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REVIEW

# Biomanufacturing in Japan: frontier research from 2018 to 2023

Qing Cao[1,2] · Yangqianhui Zhang[1,2] · Runyi Deng[1,2] · Kai Ren[1,2] · Huayong Yang[1,2] · Dong Han[1,2]

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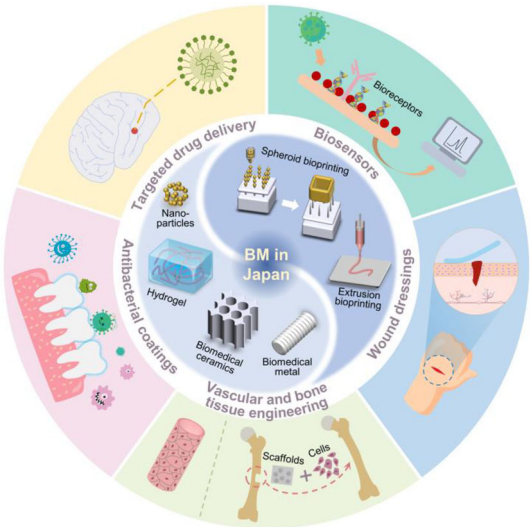
## Abstract

Biomanufacturing (BM) is a multidisciplinary area incorporating the characteristics of living organisms and engineering principles to create valuable products for various sectors, including medicine, energy, and the environment. BM has undergone a remarkable transformation in the last two decades, entering the era of BM 4.0 and becoming a pivotal driver of the sustainable revolution. Notably, Japan has made significant advances in BM, contributing to its development through the creation of innovative materials, advanced processes, and interdisciplinary applications. However, because of certain development policies, this research has not been widely recognized on an international level. This paper provides a comprehensive summary of the research progress made by renowned Japanese laboratories and researchers in biomedical materials, bio-three-dimensional (3D) printing, and biomedical applications in the last five years. Their unique contributions are introduced and analyzed, illuminating the distinctive approaches and breakthroughs within each domain. Additionally, this review highlights the current challenges and prospects of BM. The viewpoints presented in this paper are intended to serve as a valuable reference for scholars studying BM in Japan.

## Graphic abstract




**Keywords** Biomanufacturing (BM) · Japan · Biomedical materials · Bio-3D printing · Biomedical applications

✉ Dong Han
dong_han@zju.edu.cn

[1] State Key Laboratory of Fluid Power and Mechatronic Systems, Zhejiang University, Hangzhou 310058, China

[2] School of Mechanical Engineering, Zhejiang University, Hangzhou 310058, China

## The past and current of biomanufacturing

Biomanufacturing (BM) is an intriguing field as it merges the principles of manufacturing and life science. BM utilizes biological systems, including living microorganisms, resting cells, and tissues, to produce biologically significant products that have widespread applications in industries such as agriculture, energy, materials, and medicine [1]. BM is highly valued by many countries. In 2010, the U.S. government proposed a high-risk, high-reward competitive project white paper titled "Manufacturing and biomanufacturing: materials advances and critical processes" [2]. This project was expected to promote significant social impacts and benefits for the country. Additionally, in 2020, the U.S. included BM as one of 11 main directions of the "2020 manufacturing technology challenge" [3].

BM has been a significant contributor in the last three industrial revolutions, such as microbial metabolites, protein drugs, and genetically modified crops. Since the inception of BM 1.0 in 1910, marked by the production of microbial primary metabolites like acetone and ethanol, BM has witnessed three industrial revolutions. Over the past two decades, it has undergone a marked transformation and entered into the era of BM 4.0 to emerge as a pivotal driver of the sustainable revolution [1, 4, 5]. This development encompasses three key aspects: biomaterials, BM processes, and biomedical applications.

Biomaterials are essential components in the development and manufacturing processes that use biological systems and serve critical functions in various applications. Among the most employed biomaterials are biodegradable polymers such as polylactic acid (PLA) and polyglycolic acid, inorganic materials such as hydroxyapatite and zirconia for bone repair, metallic biomedical materials such as titanium (Ti) alloys and stainless steels, and natural polymers including alginates, gels, and proteins [6, 7] as well as their composites. Biomaterials possess diverse properties that tailor them to applications including tissue repair, organ replacement, and disease treatment. Several renowned laboratories worldwide have made significant progress in biomaterial research and development. For instance, the Langer Laboratory at the Massachusetts Institute of Technology, led by Robert S. Langer, has been at the forefront of polymer drug delivery research [8]; the Mooney laboratory at Harvard University, led by David J. Mooney, specializes in developing biomaterials such as hydrogels for tissue repair and immunotherapy [9]; Professor Molly Stevens at Imperial College of Technology conducts research on biomedical materials and regenerative medicine, with a particular focus on nanomaterials [10]; and Professor Seeram Ramakrishna from the National University of Singapore has actively advocated for the advancement of polymer nanofibers in materials science, preparation technology, and design [11], which aims to enable diverse applications in medicine, biology, and engineering science. These distinguished laboratories conducting pioneering research have significantly advanced the biomaterial field, establishing it as an important branch within the realm of contemporary materials discipline. Consequently, new opportunities have emerged in regenerative medicine, tissue engineering, and drug discovery.

BM cannot be separated from the development of processes. Current methods for constructing biomaterials include electrojetting and electrospinning [12], micromolding [13], microfluidics [14], and bio-three-dimensional (3D) printing [15] that provide critical support and innovations for biomedical device manufacturing and therapeutics. Bio-3D printing excels in using cells, proteins, and biomaterials to construct 3D biological models, systems, and therapeutic products, making it a key process for BM. The technology employs computer-aided design software to create 3D models of tissues and organs that are used to guide the speed and position of the printing nozzles for precise deposition of cells and materials [16]. Bio-3D printing technology has revolutionized our understanding of biology by enabling the creation of artificial biological tissues [17]. The concept of bio-3D printing has been a popular topic since its conception and has attracted significant attention from the scientific community. Professor Jennifer A. Lewis from Harvard University is known for her research on ceramic colloid assembly, function, and structure, with a special focus on multimaterial bio-3D printing [18, 19]. Meanwhile, Professor Cho Dongwoo from Pohang University of Science and Technology in South Korea has concentrated on extracting bioinks from natural tissue and used 3D cell printing technology to create or repair artificial muscles and organs [20, 21]. Professor André R. Studart from the Federal Institute of Technology in Zurich uses bio-3D printing to create biomimetic composite materials such as medical implants and smart structures [22, 23]. Although bio-3D printing is still in its early stages and faces significant challenges, it has the potential to revolutionize modern medicine and healthcare.

The objective of BM is the application of advanced material technology in the realm of biomedicine. In contrast to conventional medical approaches, BM offers improved replication of the physiological environment of the human body, along with enhanced repeatability and predictability. Numerous mature biomedical research products have emerged, including microfluidic organ chips and artificial organs. These biomaterials can replicate several structural and functional features of human physiological and disease states, and microfluidic organ-on-a-chip culture devices have gained prominence as a viable alternative to traditional in vitro and in vivo models [24]. Donald E. Ingber, a professor at Harvard Medical School and the School of Engineering and Applied Sciences, is focused on researching human organ chips. These chips are used to develop and test drug and

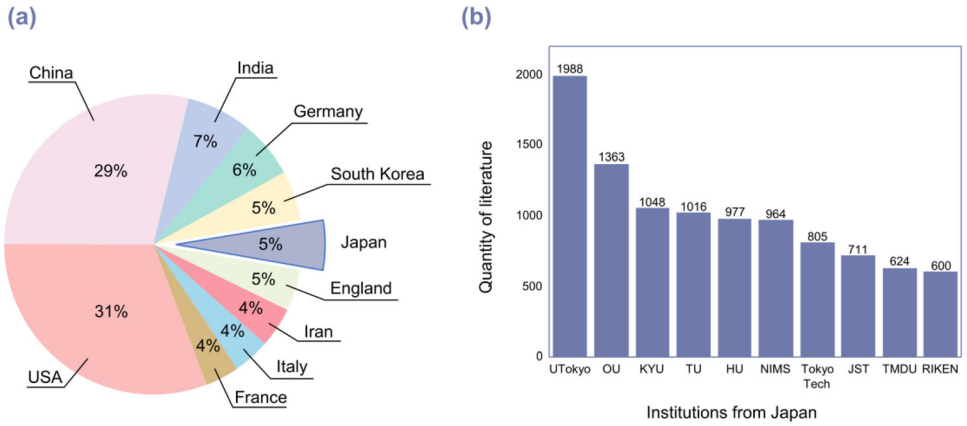



**Fig. 1** Statistics of BM research results in "Web of Science" (data as of May 10, 2023). **a** Percentage of BM research results in the top ten countries. **b** Quantity of literature from the top ten institutions involved in BM research in Japan. BM: biomanufacturing; UTokyo: the University of Tokyo; OU: Osaka University; KYU: Kyushu University; TU: Tohoku University; HU: Hokkaido University; NIMS: National Institute for Materials Science; Tokyo Tech: Tokyo Institute of Technology; JST: Japan Science Technology Agency; TMDU: Tokyo Medical and Dental University; RIKEN: Rikagaku Kenkyusho (the Institute of Physical and Chemical Research)

therapeutic antibody delivery systems, with a particular focus on the blood–brain barrier (BBB) [25]. The emergence of artificial organ technology presents a promising solution to the issue of organ shortages. By leveraging cells and biomaterials, researchers can fabricate 3D artificial organs that mimic the functions of human organs. Professor Anthony Atala, from the Wake Forest Institute for Regenerative Medicine in the U.S., is a pioneer in this field. His team successfully constructed various artificial organs, including for the bladder [26], vagina [27], and kidney [28], to lay a foundation for the practical application of artificial organs. The Doris Taylor laboratory develops new methods for rebuilding and repairing damaged heart tissues while also looking for alternate therapies [29]. This laboratory plays a significant role in advancing and innovating the field of cardiac BM. In addition to microfluidic organ chips and artificial organs, other biomedical applications such as drug delivery have reached a new level owing to the development of BM technology.

## BM in Japan

Japan has long been a leader in BM research, with the government recognizing the potential of biotechnology as early as 1984 and allocating funds for its commercial development [30]. Japan's BM industry is rapidly advancing, particularly in the medical sector, although its research production is not widely recognized at an international level. An analysis of the number of research results in BM by countries on the "Web of Science" (Fig. 1) shows that Japan accounts for only 5% of the literature in the top ten countries. This can be mainly attributed to its "Industry-University" development model. In 1998, the Japanese Diet implemented the "Promotion of Technology Transfer from University to Industry Law" [31], which aimed to encourage collaboration between academia and industry. Although this approach undoubtedly yielded significant accomplishments in commercialization by applying BM research results to industry, it neglected basic academic research, producing relatively low academic influence and popularity. Nevertheless, Japan has made significant contributions and innovations in BM that should not be overlooked.

This review undertakes an in-depth understanding of the latest research progress made by Japanese researchers in BM. It highlights the research focus of renowned laboratories in this field and analyzes the distinctive BM direction under the "Industry-University" development model. We conducted a search on the "Web of Science" for the most cited papers in BM published in Japan during 2018–2023. Consequently, we identified 15 representative scholars associated with specific biomaterials, processes, or applications (Table 1). These individuals have made considerable progress in the field of BM. In this section, we will first discuss the latest research on biomedical materials in Japan based on their work and then delve into the methods of bio-3D printing, analyzing the improvements in performance and the development of bioink types. The following are the various biomedical applications achieved through combining biomedical materials and bio-3D printing processes.

### Biomedical materials

As in western countries, the study of biomaterials in Japan first centered on dental materials, with traditional materials being the primary focus during the initial research [32].

**Table 1** Representative scholars and their research focus

| Representative scholars | Affiliations | The research focus of articles | References |
|---|---|---|---|
| Takayoshi Nakano | Osaka University | High entropy alloys for biomedical applications, nature microstructure, and function of bone tissue | [36–43, 181–188] |
| Giuseppe Pezzotti | Tokyo Institute of Technology | Enhancing the efficiency of bioceramic oxides | [57–61] |
| Kunio Ishikawa | Kyushu University | Rebuilding and regeneration of hard tissues, including teeth and bones | [62–65, 170–173] |
| Yasuhiko Tabata | Kyoto University | Using gelatin hydrogels as a drug delivery technology to increase therapeutic efficacy when combined with functional cells or medications | [77–83] |
| Jianping Gong | Laboratory of Soft & Wet Matter | Developing new types of tough and functional gels to address the low mechanical strength of hydrogels | [84–93] |
| Hiroyuki Koide | Shizuoka University | Researching the synthesis of polymer nanoparticles to achieve the adsorption and neutralization of target molecules | [95–101] |
| Equo Kobayashi | Tokyo Institute of Technology | Magnesium matrix composites prepared by spark plasma sintering | [103–106] |
| Koichi Nakayama | Saga University | "Kenzan" spheroid assembly scaffold-free bio-3D printing approach | [127–141] |
| Kazunori Kataoka | Innovation Center of NanoMedicine | Utilizing targeted nanomedicine delivery to treat neurological diseases and cancer | [145–155] |
| Hirofumi Miyaji | Hokkaido University | Appling antimicrobial coatings to the dental field | [156–160] |
| Takahiro Kanno | Shimane University | Bone regeneration material in maxillofacial surgery | [174–177] |
| Ick Soo Kim | Shinshu University | High-performance nanofibers | [164, 167, 191–197] |
| Tetsushi Taguchi | University of Tsukuba | Development of a hydrogel wound dressing with high tissue adhesion | [200–203] |
| Enoch Y. Park | Research Institute of Green Science and Technology | Biosensors for detecting pathogenic viruses | [207–214] |
| Koji Sode | Tokyo University of Agriculture and Technology | The development of second and third generation electrochemical biosensing systems for glucose monitoring enzymes in biomolecular engineering | [215–219] |

Following decades of development in medicine and material processing, biomedical materials became increasingly important in modern times, and many biomaterials with properties suitable for various applications have now been developed [33]. As shown in Table 2, biomedical materials in Japan are categorized into four main types based on their material composition: metallic biomedical materials, ceramic biomedical materials, biomedical polymers, and biomedical composites.

## Metallic biomedical materials

Metallic biomedical materials are primarily employed for treating, repairing, replacing, or enhancing human tissues or organs through implantation in the human body. Common materials used include Ti alloys and medical-grade stainless steel. For orthopedic implant materials, Ti and Ti-based alloys have become the preferred choice because of their low density and elastic modulus, which make them highly compatible with the mechanical properties of human tissues while minimizing adverse effects [34]. When a Ti implant is inserted into the body, the surrounding bone tissue initiates a biological response to the surface of the Ti material, involving processes such as osteoblast adhesion, proliferation, and differentiation to gradually establish a stable union [35]. These materials find applications in various artificial joints, including for the hip, knee, elbow, shoulder, finger, and ankle. Medical stainless steel is commonly used for repair of the skeletal system and frequently used for creating artificial joints and internal fracture fixation devices.

**Table 2** Biomedical materials in Japan

| Biomedical materials | Name | Characters | Performance improvement | References |
|---|---|---|---|---|
| Metallic biomedical materials | Titanium alloys | Low density and elastic modulus | Adjusting elemental composition, content, and microstructure | [36–55] |
| | Medical stainless steel | Rust-resistance, high strength | Changing the processing technology | |
| Ceramic biomedical materials | Bioceramic oxides | Biologically inert, high melting temperature and strength | Surface treatments | [57–61] |
| | Phosphate | Excellent stability and biocompatibility | Low-temperature dissolution–precipitation method | [62–65] |
| | Carbonate apatite | Well-balanced interconnectivity and mechanical strength | | [66–71] |
| Biomedical polymers | Hydrogel | Hydrophilic polymers, 3D network structure | Combination with functional cells or medications, a double network structure | [77–93] |
| | Polymeric nanoparticles | Large specific surface area | Adsorption and neutralization of target molecules by polymeric nanoparticles | [95–101] |
| Biomedical composites | Mg-based | Biodegradability, new bone growth irritation | Incorporation of biomedical ceramics | [103–106] |
| | PMMA-based | Processing ease, lighter weight, cost-effectiveness, aesthetic appeal, outstanding biocompatibility, inadequate mechanical properties | Doped with reinforcing fillers (nanoporous silica, titanium dioxide, or ceramic particles) | [108–111] |
| | Carbon nanotubes, graphene, and their derivatives as enhanced forms | High specific surface area, excellent electrical conductivity, thermal conductivity, biocompatibility, flame retardancy, and lighter weight | Improvement of electrical conductivity and mechanical properties of base materials | [114–119] |

PMMA: polymethylmethacrylate

The Nakano Laboratory of Osaka University, led by Professor Takayoshi Nakano, is a prominent research institute in the field of Ti alloys and medical stainless steel. Their research primarily focuses on developing new biomaterials by implementing various evaluation, analysis, and control techniques that have been developed in materials science, such as for crystallography and crystal plasticity. The performance of a Ti alloy can be altered by adjusting its elemental composition and content. This group fabricated high entropy alloys for biomedical applications (BioHEAs) using alloys consisting of five or more elements that have low toxicity (e.g., Ti-niobium (Nb)-tantalum (Ta)-zirconium (Zr)-molybdenum (Mo)) and has investigated their annealing properties [36–39]. In comparison to the commonly used medical non-magnetic stainless steel SUS316L, these new BioHEAs exhibited superior biocompatibility, mechanical properties, and processability (Fig. 2a). However, conventional fabrication methods, such as arc melting, often cause elemental segregation in BioHEAs, hindering their inherent functions of high entropy effect and solid solution hardening [40]. Recently, a laser powder bed fusion (L-PBF) was successfully used as a fabrication method, enabling ultrarapid cooling during metal solidification (up to a maximum of $1\times10^5$–$1\times10^7$ K/s) [41, 42]. This innovative approach significantly reduced elemental and phase segregation, thereby enhancing the functionality of BioHEAs. Additionally, BioHEAs with dual hexagonal closed packing structures can improve the immiscibility of constituent elements [43]. Wang et al. [44] demonstrated that the addition of aluminum (Al) content in a Ti–Nb alloy can effectively control the $\omega$-phase to develop a $\beta$-phase Ti biomedical alloy single crystal with a low Young's modulus as shown via resistivity measurement

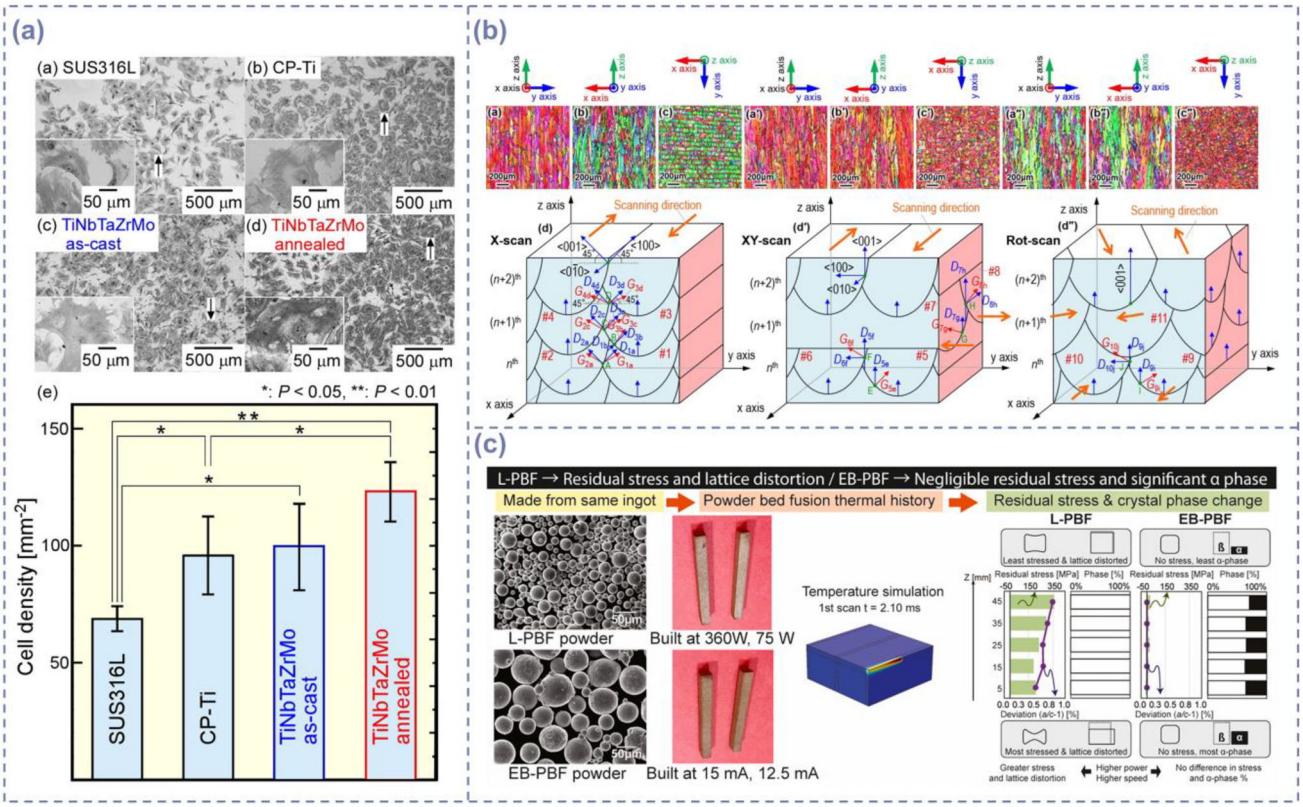



**Fig. 2** Metallic biomedical materials. **a** Comparison of the density of osteoblasts cultured on several alloys—conventional stainless steel (SUS316L), CP-Ti, and Ti–Nb–Ta–Zr–Mo. Reproduced from [36], Copyright 2016, with permission from the authors, licensed under CC BY 4.0 DEED. **b** Influence of various scanning strategies in L-PBF on alloy crystal interweaving. Reproduced from [46], Copyright 2017, with permission from the authors, licensed under CC BY 4.0 DEED. **c** The effect of two processes, L-PBF and EB-PBF, on the surface residual stress and phase stability of $\beta$-type titanium alloy Ti–15Mo–5Zr–3Al. Reproduced from [47], Copyright 2021, with permission from the authors, licensed under CC BY 4.0 DEED. CP-Ti: commercially pure titanium; L-PBF: laser powder bed fusion; EB-PBF: electron beam powder bed fusion

and transmission electron microscopy. This approach offers an alternative means of maintaining superior strength in these alloys.

The processing technology of metal implants can also be changed to enhance the mechanical properties. Sun et al. [45] developed a unique crystallographic lamellar microstructure, using the L-PBF technology in Nakano's lab that improved the mechanical properties and corrosion resistance of 316L stainless steel. In another study, the effect of various scanning strategies on texture formation was investigated for Ni-25% (atomic fraction) Mo alloy prepared via L-PBF (Fig. 2b) [46]. Altering the circumstances of sample production caused columnar cells to grow in a plane perpendicular to the scanning direction, which is crucial for forming robust textures. As shown in Fig. 2c, Takase et al. [47] examined the effect of two processing techniques, L-PBF and electron beam powder bed fusion (EB-PBF), on the surface residual stress and phase stability of an unstable $\beta$-type Ti–15Mo–5Zr–3Al alloy. The study also involved process parameter optimization for two additive manufacturing (AM) processes. In addition, laser processing methods, including L-PBF, can use air flow for the elimination of smoke generated by laser irradiation, removal of heat, and reduction of spatter generation [48]. The effect of a helium and argon atmosphere on the mechanical properties of Ti–6Al–4V (V: vanadium) alloy was investigated, highlighting the importance of atmospheric gas selection [49]. The metal AM processes offer several advantages, including reducing material waste, creating complex shapes, and shortening lead times from design to manufacturing. These benefits make the development of Ti alloys and medical stainless steel a significant step forward. In addition, AM can be used to reduce the Young's modulus of metals, thereby avoiding stress shielding caused by the gap in the Young's modulus between metallic materials and bone. This approach effectively tackles critical problems such as joint loosening when metallic materials are applied as bone implants [50]. Significant advances have also been made in this domain. For instance, alloy composite materials cobalt (Co)–chromium (Cr)–Mo [51] and Ti–6Al–4V [52] have been developed with Young's modulus similar to that of bone by using the L-PBF

and EB-PBF techniques to alter the shape of metallic materials in 2021, thus matching the anisotropic structure of living tissues. L-PBF and EB-PBF were also used to modify the crystal fabrication of Ti alloys, reducing the Young's modulus of the materials [53, 54]. Sun et al. [55] conducted a comparative study of the microstructures, crystal structures, and mechanical properties of Ti–15Mo–5Zr–3Al alloys prepared using the two processes.

### Ceramic biomedical materials

Biomedical ceramics are extensively used in load-bearing components, joint replacements, drug delivery platforms, and bionic scaffolds because of their exceptional wear resistance, high stability, and favorable biocompatibility.

Bioceramic oxides, specifically alumina and zirconia, are a significant clinical option for repairing hard tissues. The biocompatibility of these materials is closely linked to the chemical stability of their lattice structure. The lattice structure of bioceramics is a symmetrical 3D arrangement of constituent ions within a crystalline solid. This distinct structure endows bioceramics with high anticorrosion properties and reliable in vivo behavior [56]. Professor Giuseppe Pezzotti and his team at Tokyo Institute of Technology are seeking to enhance the efficiency of bioceramic oxides. The use of high-speed sintering for zirconia has become crucial in single-treatment dental restoration. Kazumichi Nonaka conducted a study to confirm the effect of high-speed sintering and sample thickness on the performance of 5% (molar fraction) yttria-stabilized dental zirconia (5Y zirconia)-sintered bodies [57]. By observing the crystal structure and microstructure of 5Y zirconia via density and translucency measurements and three-point bending and fracture toughness tests, he demonstrated that 5Y zirconia is not recommended for high-speed sintering applications because this reduces the translucency and mechanical properties. Wenliang Zhu used X-ray photoelectron spectroscopy to observe the composition and structural changes of various hip joint-containing bioceramics (with and without transition metal dyes) in hydrothermal environments [58]. This study investigated the induction mechanism of transition metal pollutants and their effect on the hydrothermal stability of bioceramics containing zirconia. Bioceramic surface treatments significantly enhance implant chemical stability and promote osteogenic activity both in vitro and in vivo. In Pezzotti's lab, Marin et al. employed a high-energy laser source/sandblasting process to pattern the surface of silicon nitride ($\beta$-$Si_3N_4$) and zirconia-toughened alumina and filled these cavities with bioglass to obtain a bioactive functionalized bioceramic surface (Fig. 3a) [59, 60]. Additionally, the team showed in 2018 that the oxygen released by the oxide ceramic femoral head can cause the oxidation of polyethylene liners, demonstrating that the pairing of an oxide femoral head and polyethylene liner may negatively affect the life of the artificial joint [61].

Another significant family of bioceramics includes hydroxyapatite (HAP), tricalcium phosphate (TCP), and other phosphate-based substances. HAP is the primary structural mineral in bones and teeth and has a hexagonal prism structure. The HAP unit cell comprises ten $Ca^{2+}$, six $PO^{4-}$, and two $OH^-$ ions. The strong coordination between these ions forms a highly stable and biocompatible network structure, making this an ideal material for bone repair and other alternative applications. TCP has a Ca/P atomic molar ratio of 1.5 and exists in two crystal phases, $\alpha$-TCP and $\beta$-TCP. $\beta$-TCP, which belongs to the trigonal crystal system, is widely used as a bioactive ceramic. Kunio Ishikawa's laboratory at Kyushu University's Faculty of Dental Sciences concentrates on biomaterials for the rebuilding and regeneration of hard tissues, including teeth and bones. HAP and $\beta$-TCP are typically produced through high-temperature sintering to generate ceramic materials with inferior mechanical properties. To address this issue, the researchers developed low-crystalline calcium-deficient HAP [62] and $\beta$-TCP (Fig. 3b) [63] using the low-temperature dissolution–precipitation method, which proved to be both economical and effective. The feasibility of using low crystallinity $\beta$-TCP as a bone substitute was also confirmed through this approach [64]. Moreover, Yuki Sugiura successfully generated an octacalcium phosphate block, which exhibits superior osteoconductivity compared with HAP and $\beta$-TCP, from the precursor ceramic block by a dissolution–precipitation reaction [65].

Japanese academics have also devoted significant attention to the study of carbonate apatite ($CO_3$Ap) blocks as promising artificial bone substitute materials. Through the dissolution–precipitation procedure using $\alpha$-TCP spheres or calcium sulfate hemihydrate particles as precursors, Kunio's lab created highly interconnected porous $CO_3$Ap blocks (Fig. 3c) [66–68]. These blocks exhibit well-balanced interconnectivity and mechanical strength and are therefore suitable for treating bone defects caused by large fractures or bone tumor resections. $CO_3$Ap has been recognized as a valuable bioactive material coating, particularly for enhancing the bioactivity of Ti implants. Studies in 2020 evaluated the effect of Ti matrix surface roughening and calcite ($CaCO_3$) coating on osteoblast differentiation and growth [69, 70], confirming the potential of $CaCO_3$ coating for clinical applications. HAP, $\beta$-TCP, and $CO_3$Ap bioceramics are all important bone substitutes. However, the performance and structural variances among these materials remained unconfirmed before 2018. To compare their physical characteristics and tissue response to bones, the lab conducted several experiments on hybrid dogs [71]. The results showed that $CO_3$Ap, prepared by the dissolution–precipitation reaction, had a higher specific surface area and lower crystallite size than those of sintered HAP

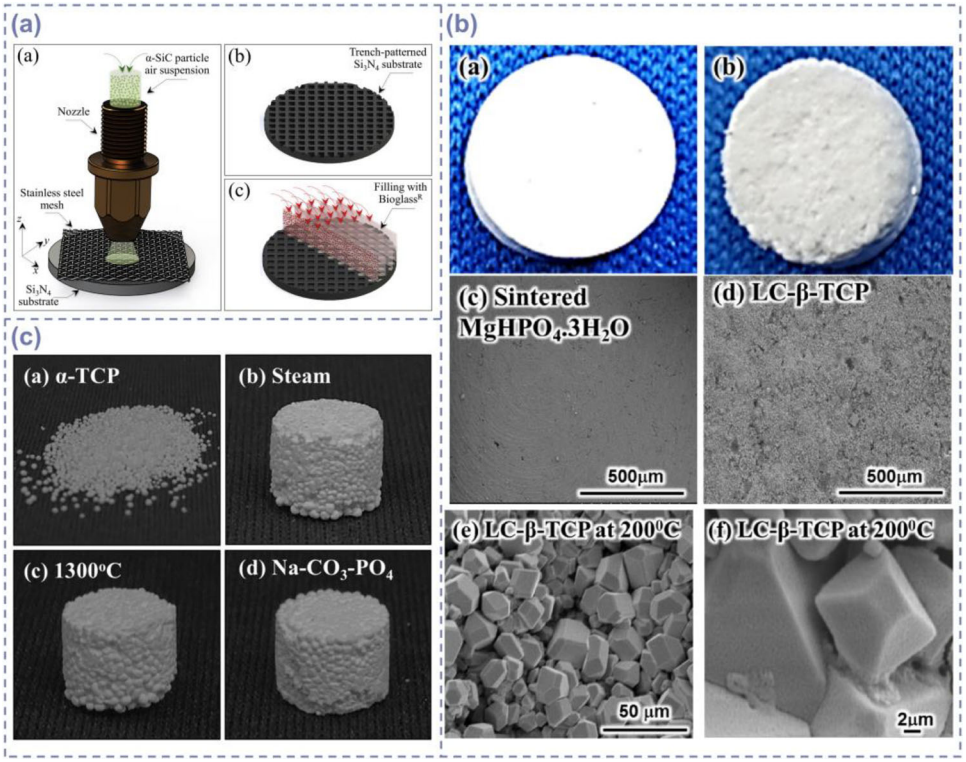



**Fig. 3** Ceramic biomedical materials. **a** Schematic diagram of the sandblasting procedure applied to the $Si_3N_4$ substrates through a stainless-steel mesh. Reproduced from [60], Copyright 2019, with permission from Elsevier B.V. **b** The low-temperature dissolution–precipitation method for the preparation of Mg-substituted $\beta$-TCP. Reproduced from [63], Copyright 2019, with permission from Elsevier B.V. **c** Fabrication of interconnected porous $CO_3$Ap from α-TCP spheres. Reproduced from [66], Copyright 2018, with permission from Wiley Periodicals, Inc. TCP: tricalcium phosphate

and sintered $\beta$-TCP, and induced the largest amount of new bone growth.

## Biomedical polymers

Compared with biomedical metals and ceramics, biomedical polymers have garnered most of the attention among Japanese researchers. Biomedical polymers can be categorized into two groups based on their origin: naturally derived polymers and synthetic polymers. Naturally derived polymers, such as proteins, and polysaccharides, exhibit favorable biodegradability and compatibility, although they have limited mechanical properties and uncontrollable degradation, and may potentially trigger immune responses [72]. However, synthetic polymers can be either biodegradable or nonbiodegradable [73]. Nonbiodegradable synthetic polymers, including polyethylene, polyethylene glycol, and polyurethane, exhibit exceptional stability in physiological environments. These polymer materials resist degradation, crosslinking, and physical wear while demonstrating superior physical and mechanical properties [74]. Biodegradable synthetic polymers, such as PLA, polycaprolactone, and polyamino acid, are generally well-tolerated, and typically do not induce immune or toxic reactions. Moreover, their degradation time can be tailored to match the desired function of the material. A search for the development of biomedical polymer materials in Japan with a focus on "biomedical polymers" on the Web of Science reveals that two materials have garnered significant attention: hydrogels and polymer nanoparticles.

A hydrogel is a hydrophilic polymer gel with a 3D network structure. Hydrogels can absorb water ranging from 10%–20% up to thousands of times its dry weight and are widely used in drug delivery and in repair and regeneration of various tissues and organs [75]. Gelatin, a natural protein derived from animal tissues, including skin, bone, and connective tissue, plays a vital role in hydrogel fabrication. Gelatin can be gradually degraded by enzymes in vivo, facilitating its interaction with various tissues [76]. At Kyoto University, Professor Yasuhiko Tabata focuses on using gelatin hydrogels as a drug-delivery technology to increase therapeutic efficacy when combined with functional cells or medications. Hydrogel microspheres improve the oxygen and nutrient supply status of cells. Inoo et al. [77, 78] used degradable gelatin hydrogel microspheres to enhance cell survival and insulin secretion in insulinoma cell aggregates. Combined with immunosuppressive mesenchymal stem cell aggregates, hydrogel microspheres can also promote cancer cell invasion in vitro and maintain cell viability [79–81]. This provides an effective means of simulating cancer invasion in vitro and potentially enhances cancer treatment. The clinical use of basic fibroblast growth factor (bFGF) is constrained by the short half-life and poor retention, despite its potential in stimulating epithelial cell proliferation and angiogenesis. Hihara et al. [82] addressed this issue by using gelatin hydrogel sheets impregnated with

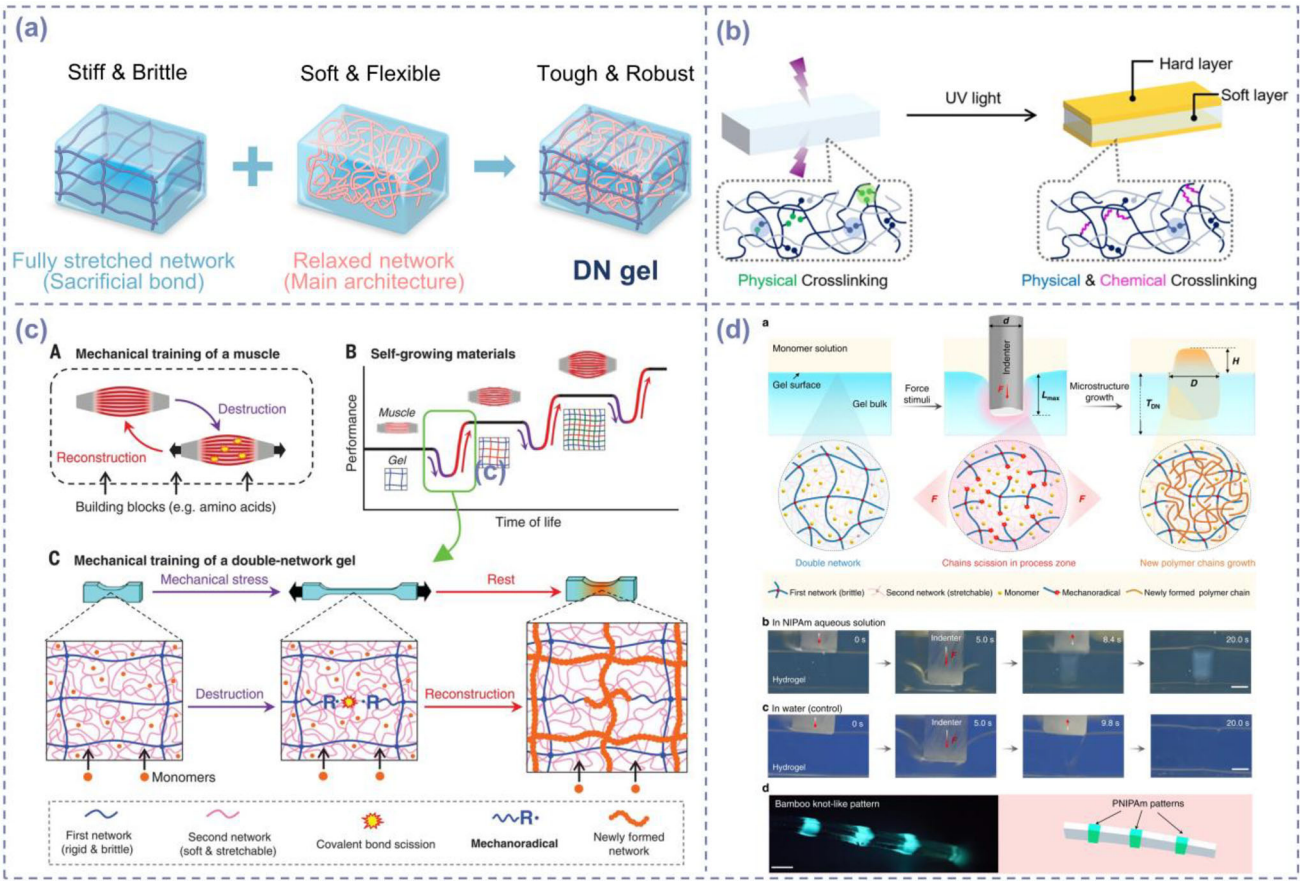



**Fig. 4** The study of double network (DN) gel in Gong's lab. **a** Structure of a DN hydrogel composed of a brittle network and a ductile network. **b** Preparation of tough hydrogel composites with interlayer structure by ultraviolet (UV) light. Reproduced from [88], Copyright 2019, with permission from American Chemical Society. **c** Conceptual scheme of the self-growth of materials induced by mechanical training. Reproduced from [90], Copyright 2019, with permission from the authors, exclusive licensee American Association for the Advancement of Science. **d** A mechanochemical strategy to rapidly grow microstructures on a DN hydrogel surface. Reproduced from [93], Copyright 2022, with permission from the authors, licensed under CC BY 4.0 DEED

bFGF to release physiologically active substances in a controlled manner to improve the viability of mouse skin flaps. Simvastatin has demonstrated clinical efficacy in the treatment of hypercholesterolemia and the promotion of bone formation. Tabata's Lab showed that the concurrent intraarticular delivery of simvastatin with gelatin hydrogel holds potential as a therapeutic approach for osteoarthritis [83].

In addition to Tabata's team, Prof. Jianping Gong from Hokkaido University's Laboratory of Soft & Wet Matter is dedicated to developing new gels to address the low mechanical strength of hydrogels. Their research focuses on understanding the mechanisms behind the toughening and functionalization of hydrogels and applying novel gels as artificial biosubstitute materials. The brittleness of network gels can be attributed to the nonuniform structure formed during crosslinking radical polymerization. In 2003, the team first introduced a highly robust hydrogel, known as the double network (DN) gel [84]. DN hydrogels typically comprise two interpenetrating polymer networks that have different physical properties: one is stiff and brittle while the other is soft and ductile (Fig. 4a) [84–86]. The toughness of DN hydrogels relies on the concept of sacrificial bonds that incorporate a weak, brittle structure into a soft, flexible matrix. The unique design enables the hydrogel to fracture over a wide area before the flexible structure breaks, allowing the dissipation of a considerable amount of energy during deformation [87]. In recent years, the team conducted further research based on the DN gel structure and created hydrogel composites with photosensitive polymers that exhibit DN effects. Through ultraviolet (UV) irradiation (Fig. 4b), physical crosslinks were transformed into chemical crosslinks, making soft physical hydrogels become rigid and less stretchable chemical hydrogels [88]. In 2019, a novel approach was introduced for the synthesis of robust DN hydrogels. This method entails chemically crosslinking linear semi-rigid polyelectrolytes within neutral networks, followed by

physical crosslinking. The resulting hydrogels exhibit exceptional properties, including high modulus, strength, fracture strain, strain energy density, and marked self-healing ability [89]. Inspired by muscle training, Gong's lab proposed a strategy to develop self-growing polymeric materials, where robust DN hydrogels with a continuous supply of monomers undergo self-growth (Fig. 4c). The material is substantially enhanced by a structural destruction–reconstruction process under repeated loading, enabling the development of self-growing gel materials for applications such as soft robotics and smart devices [90]. In 2021, a novel concept was proposed to enhance the sacrificial bond-toughening mechanism in macroscopic DN materials by using the difference in the Poisson's ratio between component materials [91]. This method was expected to strengthen the elastomeric and hydrogel systems, thereby improving their mechanical properties. Additionally, a HAP hybrid DN hydrogel (HAP/DN gel) was developed that effectively adheres to bone tissue and promotes the transformation of bone marrow-derived mesenchymal stem cells to osteoblasts [92]. Recently, the group proposed a force stamp method to grow microstructures on hydrogels using a force-triggered polymerization mechanism of DN hydrogels [93]. This technique facilitates swift spatial modulation of the hydrogel surface morphology and chemistry, thereby enabling on-demand functionality (Fig. 4d). Furthermore, Shinji Sakai and Suzuki Daisuke made notable contributions to the field of hydrogels, although we will not delve into their contributions in detail because of space constraints. With the increasing number of studies on hydrogels as a tissue engineering matrix, the implementation in medical applications has become a topic of extensive and profound concern.

Polymeric nanoparticles (PNPs) refer to particles with sizes ranging from 1 to 1000 nm that encapsulate active compounds either within their polymer cores or through surface adsorption [94]. Professor Hiroyuki Koide, from the Department of Medical Biochemistry at the School of Pharmacy, Shizuoka University, has been researching the synthesis of PNPs. His team's research goal is to achieve the adsorption and neutralization of target molecules to provide a cost effective alternative to protein–protein inhibitors [95]. In 2019, they successfully demonstrated the in vivo functionality of an abiotic copolymer hydrogel nanoparticle (HNP) engineered to bind with a crucial signaling protein, vascular endothelial growth factor 165 (VEGF165), by regulating angiogenesis, thereby suppressing tumor growth [96]. Sepsis is a severe and life-threatening condition that can cause multiple organ dysfunction. To tackle this issue, the team developed an abiotic HNP by modifying the composition of the copolymer with anionic and hydrophobic monomers. The HNP has a strong capacity and extended circulation ability to capture and neutralize histones, making it an effective treatment for sepsis [97]. To develop materials with continuous in vivo adsorption of target molecules, the group created linear polymers as an alternative to conventional nanoparticles and modified them accordingly to create lipid nanoparticles [95, 98, 99]. Inflammatory cytokine production, multiple organ dysfunction, and cell death are often induced by macromolecular toxins. Novel nanoparticles were formed by directly decorating synthetic polymeric ligands onto lipid nanoparticles that efficiently neutralized toxins in vivo and provided a platform for developing abiotic antidote nanoparticles in vivo [100]. Orally administered PNPs were also developed to capture target molecules while inhibiting their intestinal absorption for treating chronic kidney disease [101]. Although Koide's team has conducted extensive research on developing these nanoparticles, there is limited information regarding their safety.

### Biomedical composites

Biomedical composites are multiphase materials prepared by the composite processing of two or more of the previously described materials. These composites are categorized according to the matrix materials they include, such as metal-, ceramic-, and polymer-biomedical composites, among which materials based on magnesium (Mg), polymethylmethacrylate (PMMA) have been the focus of research in Japan in recent years.

Mg is commonly used in biodegradable metal implants because this avoids the requirement for implant removal and offers an efficient solution for permanent implants [102]. Mg possesses a modulus of elasticity ranging from 41 to 45 GPa, which closely resembles that of human bone, thereby reducing the stress-shielding effect and promoting new bone growth. Mg-based composites doped with biomedical ceramics exhibit enhanced mechanical properties and excellent osseointegration. These composites not only improve osteoconductivity but also induce a minimal immune response and toxicity, making them highly appropriate for bone repairs and substitutes. The team led by Prof. Equo Kobayashi at Tokyo Institute of Technology conducted a study involving the doping of 10% or 20% (volume fraction) $\beta$-TCP into Mg-based composites via the spark plasma sintering (SPS) process (Fig. 5a) [103]. Their aim was to investigate the degradation behavior and cytocompatibility of the Mg/$\beta$-TCP composites in vitro. Subsequently, they explored the effect of degradation behavior on the mechanical integrity of the Mg/$\beta$-TCP composites prepared through SPS [104], producing valuable insights for the design of Mg/bioceramic composites. Mg/HAP composites were also prepared via the SPS method [105, 106] with different compositions and grain sizes. The inclusion of HAP enhanced the mechanical properties and corrosion resistance while the smaller grain size

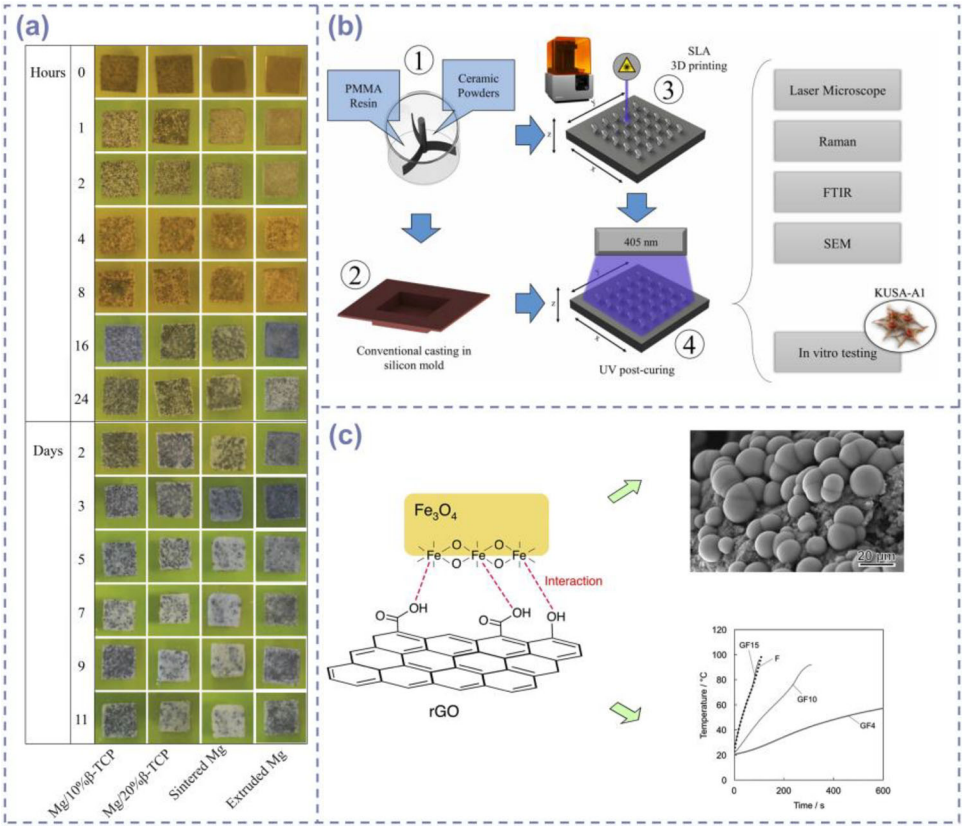



**Fig. 5** Biomedical composites. **a** Photographs of the Mg/10% $\beta$-TCP composite, Mg/20% $\beta$-TCP composite, sintered Mg, and extruded Mg at each time point before and during immersion degradation in rSBF under standard cell culture conditions. Reproduced from [103], Copyright 2019, with permission from Wiley Periodicals, Inc. **b** Production of antibacterial PMMA-based composites through stereolithography. Reproduced from [111], Copyright 2022, with permission from Elsevier Ltd. **c** Magnetite-reduced GO nanocomposites. Reproduced from [119], Copyright 2019, with permission from Elsevier B.V. TCP: tricalcium phosphate; rSBF: revised stimulated body fluid; PMMA: polymethylmethacrylate; GO: graphene oxide

significantly improved various properties required for orthopedic implant materials.

PMMA is one of the most versatile polymers suitable for various applications in orthopedics and dentistry owing to its ease of processing, lightweight nature, cost-effectiveness, aesthetic appeal, outstanding biocompatibility, and remarkable stability in the oral environment [107]. However, PMMA exhibits inadequate mechanical properties in flexural strength, modulus of elasticity, and fracture toughness. Incorporating PMMA as a matrix and reinforcing it with fillers can help to address this issue. For instance, a novel nanoporous silica filler was developed and incorporated into PMMA-based resins to enhance the mechanical properties of PMMA [108]. Since PMMA cannot bond with the bone, aseptic loosening of the implant leading to rework often occurs in total hip arthroplasty and total knee arthroplasty. To address this issue, several scholars developed a composite cement with a low content of bioactive titanium oxide ($TiO_2$) filler dispersed in PMMA and demonstrated that these cements exhibit favorable biocompatibility and bioactivity [109]. Boschetto et al. [110] also doped curcumin for the first time into PMMA to enhance the bioactivity while maintaining the mechanical properties unchanged. In addition, Marin et al. examined the antimicrobial effect of PMMA composites containing three different reinforced ceramic particles (aluminum nitride (AlN), $TiO_2$, and barium titanate ($BaTiO_3$)) through stereolithography 3D printing (Fig. 5b) [111]. Both $BaTiO_3$ and AlN composites possess antimicrobial properties, with the latter exhibiting superior overall performance.

In addition to the above two matrix composites, composites that used carbon nanotubes (CNTs), graphene, and their derivatives as reinforcements have attracted significant attention. As carbonaceous nanomaterials, they not only possess a high specific surface area but also exhibit excellent electrical and thermal conductivity, biocompatibility, flame retardancy, and lighter weight [112, 113]. The incorporation of CNTs into polymers imparts excellent electrical conductivity, laying the foundation for the advancement of biosensing devices, such as CNT-polyether ether ketone composites [114] and multiwall carbon nanotube (MWCNT)/cotton composites [115]. Momin et al. [115] developed a compact load cell using MWCNT/cotton that could successfully monitor the time-varying center of gravity of the human foot. This innovation has potential for diagnosing both patients and healthy individuals. Graphene possesses exceptional mechanical strength and can enhance the mechanical, physical, and chemical properties of biomaterials. For instance, ultrahigh molecular weight polyethylene (UHMWPE) is frequently applied in joint replacements because of its strong mechanical properties, biocompatibility, and chemical stability. However, its wear resistance cannot support long-term

use. Cheng-Ying Liu et al. [116] incorporated graphene into UHMWPE using an octa-screw extrusion process to not only resolve the abrasion resistance problem of UHMWPE but also simultaneously increase the yield strength. Furthermore, to address the problem of weak mechanical strength in conventional hydrogels, nanocomposite hydrogels containing a reduced number of graphene sheets, which can be prepared through noncovalent stripping, have demonstrated enhanced mechanical properties [117]. Zhao et al. [118] employed the low-temperature crystallization method to prepare a composite polyvinyl alcohol hydrogel (PVA-H), with graphene oxide (GO) as a reinforcing material. The incorporation of GO increased the roughness of the hydrogel surface and enhanced cell attachment to PVA-H. Nanocomposites hold promise for developing high-strength and highly biocompatible hydrogel materials with potential applications in artificial articular cartilage. Furthermore, the properties of nanocomposites comprising magnetite ($Fe_3O_4$) and reduced GO as biomaterials were investigated (Fig. 5c) [119]. Studies showed that such composites can effectively enhance osteoconductivity and exhibit favorable heat generation characteristics, making them promising for thermotherapy applications.

## Biological 3D printing

Bio-3D printing research in Japan is rapidly expanding with multiple universities and research institutions exploring new frontiers of the technology. The versatility and user-friendly nature of 3D bioprinting, coupled with precise control over the manufacturing process and shape customization, are highly relevant in BM, especially for applications in medical tissue engineering. Biometric 3D printing can be classified as extrusion, photolithography, and spheroid bioprinting [120]. Here, we focus on the performance improvement and development of bioink types in Japan on extrusion and spheroid bioprinting processes.

Extrusion bio-3D printing is the most prevalent and extensively researched bioprinting method among Japanese scholars. The process involves applying pressure to extrude bioinks from the printer nozzle to form filaments that are then layered to create the desired shape. The development and application of bioinks play a pivotal role in bioprinting technology. To attain optimal outcomes, new bioinks must strike a balance between printability, biocompatibility, and mechanical properties [121]. Traditional bioinks require additional stability and crosslinking, such as via photo-crosslinking, or temperature adjustments, as they are viscous solutions that could shear during printing. Using a semi-solid extrusion-type 3D bioprinter with UV-LED (LED: light emitting diode) exposure, Tetsuya Ozeki and colleagues from Nagoya City University developed implantable 3D bioprinted hydrogel patches embedded with nanomedicines for local administration of PEGylated liposomal doxorubicin (DOX) [122]. This involved combining semisynthesized fish gelatin methacryloyl, carboxymethyl cellulose sodium, and nanomedicine PEGylated liposomal DOX as bioinks. These bioinks were nozzle-extruded using air pressure and were formed into a light polymerized hydrogel. The process of light-assisted gelation allowed for improved compatibility of different biomaterial formulations and controlled the solidification rates of the ink. To generate 3D constructions containing human adipose stem cells, Shinji Sakai et al. also employed microextrusion and visible light techniques to fabricate hydrogel scaffolds composed of hyaluronic acid (HA) and gelatin derivatives [123]. Extrusion-based 3D bioprinting has emerged as a promising approach for creating 3D human tissues from cells in vitro. Accurately predicting drug-induced liver injury is crucial in early-stage drug discovery; however, traditional monolayer liver tissue cultures are not ideal for long-term toxicity testing because of their limited survival rate. Izumi Ide from the University of Tokyo employed a 3D bioprinter to construct a spheroid ink comprising primary human hepatocytes and hepatic stellate cells, successfully enabling the in vitro bioprinting of liver tissue [124]. The result improved the accuracy in predicting hepatotoxicity during the early stages of drug discovery. Vascularization is a vital aspect of bioprinting living structures. Professor Takeshi Nagayasu's team from the Department of Surgical Oncology at Nagasaki University stacked cell sheets combined with bioprinting, and printed alginate-fibrin gel onto gelatin gel. The process successfully produced high-cell density artificial 3D tissues with vessel-like structures measuring several hundreds of microns in diameter [125]. The fabrication of mature engineered cardiac tissue remains a major challenge. Shintaroh Iwanaga from Toyama University initially devised a fine-fiber scaffold that incorporated a support structure. Subsequently, an advanced 3D bioprinter and cell-adhesive bioink were used to construct artificial myocardial tissues [126]. Subsequently, these tissues demonstrated coordinated and synchronized contractions, exhibiting responsiveness to drug stimuli. Despite the numerous advantages and flexibility of extrusion-based bio-3D printing of diverse bioinks, particularly for the fabrication of 3D human tissues and organs, the current technology has certain limitations. The printing resolution stands out as a potential research focus for the future development of extrusion-based bio-3D printing.

Extrusion and lithography bioprinting methods are extremely material-dependent and energy-intensive. The materials as scaffolds must support all cells in the construction as well as the recipient organism, which makes it challenging to be compatible with certain biological applications. In 2015, the Nakayama Lab, headed by Professor Koichi Nakayama at Saga University in Japan, first introduced an invention that involved the assembly of spheres by microneedle named "Kenzan" to print cell spheroids with precision

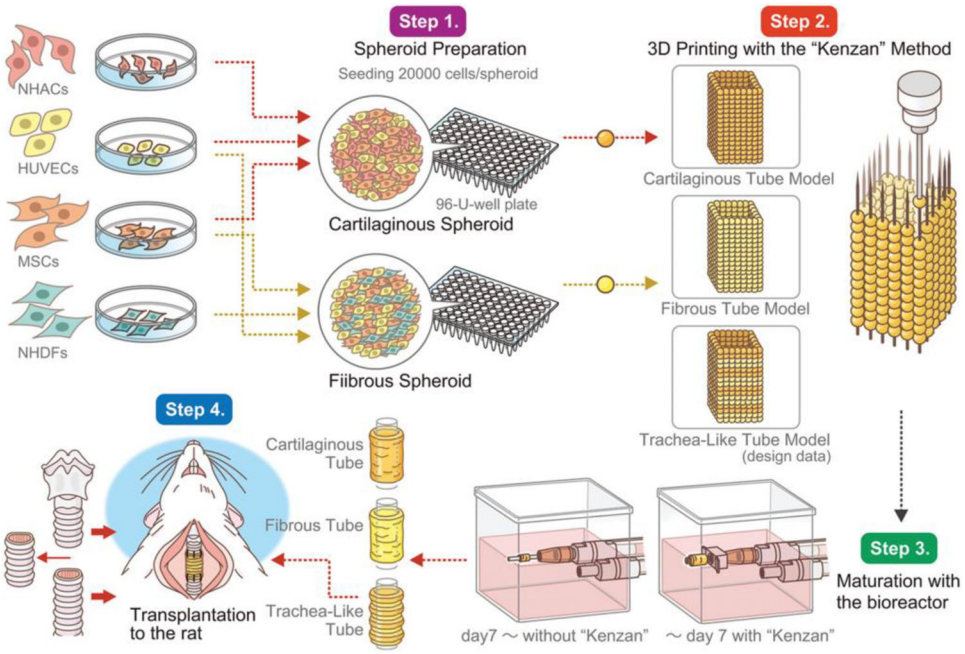



**Fig. 6** The process of printing an artificial trachea using the "Kenzan" bio-3D printing method. Reproduced from [130], Copyright 2019, with permission from WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

and accuracy without scaffolds [127]. Spheroids were precisely positioned into predesigned continuous structures with micro–nano scale accuracy using stainless steel microneedles as temporary supports. Subsequently, the spheroids were cultured until they fused into cell aggregates with the extracellular matrix, producing the desired structural organization and robustness [128]. Artificial organ scaffolds have specific limitations, including the risk of infection and irritation, reduced biocompatibility, and degradation over time. The Nakayama Lab focuses on creating complex layered structures that do not require support materials, which consequently broadens the potential applications of the technology in tissue engineering and regenerative medicine. Over the past five years, human tissues and organs have been constructed using human cells and the "Kenzan" sphere assembly process, demonstrating the advantages of scaffold-free printing. In 2018–2019, a circumferential tracheal replacement procedure was conducted using an artificial trachea made from isolated primary cells including chondrocytes, human fibroblasts, and mesenchymal stem cells via spheroid biologic 3D printing (Fig. 6) [129, 130]. This cutting-edge technique facilitated optimal tracheal transplantation and regeneration without requiring foreign materials or immunosuppressive drugs. Performing esophageal reconstruction and reducing the associated high complications and mortality are critical medical considerations following esophagectomy. Spheroid bioprinting was conducted by Yosuke Takeoka et al. [131] to fabricate a cell-based construct to replace esophageal segments. This structure was successfully transplanted into rats and maintained structural integrity for 30 days, thereby demonstrating its potential as an alternative approach for repairing esophageal defects. Other tubular tissues, including cardiac structures [132, 133] and nerves [134, 135], were also successfully fabricated via the spheroid bio-3D printing process and were implanted in rats for activity evaluation. The development of scaffold-free tubular structures through bio-3D printing represents a significant advancement in organ replacement therapies. Osteoarthritis is a major cause of pain and joint immobility, and although scaffold-based tissue engineering has emerged as a promising alternative for joint repair, it is hindered by limitations such as poor cytocompatibility and degradation toxicity. To address these limitations, the Nakayama Lab employed the "Kenzan" method to fabricate defective cartilage structures [136–138]. This approach successfully enabled remodeling of cartilage surface for articular cartilage defects. Newborns with a congenital diaphragmatic hernia usually require a patch for surgical defect closure. Spheroid printing was used to form large scaffold-free tissue patches from animal cells to be transplanted into rats with diaphragmatic defects [139, 140]. The rats survived for more than 710 days, demonstrating that cell patches created via scaffold-free printing are a safe and effective therapeutic strategy for repairing diaphragmatic defects, and providing an innovative treatment modality for pediatric surgical disorders. Additionally, the group applied the "Kenzan" method for constructing tissue constructs, which involved a time-consuming process. To enhance the clinical applicability, a cryopreservation method was developed for the spheroids, and the cell viability within cryopreserved spheroids was verified, enabling the successful fabrication of tubular structures [141].

**Table 3** Comparison of different bio-3D printing technologies

| Bioprinting technology | Strengths | Weaknesses | Technology improvement | References |
|---|---|---|---|---|
| Extrusion bio-3D printing | Complex model construction, faster bioprinting speed | Lower printing resolution, scaffold-dependent | Light-assisted gelation enhancing bioink compatibility; bioprinting of in vitro liver tissue, vascular-like structures, and artificial heart muscle tissue | [122–126] |
| Spheroid bio-3D printing | High spatial accuracy, no support materials required | Slow printing speed, unable to print complex 3D shapes | Printing of tubular structures, cartilage, and diaphragm using the "Kenzan" bio-3D printing method | [127–141] |

3D bioprinting holds immense potential for addressing various biomedical challenges, particularly in personalized medicine. 3D bioprinting can create customized organs and tissues, offering superior medical solutions for patients. Each bio-3D printing method has its own strengths and weaknesses (Table 3). Therefore, combining the advantages of different processes is important in developing novel bio-3D printing methods tailored for specific medical applications.

## Biomedical applications

Over the last five years, Japanese researchers have made remarkable advances in BM through their extensive investigations into biomedical materials and bio-3D printing processes. These research efforts have yielded valuable insights and advancements, particularly for biomedical applications. Several notable areas of application include targeted drug delivery, antibacterial coatings, vascular and bone tissue engineering, wound dressings, and biosensors (Fig. 7).

### Targeted drug delivery

Drug delivery is crucial in enhancing the effectiveness of medications and has substantially contributed to the successful treatment of diverse diseases. Targeted drug delivery has emerged as a prominent research area within drug delivery development as this allows precisely targeting of drugs to specific sites in the body without affecting nontargeted tissues [142]. Designing carriers for targeted drug delivery is of particular significance, and nanoparticles, as described in the previous sections, have emerged as promising carriers to address the limitations of conventional drug formulations and their associated pharmacokinetics [143, 144]. The substantial specific surface area of nanoparticles enables exploitation of macrophages and other cellular uptake mechanisms in organisms, producing more efficient drug delivery. Nanoparticles can transport drug molecules to specific target regions or organs within the body, enabling precise and effective drug delivery while minimizing toxicity to off-target cells. Owing to their synthetic versatility, structural diversity, and genetic immunity, nanoparticles are regarded as one of the most promising materials for targeted drug delivery.

The Kataoka/Kinoh Lab, a part of the Innovation Center of NanoMedicine and led by Professor Kazunori Kataoka, specializes in targeted nanomedicine delivery for treating neurological diseases and cancer. One promising yet challenging strategy for treating neurological diseases is delivering therapeutic antibodies to the brain through the BBB. The team developed an innovative approach that capitalizes on the physiological properties of the BBB to achieve precise delivery of nanoparticles to label the brain endothelium [145], potentially overcoming targeting limitations and facilitating the clinical application of neurotherapeutics. Furthermore, they proposed a nanocarrier system that efficiently delivers antigen-binding fragment antibodies raised against amyloid beta to the brain (Fig. 7a) [146]. The system holds significant potential for the enhanced treatment of Alzheimer's disease and other neurological disorders. The role of carnitine palmitoyltransferase 1A (CPT1A) in lipid metabolism is well established, and inhibiting its activity produces diverse pharmacological benefits, including treating obesity and brain cancer. In 2021, it was demonstrated that poly-ion complex micelles can effectively deliver CPT1A anion inhibitors to glioma cells and neurons, offering a promising platform for drug delivery in these conditions [147]. The potential for targeted precision cancer therapy using pH-sensitive nano drugs is substantial. Sabina Quader et al. developed pH-triggered nanomedicines [148, 149] that enable stable blood circulation and tumor-specific delivery by accurately sensing the pH of heterogeneous tumors and gradually releasing drugs within them. This advancement marks a significant contribution to the clinical translation of nanomedicines. The prevention of metastatic spread and local recurrence of cancer following surgical procedures poses a formidable challenge. In response, this laboratory and the University of Science and Technology of China collaboratively proposed a

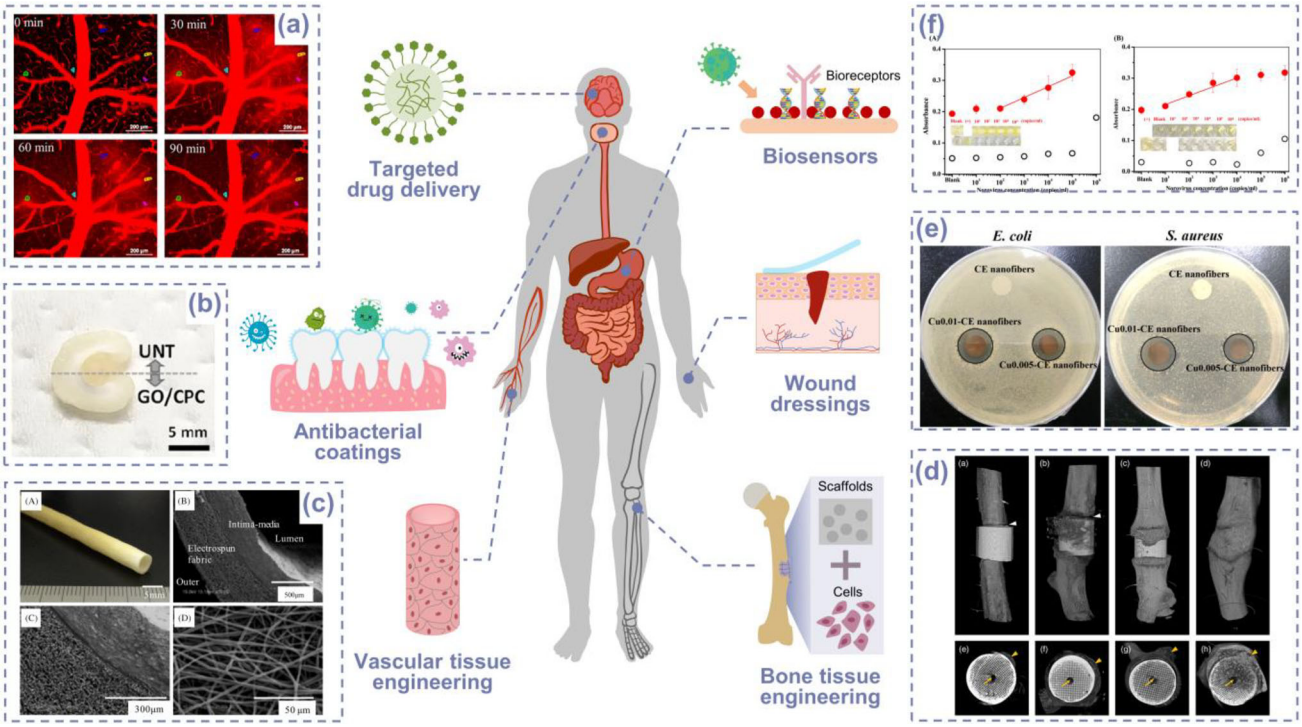



**Fig. 7** Biomedical applications in Japan. **a** Nanomicelles for targeted delivery of therapeutically active antibodies to the brain system. Reproduced from [146], Copyright 2020, with permission from American Chemical Society. **b** Tooth substrate coated with a GO-sustained antibacterial coating. Reproduced from [160], Copyright 2022, with permission from the authors, licensed under CC BY 4.0 DEED. **c** A hybrid small-diameter tube fabricated from decellularized aortic intima-media and electrospun fiber for artificial small-diameter blood vessels. Reproduced from [168], Copyright 2019, with permission from Wiley Periodicals, Inc. **d** Reconstruction of critical-size segmental defects in rat femurs using carbonate apatite honeycomb scaffolds. Reproduced from [170], Copyright 2021, with permission from Wiley Periodicals LLC. **e** CuO nanofiber wound dressings exhibiting excellent antibacterial properties. Reproduced from [196], Copyright 2021, with permission from Elsevier B.V. **f** Detection of clinically isolated NoV obtained from the human digestive system. Reproduced from [207], Copyright 2018, with permission from Elsevier B.V. GO: graphene oxide; NoV: norovirus

nanotherapeutic approach based on enzyme-converted polymers [150]. Nanotherapeutic agents are localized to the premetastatic niche and postoperative wound sites, disrupting the premetastatic microenvironment, and eliminating micro residues to radically reduce metastatic and local area recurrence.

In addition, the group is currently researching mRNA delivery mechanisms. mRNA represents a novel category of therapeutic agents used to prevent and treat various diseases. The global coronavirus disease 2019 (COVID-19) pandemic prompted active vaccine development, with mRNA vaccines emerging as one of the most prominent candidates. The rapid clinical translation of mRNA-based vaccines or therapies has been facilitated by the development of delivery vectors designed to protect and deliver fragile mRNA molecules [151]. Polyplex micelles have been used for mRNA-targeted delivery [152–155]. These nonviral vectors effectively avoid degradation by nucleases and hold considerable promise for treating refractory diseases.

## Antibacterial coatings

Bacterial contamination is a critical concern in medical treatment, representing a substantial safety threat within the healthcare industry because of the high morbidity rates and associated economic costs. Improper handling of bacteria may cause inflammation as well as endanger human life and health. Enhancing the antimicrobial properties of materials remains a major challenge in numerous biomedical applications, and Japanese research has sought to advance the development of antimicrobial coatings.

Professor Hirofumi Miyaji's research group at Hokkaido University focuses on applying antimicrobial coatings in dentistry. Fluoride-containing apatite coatings applied to tooth surfaces improve the chemical durability and antibacterial activity of the material to offer considerable promise for dental disease prevention and treatment. To ensure the practicality of these tooth coatings in clinical settings, rapid coating process is essential under atmospheric pressure and temperature. Moreover, the coating area must be accurately confined

to the specific target area of the tooth surface. Combined with a laser-assisted biomimetic (LAB) process, a rapid, single-step, and area-specific calcium phosphate-coating technique was developed [156, 157]. The LAB technique enhanced the antimicrobial activity of dental surfaces by coating substrates of artificial materials in a single step. The effect of the time course and mechanism of laser-assisted pseudo-biomineralization on the area-specific coating and antimicrobial activity was also investigated [158]. Oyane et al. [159] improved the LAB process by incorporating a dental diode laser and using the clinically approved light-absorbing molecule, indocyanine green. This enhancement enabled the successful formation of micrometer-thick fluorapatite coatings on the dentin surface within a short time frame of just three minutes. While mouthwashes containing antimicrobial surfactants demonstrate high effectiveness, their limited water resistance hampers their sustained antimicrobial activity. These surfactants are easily rinsed off and do not adhere to the tooth surface. To overcome this limitation, a new coating method was recently developed using GO (Fig. 7b) [160]. The method helped retain the surfactant on the tooth surface even after rinsing with water, thereby providing a sustained antimicrobial effect.

Other medical applications for antimicrobial coatings include the development of biomedical devices and consumables, particularly implantable devices. Chitosan, a naturally derived polymer, has renowned antimicrobial properties and is gaining popularity in the development of antimicrobial coatings. The high biocompatibility, low immunogenicity and allergenicity, and ease of processing of chitosan make it an attractive choice [161]. Kodama et al. [162] at Osaka University employed 3D printing to fabricate anatomically matched intervertebral disks integrated with Ti cages coated with an antimicrobial substance known as quaternized chitosan. The Ti cages containing the quaternized chitosan coating exhibited remarkable antimicrobial efficacy and effectively prevented structural damage from causing infection in the caudal disks of experimental rats. Boschetto et al. [163] discovered that the application of chitosan/polyethylene oxide/bioactive glass nanofiber composites as coatings on Ti surfaces enhanced the antimicrobial and osteoconductive properties. Consequently, these composites could be used in orthopedics and dentistry. In addition, bacteria can adhere to contact lenses, causing corneal infections, or inflammation. Kim et al. [164] developed and evaluated contact lenses coated with antimicrobial silver or copper nanoparticles, as well as a combination of both. The coatings effectively reduced bacteria-related adverse events during lens wear. In 2022, Jae Joon Kim from the University of Tokyo also proposed a copper-nanomesh antimicrobial skin protection platform that acts as a second skin layer [165]. This helped prevent crossinfection while minimizing changes to intrinsic skin properties such as interface morphology, temperature change, and skin humidity in response to the COVID-19 pandemic.

### Vascular and bone tissue engineering

Tissue engineering is a rapidly growing discipline that uses growth factors, cells, and scaffolds to regenerate or replace damaged tissues. Biomedical applications of tissue engineering are of paramount importance in this field for the construction of functional biological structures in vitro, thereby addressing the critical shortage of donor organs.

The rise in mortality rates caused by cardiovascular disease has emerged as a prominent global issue. Autologous vascular grafts currently serve as the preferred approach for revascularization procedures but can suffer from inadequate blood flow patency due to thrombosis. Moreover, certain populations face a scarcity of suitable autologous vessels for grafting. Japanese researchers explored vascular tissue engineering to address these issues. To replicate the function and structure of natural blood vessels, they combined vascular tissue engineering with electrostatic spinning techniques. The process of producing polymer fibers with diameters ranging from 2 nm to several microns by employing solutions of both natural and synthetic polymers and is referred to as electrostatic spinning [166]. These fibers possess several advantages, including high porosity, a large specific surface area, a diverse composition, and a uniform diameter distribution. Ick Soo Kim and colleagues [167] prepared vascular tubular scaffolds using electrostatically spun nanofibers encapsulated with PVA hydrogels. These scaffolds, incorporating DN polymers, demonstrated enhanced tensile strength and excellent biocompatibility. The precisely controlled composition of the scaffold makes this a suitable option for vascular tissue engineering. In small-diameter vascular applications, specifically those with diameters <6 mm, such as coronary artery bypass grafting, currently available synthetic polymer vascular grafts are prone to obstruction caused by thrombosis or intimal hyperplasia. Consequently, creating a small-diameter vessel that can effectively resist infection, prevent thrombosis, and facilitate seamless implantation has emerged as an increasingly vital focus in vascular tissue engineering. Pingli Wu et al. [168] fabricated hybrid small-diameter vessels by wrapping decellularized aortic intimamedia sheets around tubular 4-mm stainless-steel mandrels and then coating them with electrostatically spun segmental polyurethane (Fig. 7c). Takashi Tanaka et al. [169] also developed a 1.5-mm diameter elastin-silk fibroin double-raschel knitted vascular graft that exhibited increased patency and remodeling ability.

Bone is the second most transplanted tissue worldwide, with over four million procedures conducted annually that use bone grafts or bone replacement materials to address bone defects [15]. Patients may opt for bone grafts harvested

from their own bodies or choose metal products and bone substitutes to facilitate bone regeneration. However, these alternatives pose risks such as disease transmission, immune reactions, wear and tear, and bone failure. The development of innovative substitutes for traditional bone grafts has been the focus of extensive research in bone tissue engineering (BTE). As previously mentioned, Kunio Ishikawa's group is a pioneer in the study of BTE and investigates biomaterials linked to the reconstruction and regeneration of hard tissues such as teeth and bones. Their recent research focused on using $CO_3$Ap as a scaffold material for bone reconstruction because of its similarity to bone and its presence as a bone component. In 2021, the team successfully developed a cellular scaffold (honeycomb scaffold (HCS)) containing $CO_3$Ap with 3% carbonate [170]; the reconstruction process of the defective rat femur using this scaffold is shown in Fig. 7d. The results demonstrated that HCSs using only $CO_3$Ap were equally effective as protein and cellular scaffolds for bone reconstruction while offering superior cost-effectiveness and safety. To restore bone defects, the pore structure of the stent is critical. The team fabricated three carbonate apatite HCSs with different pore sizes: large ($\geq$100 μm) [171], micro ($\leq$1 μm) [172], and nano (several hundred nanometers) [173], to investigate the effect of channel sizes on mechanical strength and bone regeneration. Based on the diverse impact of pore sizes on bone regeneration, a robust strategy was formulated to design scaffolds with distinct functionalities. Another scholar studying the application of BTE, Takahiro Kanno, associate professor at Shimane University's Graduate School of Medicine, has investigated using 3D porous uncalcined and unsintered hydroxyapatite/poly-D/L-lactide (3D-HA/PDLLA) composite as a bone regeneration material in maxillofacial surgery. He demonstrated the use of the novel composite 3D-HA/PDLLA as a cellular scaffold, both in vitro and in vivo, to treat patients with irregular bone abnormalities in the craniofacial region [174–176]. A new generation of nanomaterials, which incorporates 3D-HA/poly-L-lactide (PLLA) with co-glycolic ester (PGA), exhibits enhanced properties including a faster resorption rate and increased potential for bioactivity/osteoconductivity. Building upon this, he evaluated the capacity of 3D-HA/PLLA/PGA for bioactive/osteoconductive bone regeneration and bioresorption in maxillofacial bone for the first time [177]. Additionally, hydrogels play a crucial and efficient role as scaffolds in BTE. In addition to their superior biocompatibility, low toxicity, and capacity for bone regeneration, they can encapsulate biomolecules and cells in situ [178]. Researchers such as Sachiko Iseki and Giuseppe Pezzotti have conducted extensive studies on applying crosslinked nanogels to enhance cranial healing [179] and repair large bone defects [180].

Takayoshi Nakano's group showed that the mechanical functionalization of bone is not only influenced by the bone mass but also by the apatite crystallographic texture, which is a critical factor affecting bone quality [181, 182]. In intact bone, apatite is aligned in the same direction as the collagen fibers, whereas in artificial bone, the anisotropy of the collagen and apatite bone matrix varies depending on the anatomical region and may be influenced by the surrounding mechanical conditions [183, 184]. Consequently, this could cause more severe pathological bone dysfunctions, such as rheumatoid arthritis [185] and osteoporosis [186]. Long-term bone stability can only be achieved when the crystal structures of the original host bone and the newly formed bone align in the same direction. However, this crucial aspect was not considered or realized by other researchers studying BTE. To address this issue, Nakano's lab made significant progress by developing two innovative metal artificial bones with through-hole groove structures using the metal 3D printing process [187, 188]. Without requiring autologous stem cells, this honeycomb tree structure formed a scaffold to effectively guide the alignment of natural microstructures found in biological tissues, such as bone extracellular matrix (collagen/apatite), facilitating the early stages of implantation and promoting functional osseointegration (Fig. 8). The innovative concept allows for the design of high-performance artificial bone grafts suitable for clinical applications.

### Wound dressings

As the largest organ on the surface of the body, the skin serves as a protective layer that also regulates body temperature, excretes sweat, and senses external stimuli. Following an injury, if the skin heals on its own, it often takes longer to recover and may result in scar tissue formation. Wound dressings serve as a temporary external barrier to infection and promote skin cell reorganization. This facilitates the infiltration and integration of host tissue, ultimately improving wound healing and minimizing scarring [189]. A wide range of wound barrier materials, including nanofibers, films, hydrogels, emulsions, and others, have been extensively investigated. Among these materials, nanofibers and hydrogels have attracted significant attention from Japanese researchers and become the focal point of their studies.

The primary challenge in wound healing is the potential risk of bacterial infection and the subsequent inflammation at the injury site. Hence, developing wound dressings that exhibit antimicrobial properties is imperative to combat these concerns. Nanofibers possess extremely small diameters and substantial surface areas that offer abundant and specific sites for cell adhesion and growth. Moreover, their high porosity provides an effective barrier against external pathogens and facilitates excellent air and moisture permeability, making them suitable as antimicrobial wound dressing materials [190]. The Kim Lab at Shinshu University, led by Professor Ick Soo Kim, is a prominent research facility in high-performance nanofibers and focuses on developing

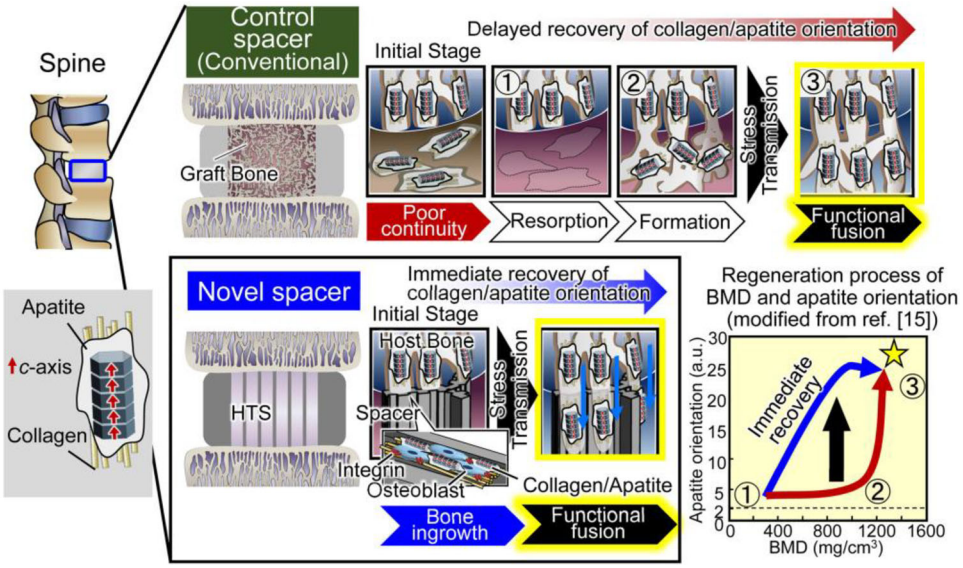



**Fig. 8** Schematic illustration of the potential advantage of the novel spacer, which guides bones with anisotropic collagen and apatite orientation in the through-pore and groove direction to stabilize vertebrae immobilization. Reproduced from [188], Copyright 2022, with permission from the authors, licensed under CC BY 4.0 DEED

antimicrobial dressings and other medical applications. For several decades, silver has been combined with natural or synthetic polymers to create an effective antimicrobial agent. The team made the first report of the synthesis of silver-silica embedded polyvinyl alcohol nanofibers (SSN-PVA) for antimicrobial purposes [191]. The SSN-PVA not only incorporates the advantages of the nanofiber structure present in PVA mats but also demonstrates remarkable antimicrobial properties and reduced silver release. Silver sulfadiazine (AgSD) is a highly effective antimicrobial agent, particularly for burn wound dressings. Doped polyacrylonitrile nanofibers with AgSD were developed for studies on their antimicrobial properties [192]. Abdul Wahab Jatoi proposed a composite nanofiber consisting of electrospun cellulose acetate, zinc oxide, and silver nanoparticles, with dopamine hydrochloride as a reducing agent [193]. This composite nanofiber prevented harmful side effects resulting from the excessive release of or exposure to silver during long-term sustained antimicrobial dressing therapy. Patients with diabetes have a weakened immune response and impaired tissue regeneration and are highly susceptible to nonhealing skin ulcers and associated complications. To tackle this challenge, a novel dual natural composite wound dressing was proposed that promotes the healing of diabetic wounds and enhances antimicrobial activity through the incorporation of gentamicin and silver nanoparticles, respectively [194]. In addition to silver-based antimicrobial agents, copper has gained recognition as a liquid disinfectant and antibiotic. Copper can be combined with other materials to enhance wound healing and promote tissue regeneration during the wound treatment [195]. In a study conducted by Azeem Ullah, lignin was used to synthesize cupric oxide (CuO) nanoparticles on cellulose nanofibers [196]. The resulting material was effective in wound dressings and other antimicrobial applications (Fig. 7e). In addition, the lab investigated a novel and cost effective wound dressing endowed with antibacterial properties. Electrospinning was employed to fabricate ultrafine and garlic acid-infused nylon-6 nanofibers that had exceptional mechanical characteristics [197].

As wounds are located in bodily tissues, wound dressings are required to meet stringent criteria. The moist environment of these wounds can easily cause inflammation and ulcers if not treated promptly. Hydrogels exhibit exceptional hydrophilicity, biocompatibility, and a 3D porous structure resembling the extracellular matrix, and are consequently highly promising for use in wound dressings. The enhanced adhesion properties of hydrogels facilitate wound closure and minimize the infection risk by preventing contact with the external environment. Prof. Jianping Gong's group proposed a combination of macroscopic surface engineering and nanoscale dynamic bonding to develop rapid, strong, and reversible underwater adhesion of toughened hydrogels [198]. The tough hydrogels with dynamic ionic and hydrogen bonding exhibited remarkable underwater adhesion capabilities on a variety of substrates, including hard glass, soft hydrogels, and biological tissues. Endoscopic submucosal dissection (ESD) surgery is used for dissecting early gastrointestinal cancers. However, this minimally invasive treatment carries a risk of perforation and bleeding [199]. To prevent the effect of intraluminal factors and wound infection caused by ESD, it is crucial to use dressings that possess strong tissue adhesion and stability, particularly in a challenging microenvironment characterized by peristaltic motion and fluid shear stress. Professor Tetsushi Taguchi's team at the University of Tsukuba used hydrophobically modified Alaskan pollock gelatin that has the potential to enhance the adhesive properties of living tissues, especially blood vessels and

lungs, through hydrophobic interactions [200, 201]. Additionally, the group developed a sprayable colloidal wound dressing comprising hydrophobic particles that exhibits high tissue adhesion even under moist conditions [200, 202, 203]. Among the studies, decyl group-modified Alaskan pollock gelatin microparticles (C10-MPs) were demonstrated to adhere to intestinal plasma membrane tissue through hydration, forming a colloidal gel layer without the requirement of a crosslinking agent [203]. Remarkably, this gel layer exhibited nonadhesive properties toward other tissues, thus showcasing its potential as a promising material for preventing postoperative organ or tissue adhesions. For minimally invasive surgery, bioadhesive hydrogel wound dressings that can be enzymatically or hydrolytically degraded in the body are valuable since they can dissolve in the body without requiring surgical removal. Tomoko Ito et al. introduced a new method called solid/solution interfacial complexation to create a highly bioadhesive hydrogel made of polyacrylic acid and polyvinylpyrrolidone with low cytotoxicity [204]. The hydrogel firmly adheres to wounds, effectively halts bleeding, and gradually dissolves within the body.

### Biosensors

Biosensors are analytical electronic devices that include biosensitive elements, signal transducers, and other components. Biosensors are designed to detect biological changes resulting from interactions between receptors and target analytes and subsequently convert these changes into measurable electrical parameters [205]. Biosensors can detect a wide range of biological materials, including antibodies, enzymes, nucleic acids, and cells, making them indispensable components in the biomedical industry.

The detection of viruses as infectious agents is a common area of focus in sensor research [206]. The Research Institute of Green Science and Technology at Shizuoka University in Japan, specifically Professor Enoch Y. Park's group, conducted extensive research on biosensors for detecting pathogenic viruses. For example, in 2019 [207], they used silver ion-doped gold nanoparticles with augmented peroxidase-like activity in a colorimetric bioassay for the detection of norovirus (NoV), a prevalent cause of acute gastroenteritis (Fig. 7f). The method could detect clinical NoV in human fecal samples, exhibiting markedly superior sensitivity compared with that of commercially available immunoassay kits. Thereafter, several novel biosensing systems with improved sensitivity for NoV detection were designed based on the signal amplification technology of liposomes [208], the graphene-mediated surface-enhanced Raman scattering effect [209], and the hollow nanostructure of chromium tetraoxide ($Co_3O_4$) nanocages enhancing enzyme activity [210]. The detection of the hepatitis E virus (HEV) is of paramount importance as it is a primary contributor to acute viral hepatitis on a global scale. The team developed a pulse-triggered ultrasensitive electrochemical sensor using graphene quantum dots and polyaniline nanowires embedded in gold [211]. This sensor could detect various HEV genotypes, enabling the development of highly efficient sensing methods for HEV detection. In a study by Akhilesh Babu Ganganboina of the group [212], inorganic quantum dots were packaged in vitro within HEV-like particles to create a highly sensitive fluorescent biosensor for HEV antibody detection. Moreover, he successfully engineered optically active quantum dots enclosed within iron oxide hollow shells based on magnetic nanomaterials [213]. These quantum dots were employed as the first electrochemical/fluorescent bimodal probes for the detection of various viruses, including HEV, HEV-like particles, NoV, and NoV-like particles, thereby opening a promising avenue for efficient and rapid viral diagnostics. For respiratory viruses, inspired by the self-assembly method, the chromogen substrate 3,3',5,5'-tetramethylbenzidine was introduced into the biosensor by being carried within a poly(lactide-co-glycolide) encapsulated nanoparticle [214], enabling highly sensitive detection of airborne respiratory viruses.

Aside from virus detection biosensors, biosensors for blood glucose detection are also widely recognized by the public because of their high market demand. These biosensors employ enzymes to catalyze the breakdown of glucose in the blood, enabling the transfer of electrons to the electrodes and facilitating the measurement of the blood glucose concentration. Prof. Koji Sode, from Tokyo University of Agriculture and Technology, studies innovative biosensing technologies for novel biological processes using synthetic biology approaches. His notable achievements include developing second- and third-generation electrochemical biosensing systems for glucose monitoring enzymes in biomolecular engineering. In 2019, his group developed a third-generation open-circuit potential glucose sensor for continuous glucose monitoring based on the direct electron transfer (DET) of flavin-adenine dinucleotide-dependent glucose dehydrogenase complex (FADGDH) [215]. In the same year, a third-generation impedance sensor was constructed using DET of glucose dehydrogenase [216]. This groundbreaking study marked the first report of a glucose detection sensor employing a DET-type redox enzyme, using the principles of Faraday electrochemical impedance spectroscopy. These achievements provide an alternative platform for future barrier immunosensing systems that eliminate the need for redox probes. Aptamer-based electrochemical sensors have garnered significant interest for progress in diagnostic biomarker assays because of their rapid response, stability, and flexible designs that can be miniaturized. Glucose dehydrogenase was combined with zinc finger proteins to label DNA aptamers for electrochemical glucose detection [217]. To

**Table 4** Biomedical products with medical certification

| Biomedical applications | Product models | Companies | Indications and usage |
|---|---|---|---|
| Targeted drug delivery | ADCETRIS® (brentuximab vedotin) | Takeda Pharmaceutical Co., Ltd. | Classical Hodgkin's lymphoma and certain T-cell lymphomas |
| | ENHERTU® (fam-trastuzumab deruxtecan-nxki) | Daiichi Sankyo Co., Ltd. | Human epidermal growth factor receptor 2 positive breast cancer and nonsmall cell lung cancer treatment |
| | Lenvima® (lenvatinib) | Eisai Co., Ltd. | Treatment of differentiated thyroid, hepatocellular, and endometrial cancer treatment |
| Vascular implantation | Gelweave™ | Terumo Medical Corp. | Repairing the thoracic or thoracoabdominal aorta |
| | Anaconda™ | Terumo Medical Corp. | Precise repair of unique aortic aneurysms |
| | Artegraft® | Kaneka Corp. | Hemodialysis, lower limb bypass, and arterial trauma |
| Bone implantation and repair | Aquala® | KYOCERA Corp. | Artificial hip joint |
| | Tactoset® | Anika Therapeutics, Inc. | Providing minimally invasive treatment options for bone marrow lesions or dysfunctional fractures |
| | Hyalofast® | Anika Therapeutics, Inc. | Repairing cartilage and osteochondral lesions |
| Wound dressings | Hyalomatrix® | Anika Therapeutics, Inc. | Promoting orderly reconstruction of dermal tissue, protective, and flexible wound coverings |
| Biosensors | HISCL™ SARS-CoV-2 Ag | Sysmex Corp. | Qualitative testing for the novel coronavirus COVID-19 |
| | 4SURE Smart | Nipro Medical Corp. | Precise detection of blood sugar in patients with Type 2 diabetes |

COVID-19: coronavirus disease 2019

enhance glycemic control administered via insulin administration, Mukund Khanwalker employed an anti-insulin single chain variable fragment as a biosensing molecule with a single frequency Faraday electrochemical impedance spectrum [218]. The sensor allows rapid and sensitive measurement of insulin across a dynamic physiological concentration range, holding great potential in the development of next-generation instant sensors. Additionally, Sode's laboratory rationalized the design of DET type L-lactate dehydrogenase to develop multiplexed biosensor with sensors for simultaneously detecting lactate and glucose, which was the first report of a dual sensing system for lactate and glucose based on DET enzymes [219].

## Biomedical products with medical certification

Several Japanese biomedical products that have received medical approvals based on the biomedical applications described above are summarized in Table 4. For targeted drug delivery, several medically approved products exist (Figs. 9a–9c). One is ADCETRIS® (brentuximab vedotin) (Fig. 9a), which obtained marketing authorization from the European Commission in January 2012 [220]. This is an antibody–drug conjugate used to treat specific types of lymphoma. ADCETRIS® combines an anti-CD30 monoclonal antibody with a cytotoxic drug to achieve precise targeting and delivery against CD30-expressing cancer cells. Several artificial blood vessels have been developed for aortic applications (Figs. 9d–9f). Compared with other polymer materials, Artegraft® stands out as a bovine carotid artery graft with a processed biofiber matrix [221]. This distinctive feature enhances long-term patency and provides a tightly woven, crosslinked, flexible, and compliant conduit for patients who are not suitable candidates for bypass surgery using their own veins or arteries. KYOCERA Corp. and the University of Tokyo collaborated to develop a product of the Aquala® hip joint (Fig. 9g) [222]. The artificial hip joint was constructed using a multifunctional polymer


**Fig. 9** Biomedical products with medical certification in Japan. **a** ADCETRIS® (brentuximab vedotin), **b** ENHERTU® (fam-trastuzumab deruxtecan-nxki), **c** Lenvima® (lenvatinib), **d** Gelweave™, **e** Anaconda™, **f** Artegraft®, **g** Aquala®, **h** Tactoset®, **i** Hyalofast®, **j** Hyalomatrix®, **k** HISCL™ SARS-CoV-2 Ag, and **l** 4SURE Smart

material with a phospholipid structure closely resembling that found in human cell membranes. This material exhibits excellent hydrophilicity and biocompatibility, producing a significant reduction in the coefficient of friction. Consequently, the service life of Aquala® has been significantly enhanced. And Tactoset®, as shown in Fig. 9h, is a synthetic, biocompatible, hyaluronic acid-enhanced calcium phosphate bone graft alternative material for filling bone gaps or defects in the skeletal system [223]. Hyalofast® (Fig. 9i) is a biodegradable, nonwoven scaffold composed of the HA derivative HYAFF® that is designed to support the encapsulation of mesenchymal stem cells for the repair of cartilage and osteochondral lesions [224]. Hyalomatrix® (Fig. 9j), manufactured by Anika Therapeutics, Inc., is a sterile, biodegradable, advanced wound dressing exclusively derived from HYAFF® [225]. This derivative offers a 3D scaffold that facilitates cell invasion and capillary growth, fostering organized reconstruction of dermal tissue while providing wound protection. Several biosensors are widely available on the Japanese market, including HISCL™ SARS-CoV-2 Ag (Fig. 9k) for detecting the novel coronavirus COVID-19 and 4SURE Smart (Fig. 9l) for detecting blood glucose in patients with Type 2 diabetes.

## Conclusions and outlook

This article provides a comprehensive review of recent advancements in BM in Japan over the past five years. Drawing from exemplary laboratories and scholars, we systematically outlined the characterization and performance enhancements of three key types of biomedical materials—biomedical metals, ceramics, and polymers, and assessed the advantages and limitations of two processes—extrusion and spheroid bioprinting. Furthermore, this article focuses on five areas of biomedical applications that derive from these materials and processes: targeted drug delivery, antibacterial coatings, vascular and bone tissue engineering, wound dressings, and biosensors. Several medically certified biomedical products based on the above applications are also summarized. Our review highlights the significance of research in nanotechnology, recognizing the crucial role of precise processing and control in the micro/nano domain for future growth in the Japanese medical market.

Japan's "Industry-University" approach and its highly specialized BM research infrastructure have positioned it as a frontrunner in developing biomedical applications compared with other countries. To summarize, Japan has achieved

remarkable progress in BM by implementation of innovative materials, optimized processes, and interdisciplinary applications. These accomplishments are noteworthy and deserve careful consideration. However, challenges remain that need to be addressed, such as ensuring the biosafety of biomedical materials, promoting the integration of multiple processes in bio-3D printing, and facilitating the clinical translation of biomedical applications. Future research should prioritize evaluating the safety of the material and exploring suitable manufacturing processes to produce personalized and safe medical products. In the field of BM, we firmly believe that Japan has the potential to achieve sustainable development and play a more significant role in addressing global challenges. Furthermore, we consider that this review offers readers a comprehensive overview of Japan's advancements in BM, emphasizing its strengths and weaknesses, and paving the way for the development of impactful biomedical products in the future.

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## Declarations

**Conflict of interest** HYY is an editor-in-chief and DH is an academic editor for *Bio-Design and Manufacturing*, and both were not involved in the editorial review or the decision to publish this article. The authors declare that they have no conflict of interest.

**Ethical approval** This study does not contain any studies with human or animal subjects performed by any of the authors.

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