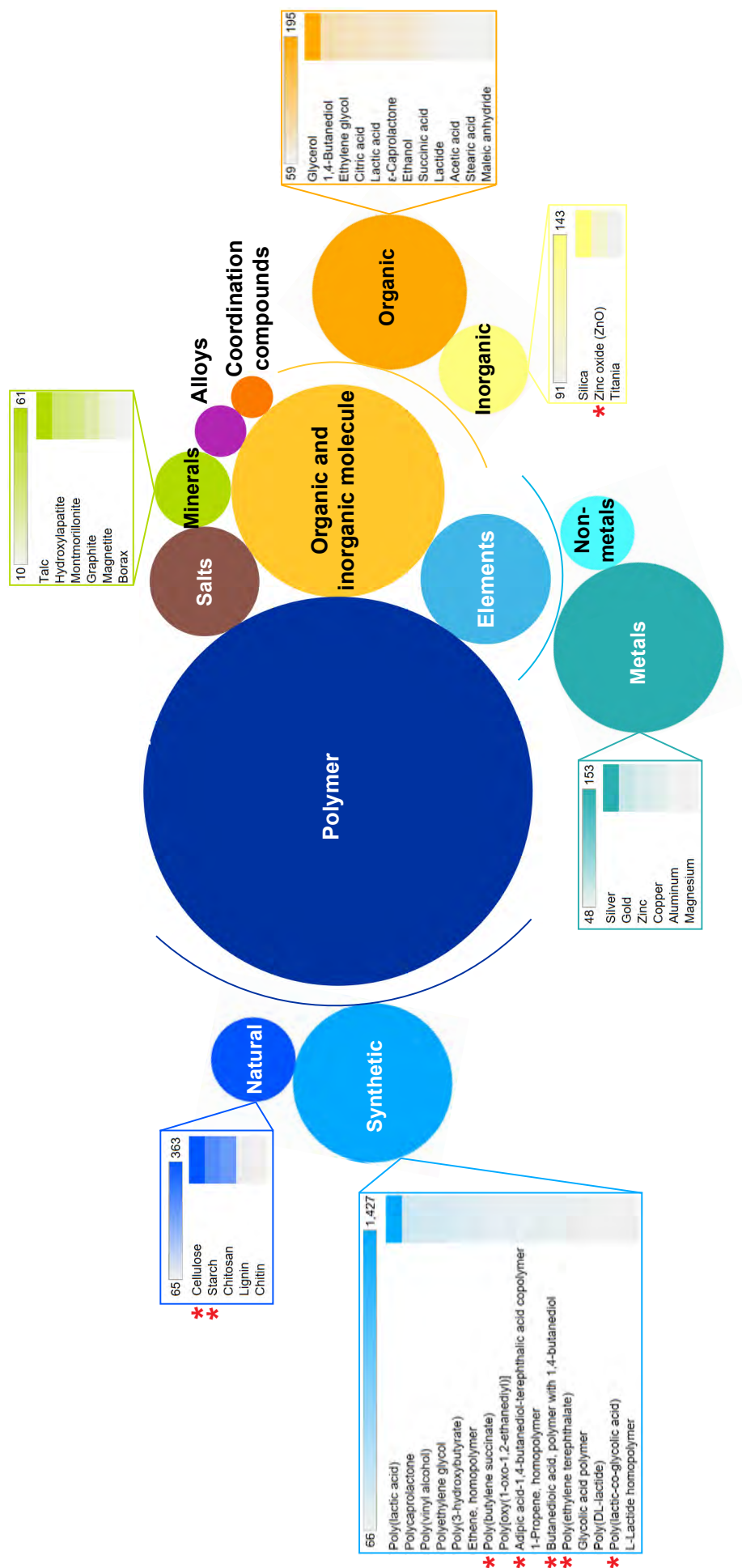


Figure 5. Bubble chart showing distribution of substances used in sustainable biomedical materials in terms of number of publications (journals and patents) from 2003-2023.

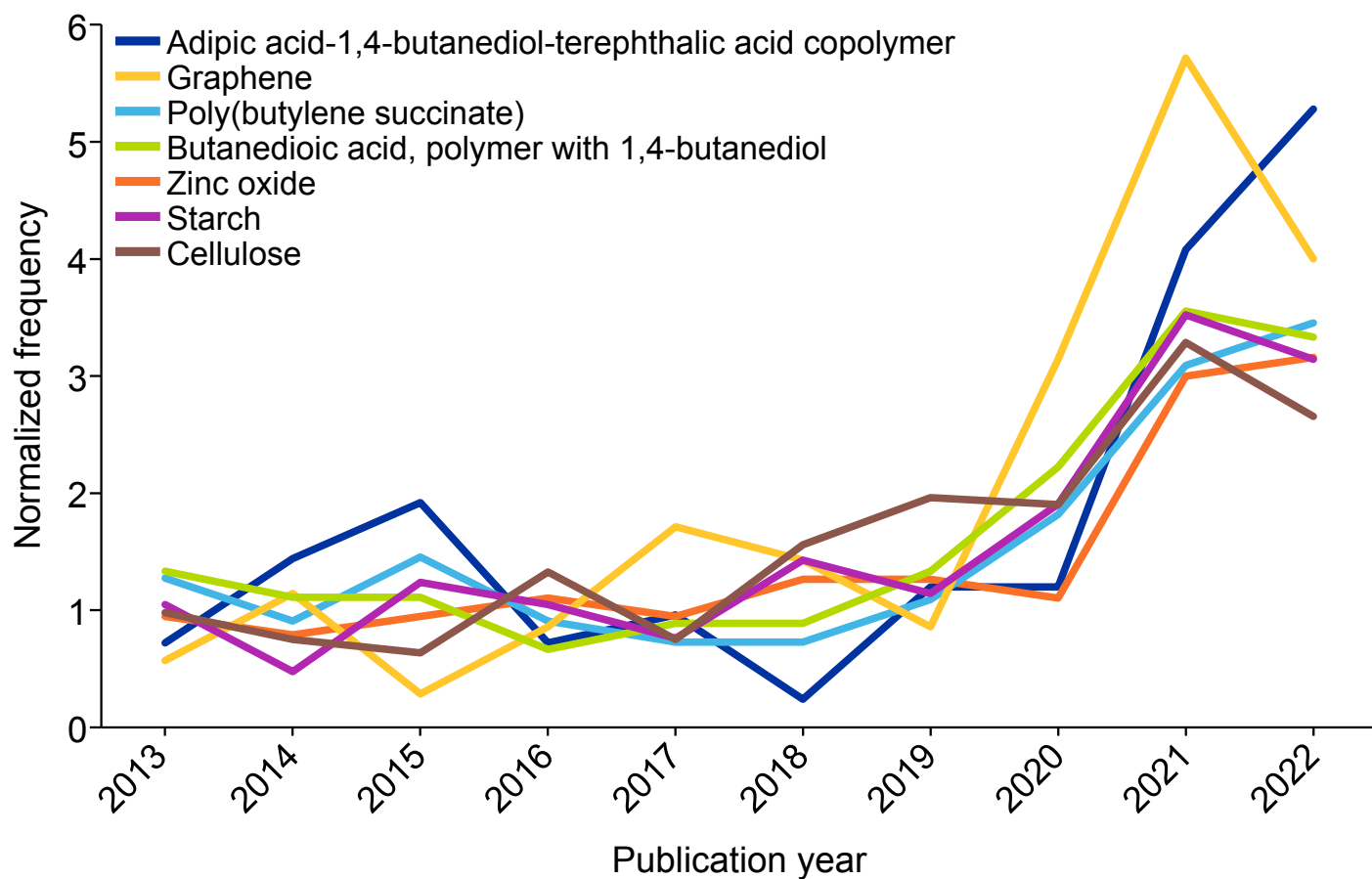


Figure 6. Normalized frequency of representative emerging sustainable biomedical materials in journal and patent publications from 2013-2022.

Notable journal articles and patents

Table 1 is a set of research articles published from 2020-2023 that represents emerging trends in the field of sustainable biomedical materials. These references provide examples of the materials and applications which appear prominently in our analysis of the literature in this area as presented in Section III. Selection criteria for these examples also included high citation count, and/or publication in high impact factor journals.

A notable example from **Table 1** is a single-use face mask reported by Choi et al.,⁷⁵ which contains a poly(butylene succinate)-based filter material coated with chitosan nanomaterials that leverages the polar groups present on the chitosan surface. This nanofiber/microfiber integrated filter provides a high particulate matter removal efficiency (98% of 2.5 μm PM, similar to an N95 filter) with a low pressure differential across the filter, which is important for breathing comfort. This filter material further retains its performance after exposure to moisture. Biodegradability of the material was also demonstrated, with complete decomposition within four weeks after the mask is disposed in a composting soil.

Novel biomedical materials have also been designed specifically to be recyclable. A notable example of this is an electronic skin (an important material in human-computer interfaces^{90, 91}) developed by Li et al.⁹² This material, which is composed of cellulose nanofibrils (CNFs), poly(vinyl alcohol), and EGaln liquid metal droplets, can be recycled by simply cutting it into small pieces, dissolving it in water, then re-casting it. Notably, this e-skin also addresses limited stretchability,⁹³ a common issue with the use of liquid metals in electronic skin, by forming the material into a Kirigami structure. Through different cutting methods, these structures can perform various stretching types while maintaining consistent electrical properties.

Gold nanoparticles (AuNPs) are used for drug delivery,⁹⁴ biosensing,⁹⁵ catalysis,⁹⁶ and other applications. Sustainable synthesis of AuNPs has become an active area of research,⁹⁷ with biosynthesis approaches being one important class. As an example, Subbulakshmi et al.⁹⁸ utilized a type of marine red seaweed, *Gelidiella acerosa*, to produce AuNPs that showed antibacterial

properties against gram positive bacteria, photocatalytic degradation of commercial dyes.

Notable patents and patent applications on sustainable biomedical materials published from 2018-2023 are listed in **Table 2**. Some of these involve matching existing sustainable materials, such as poly(lactic acid), polycaprolactone, and cellulose, with biomedical applications where non-sustainable materials are currently used. Examples include US20200189230A1 (multilayer abrasive medical wipe made using cellulose, poly(lactic acid), or other biodegradable materials), AU2021106722A4 (biodegradable medical gloves made from polycaprolactone, starch, and glycerol), and WO2022026784A1 (recyclable absorbent packaging containing cellulose).

The list also contains examples of modifying sustainable materials to give them additional features (such as antimicrobial, anti-wetting, or specific mechanical properties), allowing them to meet the requirements of an existing commercial application. These include CN114349940A, which discloses a method for copolymerizing PLA and PCL to make biodegradable protective gloves. The use of PCL softens and lowers the melting point of the PCL, both important for the application, and eliminates the need for phthalate plasticizers.

A second example is WO2023089562A1, which discloses a method to deposit bio-based saccharide fatty acid esters onto cellulose-based materials to make them hydrophobic and lipophobic. This approach can replace the use of fluorocarbons, silicone, and petroleum-derived materials as surface treatments.

A notable application discussed in previous sections was the use of sustainable materials treated with antimicrobial materials for face masks. As an example, CN115704183A describes forming a face mask filter using melt-blown PLA fibers, then treating the filter with a suspension of carbon nitride and nanoscale TiO_2 particles, which can inhibit bacteria and virus activity through photocatalytic effects.

Table 3 contains a list of products that incorporate sustainable materials, and the companies that make each product, with references to product literature. The products in the table can be

grouped into PPE (including gloves and face masks), pharmaceutical packaging, general medical packaging, and other applications. The materials represented in the table include poly(lactic acid),^{48, 99} cellulose,^{50, 100-102} as well as other plastics derived from natural sources such as sugarcane¹⁰³ and castor oil,¹⁰⁴ and sustainable materials with antimicrobial coatings.¹⁰¹

In many cases, the sustainable materials in **Table 3** are meant to replace non-sustainable materials that are used currently. These include plant material-derived face masks,¹⁰⁵ biodegradable examination gloves,¹⁰⁶ and pharmaceutical packaging that can be recycled

or composted.^{100, 107} An illustrative example is a reusable pharmaceutical container combined with a compostable refill pouch.¹⁰⁸ Beyond these examples, medical packaging and devices have been designed to reduce the amount of waste they generate, through product design or recycling programs.^{109, 110}

A final important aspect to the examples in **Table 3** is that they represent a range of company sizes, from large, established chemical and medical supply companies to smaller startup operations. For startups, the amount of investment raised to date, where available, has been included in the “company” column of **Table 3**.

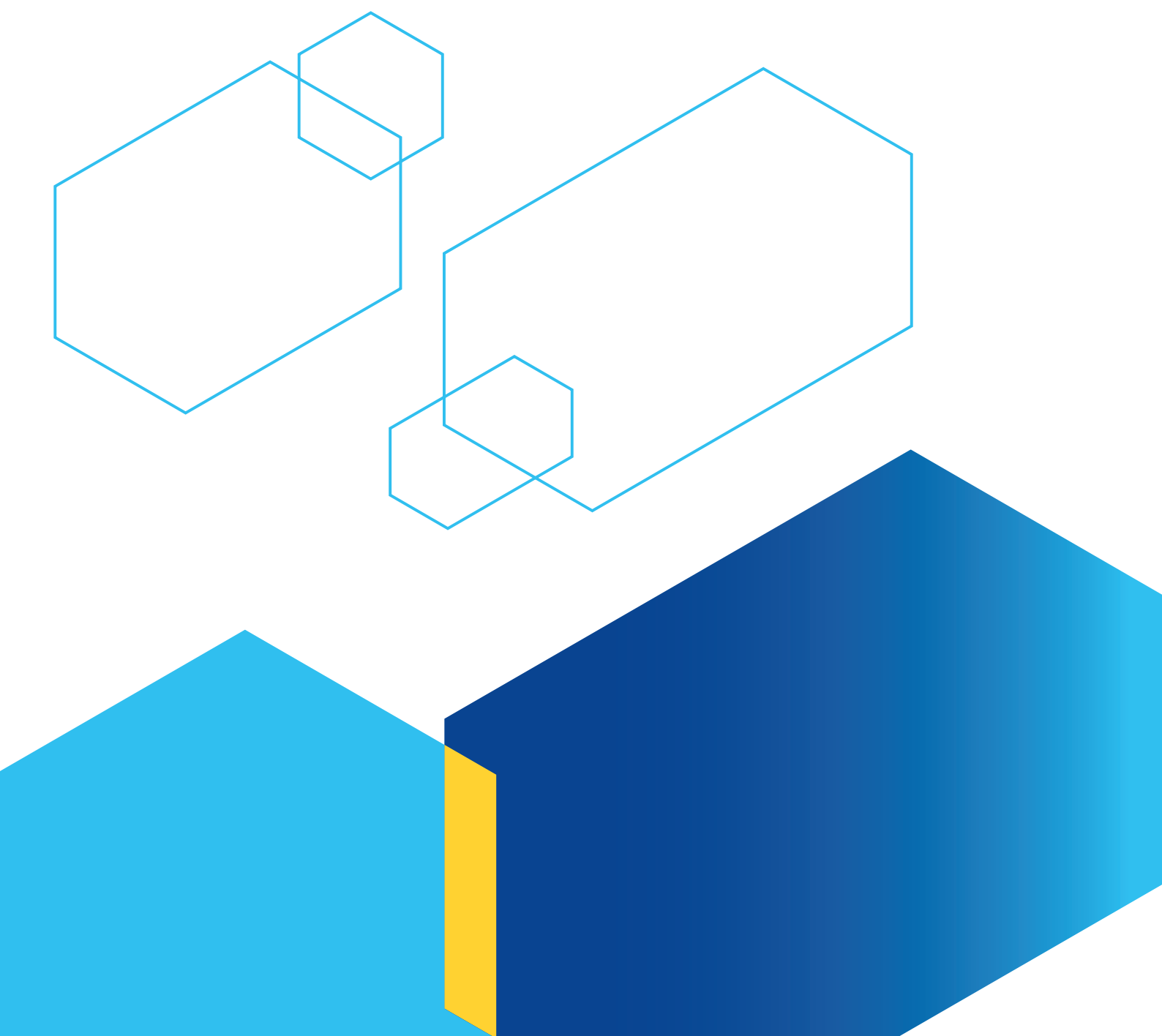


Table 1. Notable journal articles on sustainable biomedical materials in recent years.

Year	Title	Journal	Research Institute	Application
2020	Poly(lactic acid) based biocomposite films reinforced with silanized nanocrystalline cellulose ¹¹¹	International Journal of Biological Macromolecules	Zhejiang Sci-Tech University	Addition of nanocrystalline cellulose (NCC) to PLA to improve its barrier, thermal, and mechanical properties. Modification of the NCC with 3-aminopropyltriethoxysilane significantly improved the thermal stability of the composite material.
2020	Sonication amplitude and processing time influence the cellulose nanocrystals morphology and dispersion ¹¹²	Nanocomposites	Western New England University	Cellulose nanocrystals were dispersed in a PVA-water matrix using sonication. The effect of sonication time and amplitude on the shape, size, and crystallinity of the cellulose was characterized.
2020	Antibacterial Al-doped ZnO coatings on PLA films ¹¹³	Journal of Materials Science	Italian National Agency for New Technologies	Al-doped ZnO / PLA film composites for food packaging and biomedical applications. The purpose of the Al-doped ZnO is to provide antibacterial and UV-blocking properties while maintaining high transparency in the visible range.
2020	A sustainable synthetic route for biobased 6-hydroxyhexanoic acid, adipic acid, and ϵ -caprolactone by integrating bio- and chemical catalysis ¹¹⁴	Green Chemistry	Lund University	Sustainable, bio-based process to synthesize ϵ -caprolactone, a precursor for polycaprolactone by first oxidizing 1,6 hexanediol to 6-hydroxyhexanoic acid using the bacteria <i>Gluconobacter oxydans</i> , followed by conversion of 6-hydroxyhexanoic acid to ϵ -caprolactone using zeolites and acidic ion exchange resin as catalysts
2021	Biodegradable, Efficient, and Breathable Multi-Use Face Mask Filter ⁷⁵	Advanced Science	Korea Research Institute of Chemical Technology	Biodegradable, moisture-resistant, highly breathable, and high-performance fibrous mask filters with biodegradable fibers coated with cationic chitosan.
2021	Needleless electrospun phytochemicals encapsulated nanofibre based 3-ply biodegradable mask for combating COVID-19 pandemic ⁷⁹	Chemical Engineering Journal	India Ministry of Defence	Design of a three-layered face-mask by using biodegradable poly(lactic acid) and cotton with encapsulated phytochemicals in the inner-filtration layer.
2021	Lead-free nanocomposite piezoelectric nanogenerator film for biomechanical energy harvesting ¹¹⁵	Nano Energy	Cadi Ayyad University	Self-poled, lead-free, biocompatible, and bio-flexible piezoelec. nanogenerator (BF-PNG), $\text{Ba}_{0.85}\text{Ca}_{0.15}\text{Zr}_{0.10}\text{Ti}_{0.90}\text{O}_3$ nanoparticles, are functionalized with polydopamine and embedded in biodegradable poly(lactic acid).
2022	System-level integrative analyses for production of lignin hydrogels ¹¹⁶	Green Chemistry	Kyung Hee University	Two strategies for the synthesis of a biomedical lignin hydrogel. While choosing the raw materials, native vs. methacrylated, these strategies consider the overall technoeconomic analysis and life-cycle assessment of the process.
2022	A Self-Supporting, Conductor-Exposing, Stretchable, Ultrathin, and Recyclable Kirigami-Structured Liquid Metal Paper for Multifunctional E-Skin ^{92, 116}	ACS Nano	Zhengzhou University	The traditional liquid metal electrodes has low performance of electrophysiological monitoring due to limited direct skin contact. This study reported a kind of LM electrode which is self-supporting, conductor-exposing, stretchable, ultrathin, and recyclable for multifunctional E-skin.
2023	Tough, anti-drying and thermoplastic hydrogels consisting of biofriendly resources for a wide linear range and fast response strain sensor ¹¹⁷	Journal of Materials Chemistry A	Wuyi University	To overcome the challenges of nonlinearity and long response time in wearable devices, this study presented a wide linear range and fast response strain sensor based on ionic conductive hydrogels, composed of biodegradable PVA, chitosan, and biogenic phytic acid.
2023	Biogenic gold nanoparticles from <i>Gelidiella acerosa</i> : bactericidal and photocatalytic degradation of two commercial dyes ⁹⁸	Applied Nanoscience	Alagappa University	Investigation of marine red seaweed generated gold nanoparticles (AuNPs), which showed activity against bacteria <i>Staphylococcus aureus</i> and can be degraded upon exposure to sunlight.

Table 2. Notable patent publications on sustainable biomedical materials in recent years.

Patent or Pub. number	Pub. year	Patent assignee	Title	Description
CN107629424A ¹¹⁸	2018	Toray Advanced Materials Research Laboratories China Co Ltd	Microporous polylactic acid membrane	Biodegradable poly(lactic acid) film that has 1-3000 nm pores on its interior, and on one surface, but not the other surface, for use in packaging and biomedical applications
US20200189230A1 ¹¹⁹	2020	North Carolina State University	Composite sheet comprising biodegradable or compostable materials and uses thereof	Biodegradable, multi-layer sheet where the outer abrasive layer is made by melt-blowing polymer fibers, for use as a medical wipe
CN112521663A ¹²⁰	2021	Hubei Guanghe Bio-tech Co., Ltd.	Fully degradable medical packaging bag and preparation method thereof	Melt-blended biodegradable material for medical packaging containing silane-modified polyhydroxybutyrate/alginate, starch, polycaprolactone, poly(lactic acid), TiO ₂ , and other additives.
AU2021106722A4 ¹²¹	2021	Mohanty et al.	Biodegradable disposable gloves	Biodegradable polycaprolactone gloves with a patterned ergonomic design
CN113512185A ¹²²	2021	Jiangnan University	Preparation of thermoplastic biodegradable glove material with excellent tensile recovery performance and mechanical properties	Gloves made by melt blending two biodegradable polyesters, followed by a transesterification reaction
CN114349940A ¹²³	2022	Shandong Hengchang Medical Technology Co., Ltd.,	Preparation method of polylactic acid-based self-plasticized fully biodegradable gloves	Method for reducing the rigidity of poly(lactic acid) by copolymerizing it with ε-caprolactone for use in gloves, eliminating the need for phthalate plasticizers
WO2022026784A1 ¹²⁴	2022	The Procter & Gamble Company	Absorbent article package material with natural fibers	An absorbent material that contains natural fibers: cellulose-based fibers, bamboo based fibers, cotton, for packaging purposes
KR2436259B1 ¹²⁵	2022	Ecoclean Platform Corp	Hazardous substance adsorption member comprising biodegradable polymer to which natural product-derived composition is applied	Absorbent material made using melt-blown poly(lactic acid) fibers, porous silica, and naturally derived antibacterial and antiviral substances, that can be used for gauze, bedding, and other biomedical applications
WO2023089562A1 ¹²⁶	2023	Greentech Global Pte. Ltd	Water-insoluble, high melting point saccharide fatty acid esters (SFAE)	Method for treating cellulose based materials with renewably sourced coating compositions to make them hydrophobic and lipophobic
ZA2022011225A ¹²⁷	2023	Anhui Polytechnic University	Chitosan-starch composite film, preparation method and application thereof	Method for synthesizing a chitosan-starch composite film, where the amino groups of chitosan are first protonated using acetic acid before combining it with starch; the film can be used for medical packaging
CN115594962A ¹²⁸	2023	Shandong Intech Medical Technology Co., Ltd.	Biodegradable surgical gown and preparation thereof	Biodegradable, low cost surgical gown material made by melt blending polyhydroxyalkanoate, poly(lactic acid), and other additives
CN115704183A ¹²⁹	2023	Dahe Technology Development (Nanjing) Co., Ltd.	Biodegradable polylactic acid antibacterial melt-blown cloth for mask	Poly(lactic acid) based face mask that contains photocatalytically antibacterial TiO ₂ particles

Table 3. Examples of commercial sustainable materials for biomedical applications.

Application	Company	Product summary	Reference	Location
Personal protective equipment (PPE)	Ahlstrom	100% bio-based, biodegradable face mask made from PLA fibers (outer layers) and cellulose-based fibers (filter) ^{a,b}	130, 131	Finland
	G95	100% plant-based KN95 face mask ^{a,b}	105	USA
	Inovenso	Electrospun fiber materials for face mask filters made from polycaprolactone, PVA, and collagen ^b	132	USA
	Kingfa Science and Technology	Biodegradable PLA and nitrile gloves, surgical masks, and other PPE ^{a,b}	133	China
	Platinum Health	Biodegradable nitrile examination gloves ^b	106	USA
Pharmaceutical packaging	Amcor	Recyclable pharmaceutical blister packaging ^b	107	Switzerland
	Astellas	Biomass-derived plastic for pharmaceutical blister packaging (claimed to be the world's first) ^a	103	Japan
	Cabinet Health	Compostable pharmaceutical packaging made of cellulose and other bio-sourced materials ^{a,b}	134	USA
	Grounded	Compostable, recyclable pharmaceutical packaging ^{a,b}	108	Australia
	Körber	Paper and cardboard-based pharmaceutical packaging and rapid tests ^{a,b}	100	Germany
General medical packaging	Billerud	Medical packaging paper, recyclable and sourced through sustainable forestry ^a	102, 135	Sweden
	Biorigin	Medical paper products with antimicrobial and hydrophobic coatings, made using recycled/compostable materials ^{a,b}	101	USA
	Coveris	Sustainable and recyclable medical packaging ^b	136	Austria
	Medline	Compostable poly(lactic acid) patient belonging bag ^b Endoscope transport tray made from recycled sugar pulp ^a	99, 137, 138	USA
	Qingdao Fullsun Biotechnology	Biodegradable corn starch / poly(lactic acid) blend biohazard medical waste bags ^{a,b}	139	China
Other / general applications	Arkema	Rilsan® MED, a polyamide produced from castor oil is used in healthcare applications ^a	104, 140	France
	Eastman	Eastar Renew 6763, a recyclable polyester-based material used for rigid medical packaging ^a	141, 142	USA
	Henan Lantian Medical Supplies Co.	Poly(lactic acid) and cellulose-based biodegradable medical textiles ^{a,b}	143-145	China
	Mediclo	Medical apparel made using plant-based or recycled polyester fibers ^a	146	USA
	NewGen Surgical	Sugarcane bagasse-based surgical supplies ^{a,b}	147	USA

a. Made using sustainably sourced or bio-based materials; b. Engineered to be recyclable, biodegradable in the environment or landfills. Raised amounts are from Pitchbook (my.pitchbook.com, accessed Nov. 20, 2023).

Challenges and perspectives

Challenges to wider adoption of sustainable materials for biomedical applications include their sensitivity towards common sterilization methods,¹⁴⁸ high cost of synthesis and fabrication compared to the conventional,^{5, 149} faster degradation in performance of the materials, hydrophilicity, difficulty with processing,^{5, 150} and environmental sensitivity (PLA, for example, is prone to degradation under certain enzymatic conditions).⁵ Fabrication of sustainable materials can be complicated,⁵ in part due to complex extraction process from the natural sources, which in turn increases the cost. Addressing these issues is an active area of research. For example, the sensitivity of polylactic acid towards sterilization methods can be overcome by using additives such as zinc oxide.¹⁴⁸

PLA is widely used in sustainable packaging applications across several industries. While PLA is biodegradable and made from abundant natural sources, environmental analysis of processes used to make it must also take into account energy input requirements, as was recently done for a process used to make PLA using wheat straw as a feedstock.¹⁵¹ If these processes are significantly more energy-intensive compared to processes used to make alternative, non-sustainable materials, then the overall environmental effect may not be positive.

As discussed in previous sections, PLA has drawbacks such as brittleness, degradation under specific conditions, high gas permeability and low thermal resistance.^{152, 153} Composites of polylactic acid with other biodegradable polymers, non-biodegradable polymers and oxides are under study to overcome these drawbacks.^{152, 154} Co-polymerizing PLA with other sustainable polymers is also reported to overcome the drawbacks of PLA.¹⁵⁵

Polyhydroxyalkanoates (PHA) are another group of biodegradable polymers which are challenging to synthesize due to high cost, difficulty in customizing properties, and complexity associated with its synthesis from the bacteria.^{149, 156} To avoid this, alternate methods for the synthesis of PHA are under development.^{157, 158} PHA lacks intrinsic antibacterial activity, impact resistance,

and thermal stability, which can be overcome by forming composites with graphene.¹⁵⁹ Another strategy to improve the properties of PHA is the use of multi-PHA blends.¹⁶⁰

One of the problems associated with cellulose nanocrystal based materials is their hydrophilic surface properties, and difficulty with their dispersion when using them in polymer matrix composites.³⁷ To decrease the hydrophilicity of cellulose nanocrystals, surface modifications with hydrophobic functional groups and coatings are under development.¹⁶¹

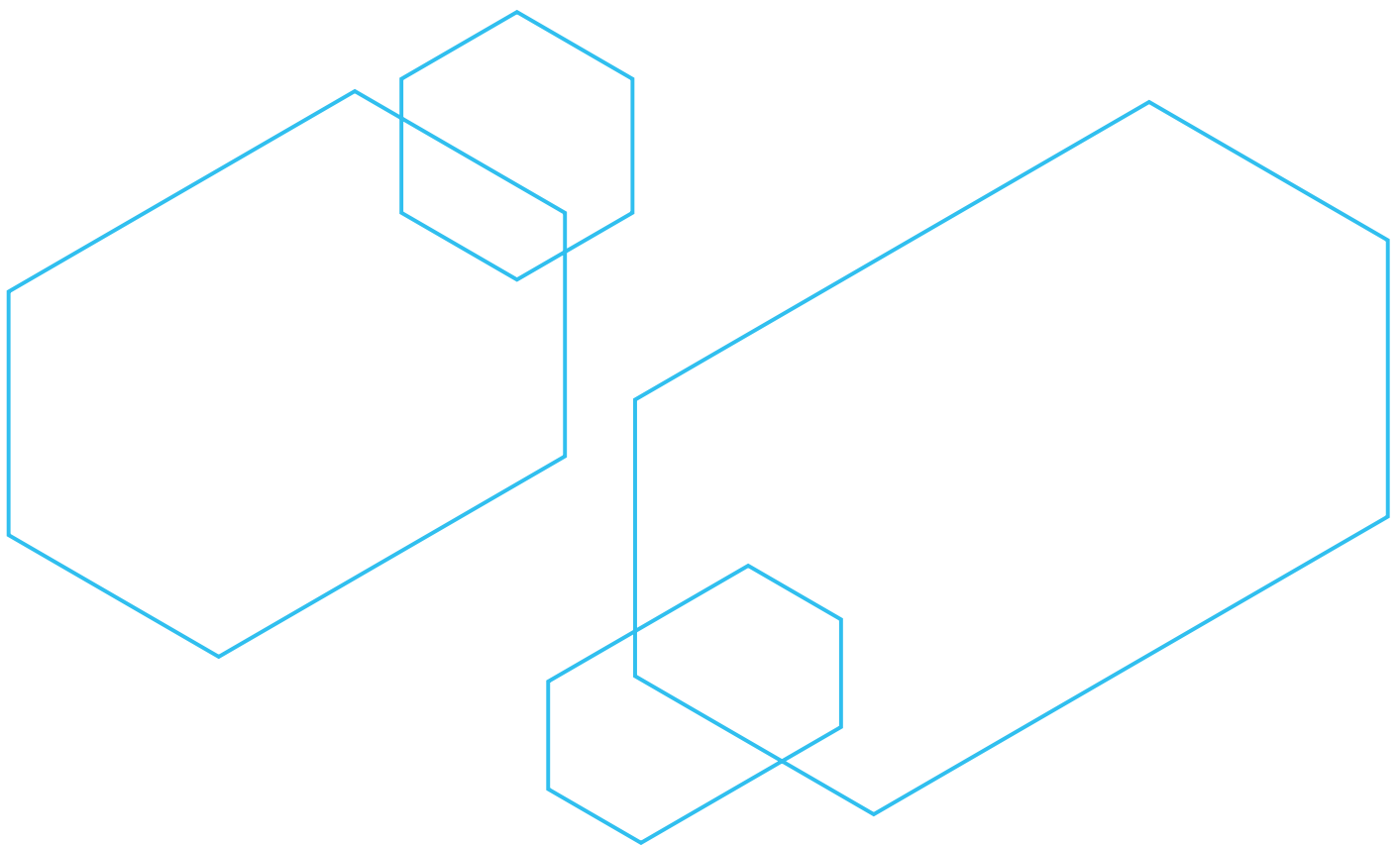
Succinate polyesters are a group of bio-based synthetic biodegradable polymers which face challenges due to the use of metallic catalysts during their synthesis,¹⁶² making them difficult to use for biomedical applications.¹⁶³ In addition, the high temperature used in this method also leads to large variations in chain lengths. To overcome these issues, biotechnological synthesis routes like enzymatic catalysis methods are under development.^{164, 165}

In terms of manufacturing methods, as discussed earlier in this chapter, electrospinning can be used to make biodegradable nanofibers and other materials from sustainable materials. However, many electrospinning processes use a significant amount of solvents which are not environmentally friendly.⁵ Greener alternatives to electrospinning are under development which will help in reducing the impact of such methods.^{166, 167}

PPE and packaging are applications with high interest for sustainable materials development. However, practical challenges related to material properties remain. For example, cellulose-based face masks have difficulty matching the filtration efficiency and breathability of conventional non-biodegradable face masks.⁶ In addition, large scale production of cellulose based masks remains a challenge.⁶ It is desirable to achieve a balance between the desired mechanical properties and the biodegradability.¹⁶⁸ Various organizations are working on the development of cellulose based materials for sustainable applications, with production expected to grow once manufacturing processes become more affordable.¹³

For sustainable packaging materials, obstacles to more widespread use include high cost, poor barrier and mechanical properties.¹⁶⁹ To overcome these challenges, composites of multiple sustainable materials are under development for packaging applications.^{170, 171} Furthermore, higher level design strategies can help in addressing some of the inherent drawbacks of the materials.^{172, 173}

Often, sustainable materials must also displace incumbent non-sustainable options for a given application. Sustainable materials face difficulties in replacing current materials; the costs of sustainable materials are in many cases higher than those of current materials, resilient supply chains need to be established for them, and for some uses regulatory approval for the replacements must be obtained which requires additional testing and resources.



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X. Conclusions

In this section, we will first summarize the recent journal and patent publication trends observed across the eight topic areas, then discuss prominent themes in the applications and challenges found throughout this report, and finally identify the major material types that are currently being researched to address these complex applications and challenges.

By examining journal publication trends, we can roughly classify the eight topic areas as either having rapid and exponential growth from 2013-2023, or as having research activity even before that time which has steadily increased until now. The former category, which includes bioinks and self-healing materials, has seen a roughly tenfold increase in publication frequency in the last 10 years. The latter category, which includes the other six topics, has increased in journal publication frequency by between two- and fourfold since 2013, indicating continued strong interest in these topics.

Most of the topic areas have seen a correlating increase in the frequency of patent publications. The exceptions to this are programmable, protein-based, and to a lesser extent lipid-based materials, where patent activity has been relatively flat. While the data does not point to a specific cause for this, the trend indicates that university research activity has increased more rapidly compared to commercialization over the last 5-10 years. This may indicate that there are perhaps fundamental materials challenges preventing more widespread commercialization that still need to be solved through scientific research.

For each of the eight topic areas, we identified a list of the 15 most influential research institutions in terms of number of publications and the average number of times each publication was cited. In most cases, the leading institution by these measures was different for each topic. There were, however, several institutions which appeared frequently across multiple topic chapters, including the Chinese Academy of Sciences, the University of California, Zhejiang University, Tsinghua University, Sichuan University, and Nanyang Technological University. The set of commercial entities with the largest number of patents tends to be quite different from chapter to

chapter, indicating a high degree of specialization within commercial research and development in these fields.

The most prominent applications discussed in this report across all topic areas were drug delivery, wound healing, tissue engineering, and sensors. Drug delivery, in particular, was discussed in the majority of the chapters, being a primary application for lipid-based, programmable, self-healing, and protein-based materials, and a secondary application for bioinks. The prominence of drug delivery as a research area in this report appears to reflect a larger, interdisciplinary effort to improve the targeting of drugs, especially anticancer drugs, while minimizing side effects due to nonspecific drug release.

The emergence of sensors as an application area is also related to an interdisciplinary trend, in this case to monitor and collect data from the human body and to use that data for diagnosis and treatment. Within this report, the types of materials that are used in sensor applications are used for their high chemical specificity, mechanical resilience, or their ability to connect key parts of the body with electronic devices (as discussed in the programmable, self-healing, and bioelectronic materials chapters).

While the materials described in this report have the potential to significantly improve the diagnosis and treatment of disease through these applications, in many cases a significant amount of research and development work remains before widespread clinical use is possible.

A major challenge across many of these emerging areas is the need for more extensive *in vivo* and clinical testing to identify and resolve possible issues with toxicity, immune response, and long-term biocompatibility of materials that are implanted or injected into the body. That challenge is made more complex by the use of materials that are not traditionally found in biomedical applications, and materials whose structure and properties are affected by conditions used in their synthesis. Regulatory agencies such as the FDA, CFDA, or EMA do not traditionally issue approvals for individual

biomaterials. Instead, testing of full medical devices or drugs made using these materials will be done in coordination with these agencies.¹

A second challenge identified in multiple chapters is the need for materials that combine highly controlled and specific functions with durability, resilience, and predictable functioning in body. Examples include flexible bioelectronic interface materials, sensors, and implants that must move along with dynamic organs such as the heart, and stimulus-responsive drug delivery materials intended to respond to a specific chemical stimulus in an environment with many overlapping potential stimuli.

Challenges to more widespread uses of the materials discussed in this report also exist outside of the applications themselves. For example, for some of the materials discussed here, economically viable, high quality, high yield manufacturing processes do not yet exist. This is particularly true for composites made specifically for highly demanding applications that require multiple, orthogonal properties (electrical conductivity and self-healing properties, for example).

As shown by the data presented in this report, these potential applications and challenges are currently being addressed through the development of a wide range of both novel materials, and materials that are being inventively repurposed for biomedical applications. Material types that were referenced across several chapters include:

- Naturally-derived polymers, such as chitosan, cellulose, hyaluronic acid, alginate, collagen, gelatin, and silk, which have the advantages of biocompatibility and natural abundance. There are also well-developed routes to chemically modify these materials to change their properties and add novel functions such as self-healing or stimulus response.
- Biocompatible and biodegradable synthetic polymers, including polyethylene glycol, poly(lactic acid), polyvinyl alcohol, and polycaprolactone.

- Hydrogels, often made using the polymers listed above. In addition to their similarity to human tissue, this report contains many examples of hydrogels that are engineered to perform complex functions, including hydrogel-based actuators, sensors, and drug delivery systems.
- Nanoscale materials, including graphene, carbon nanotubes, and metal nanoparticles.

Stimulus response was also observed in multiple topic areas, in the programmable material chapter where this was a focus, as well as in the lipid-based, self-healing, and bioinks chapters. The stimuli engineered into these materials were both endogenous (pH, enzyme, redox, and other specific chemical triggers) and exogenous (light, temperature, magnetic field, ultrasound). In some applications, multiple materials were combined to generate a stimulus response, for example combining a photothermally responsive material with a temperature-responsive polymer. In the majority of cases, the responses involved release of a drug or gene therapy material, or some other therapeutic function.

Another strong trend was the combination of multiple functional polymers, or polymers with other materials (carbon nanomaterials, hydroxyapatite, cells, and metal nanoparticles, for example). This is typically done to precisely control mechanical properties or to incorporate multiple overlapping functions in a single material.

A less explored area, but one with immense potential, is the use of artificial intelligence, computational modeling, and other computing tools to aid in the development of biomaterials, as an extension of how these tools are presently being used for drug discovery.² With the astonishing speed that AI is currently evolving, it is not surprising that these tools are already being used to understand and predict the dynamics of self-healing polymers using image analysis from healing experiments,³ to virtually screen libraries of lipids for use in mRNA-delivery lipid nanoparticles,⁴ to model the release of drugs from programmable hydrogels in the presence of multiple stimuli,⁵ and to identify peptides that have the ability to form hydrogels by combining

machine learning with selected experiments.⁶ (Notably, in this final example, a tetrapeptide hydrogel developed using the machine learning model was demonstrated to improve the immune response of a COVID-19 vaccine.) These examples illustrate the potential for AI tools to speed up the development of new biomaterials by processing and extracting information from large data sets, and reducing experimental iterations.

The exploration of biomaterials across the various chapters demonstrates both the advancements and obstacles in this evolving field. Increasing academic interest contrasts with a lag in

commercial patent activity, pointing to hurdles in translating research into practical applications. These materials hold promise in drug delivery, sensors, and other applications, with the potential to refine and revolutionize areas of healthcare. However, challenges persist in rigorous *in vivo* testing and establishing feasible manufacturing methods. The use of diverse material types, coupled with engineered stimuli and AI tools, represent multifaceted approaches to address these challenges, paving the way to reshape healthcare practices through the use of new materials.

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XI. Methods

For this report, eight topic areas were selected that represent the most active and promising fields of research within biomaterials. The selection of these topic areas was a multi-stage process. First, a broad survey of the biomaterials field was conducted using natural language processing to identify concepts with a particularly high rate of growth in journal and patent publications between 2020-2022. This analysis was combined with citation graph cohesiveness, which is a measure of how many times publications containing a particular concept have been cited by other publications, to generate a list of candidate topics. Next, final topics were selected from these candidates for a Phase I and Phase II report (this document) through collaboration between subject matter experts at CAS and Westlake University.

The data used in this report is drawn from the CAS Content Collection™, a repository of diverse scientific knowledge containing over 59 million records from chemistry, biomedical sciences, material sciences, and other topics, which has been extensively curated by subject matter experts (SMEs). The substances referenced in each publication are indexed based on their CAS registry numbers, as well as their functional role in the document and substance classification. More than 35 roles exist, with examples including therapeutic use, pharmacological activity, and technical and engineered material use. Substance classes include organic/inorganic small molecules, protein/peptide sequences, polymers, elements, and alloys, among others. The key concepts in each document were also manually indexed, similarly classified, and included in the data set.

For each of the eight topic areas, a search query to identify the relevant document set from the CAS Content Collection was developed, then iteratively adjusted by SMEs to minimize noise based on manual quality checks. This resulted in sets of between roughly 4,000 and 120,000 for each topic, published from 2003-2023. The data extracted from these documents was comprehensive, consisting of four types: substance, concept (both as described above), document, and patent activity data. Document data includes title, abstract, publication year,

the number of times cited (for journal articles), as well as information on the authors, research institutions, and patent assignees.

Patent activity data includes detailed information about patent families and individual patents filed in 97 patent offices worldwide. From this data, leading assignees and time trends based on patent families were identified. This data also allowed for the determination of chronological flow of filing initial patent applications within patent families through national patent offices, the World Intellectual Property Organization (WIPO), and the European patent office (EPO), leading eventually to individual patent publication activities within national patent offices. In this context, an activity is defined as an event that leads to the publication of a patent document, for example application publications, issuing of patents, and certain other events.

Data from the document sets was analyzed by performing searches and filtration based the title, abstract, claims, CAS indexed terms and for CAS registry numbers in the substance data unless otherwise specified. To ensure accurate and complete analysis, the searched keywords included multiple synonyms as well as abbreviations, while taking care to minimize the number of incorrectly identified documents. Data analysis was performed using Tableau, and figures were prepared using a combination of Tableau, Microsoft Excel, and Adobe Illustrator.

When defining the countries/regions and organizations associated with a given document, the affiliation of the first author or the patent assignee was taken as the affiliation of the document. When multiple organizations were affiliated with a particular journal or patent publication, only the first author or first patent assignee's affiliated organization was considered. The countries/regions of origin were designated as the location associated with the first author's or first patent assignee's location.

Each chapter was reviewed by at least one independent subject matter expert in the relevant topic area, in order to confirm technical accuracy

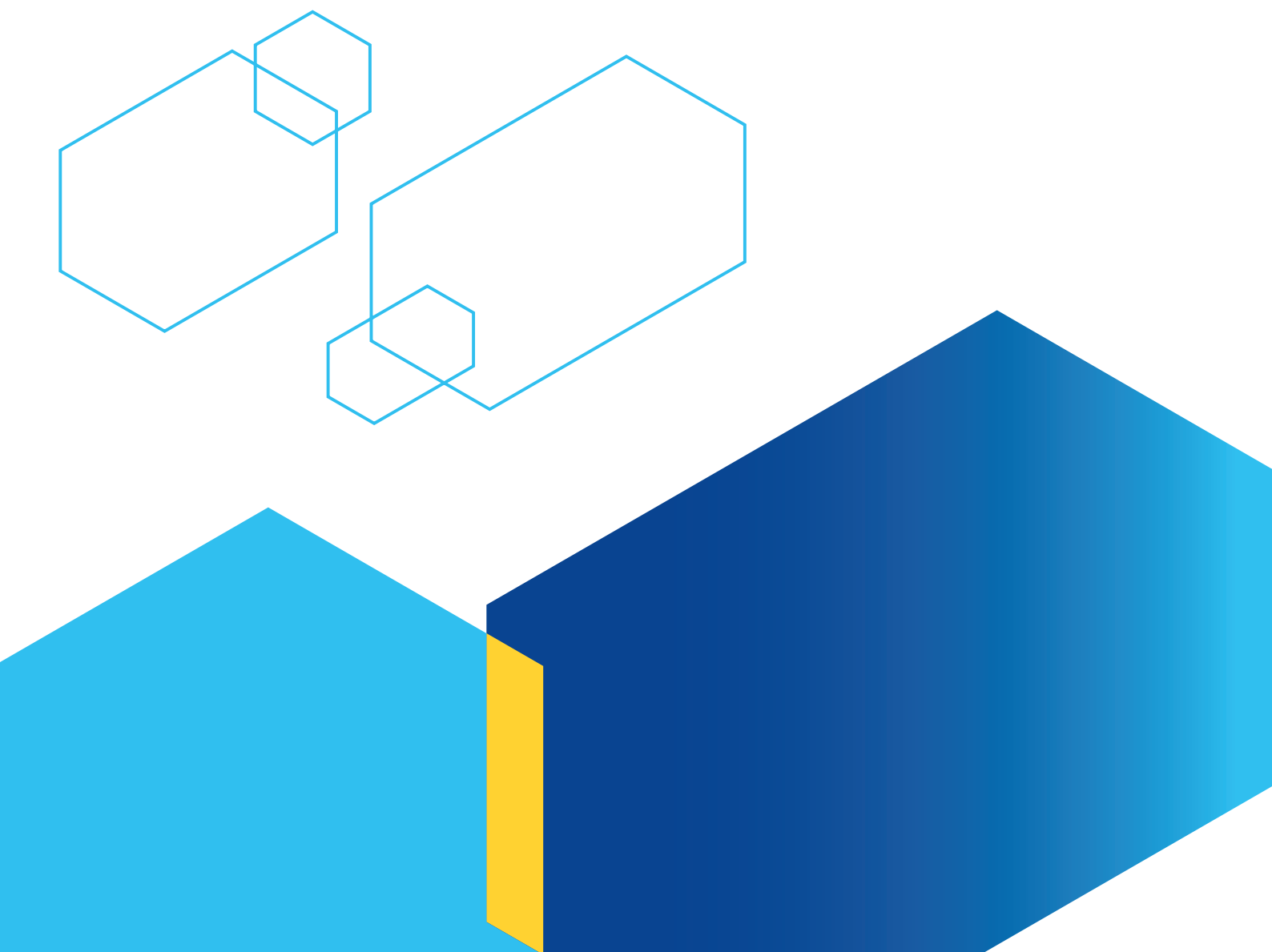
and completeness. Additional discussion and references were added to several of the chapters based on guidance and feedback from these experts.

Overall, the methodology described above encompasses a substantial volume of indexed scientific content, advanced data analytics skills, and a diverse array of biomaterials subject matter

experts. The utilization of modern tools to analyze millions of documents, seamlessly guided and interpreted by subject matter experts, was made feasible through the exceptional resources dedicated to this project. Importantly, this project also involved collaborative efforts between teams at Westlake University and CAS, operating at a detailed technical level, and leveraging the comprehensive CAS Content Collection.

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