Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in
Biomedical Engineering

Intelligent and smart biomaterials for sustainable 3D printing applications

Elena Herrera-Ponce de León[1,2,3], Alexander U. Valle-Pérez[1,2,3], Zainab N. Khan[1,2,3] and Charlotte A. E. Hauser[1,2,3]

Abstract

Smart and intelligent biomaterials can be designed to carry out special tasks in modern medicine and sustainability, and engineered to identify and respond to environmental stimuli. Therefore, intelligent biomaterials have a large number of applications that can go from health (e.g. tissue engineering, drug delivery and biosensors), to more recently explored environmental applications involving ecosystem restoration (e.g. coral reefs and environmental remediation). The use of 3D printing technology opens the vision towards automated biomanufacturing with more precision and definition. With this broad range of applications, smart and intelligent biomaterials are used separately or in combination with 3D printing to enable the design of eco-friendly and sustainable solutions that can be used to overcome challenges for both; modern medicine and the environment.

Addresses

[1] Laboratory for Nanomedicine, Division of Biological and Environmental Science and Engineering, King Abdullah University of Science and Technology, Thuwal 23955-6900, Saudi Arabia

[2] Computational Bioscience Research Center (CBRC), King Abdullah University of Science and Technology, Thuwal 23955-6900, Saudi Arabia

[3] Red Sea Research Center, King Abdullah University of Science and Technology, Thuwal, Jeddah 23955, Kingdom of Saudi Arabia

Corresponding author: Hauser, Charlotte A.E (charlotte.hauser@kaust.edu.sa)

Current Opinion in Biomedical Engineering 2023, **26:**100450

This review comes from a themed issue on **Intelligent Biomaterials 2023**

Edited by **Seeram Ramakrishn**, **Ravin Narai**, **Himansu Sekhar Nanda**, **Masoud Mozafari** and **Gulden Camci-Unal**

For complete overview of the section, please refer the article collection - Intelligent Biomaterials 2023

Received 16 September 2022, revised 18 January 2023, accepted 24 January 2023

https://doi.org/10.1016/j.cobme.2023.100450

Keywords

Intelligent and smart biomaterials, Sustainability, Ecosystem restoration, Tissue engineering, Coral 3D printing, Bioprinting, Hydrogels.

Introduction

In a constantly-changing world, the ambition of human society heightens to drive and pursue new technologies that are not only better in their application, but in their whole process. Technological advances in the development of intelligent and smart biomaterials can strongly contribute towards designing sustainable solutions. By definition, a smart material can perceive and respond to its surroundings; however, it cannot improve or optimize its response. On the other hand, an intelligent material is capable of comprehending experiences, is self-aware of its surroundings, and can respond purposefully, thus, being able to improve and optimize its response. Therefore, the material can interact according to the situation [1,2]. These stimuli can be categorized into physical (light, magnetism, electricity, temperature and ultrasound), chemical (pH, solvents, ionic strength) and biological (hypoxia, glucose level, enzymes, oxidative stress) [3–6]. Hence, smart materials' response to stimuli can be user-defined (light, temperature, pH, electromagnetic fields, ultrasound) or triggered by cell/tissue-dictated (enzyme secretion, protein interactions). In contrast to the previous definitions, more traditional or normal materials are restricted in several functionalities like their adaptability, self-control, sustainability and intelligence, which are key characteristics required in novel biomaterials [1,3].

A key element present in intelligent and smart materials is that their structural composition enables the active communication through its matrix and to the environment; for instance, hydrogel-based materials enable smart communication between surrounding biomolecules and nutrients while maintaining biocontainment of engineered microorganisms within their matrix [7–9]. For this reason, intelligent and smart biomaterials provide interesting, eco-friendly, and sustainable potential solutions to address contemporary challenges. These can be applied in the medical field as an alternative to reconstructive surgeries, for cases such as injuries, birth defects, treatment for obesity-which is linked to other diseases such as diabetes, heart diseases and chronic illnesses-and even prevent skin damage caused by excessive ultraviolet exposure (UV light)

[10–12]. However, they are not exclusive for clinical application since they can also be exploited for the development of solutions to address environmental challenges such as climate change [13]. For instance, novel solutions can be developed to mitigate coral bleaching [14–16], which disrupts the coral symbiotic relationship with the coral and its zooxanthellae, exposing the coral to diseases that could even lead to death.

The development of smart materials unlocks the potential to enhance materials to act as stimuli responsive building blocks, biosensor, scaffolding material, or as a material that reacts with time for regenerative medicine. A technique that can especially open a pathway to a diverse number of applications, incorporating smart and intelligent biomaterials with 3D printing, is direct ink writing (DIW), which introduces freedom in design, stability and multifunctionality into the printed structures [17]. In this review, we discuss and highlight forefront technologies and novel applications of recently developed smart and intelligent biomaterials for health and environmental applications, with a particular emphasis on their role for sustainability (Figure 1).

Intelligent and smart biomaterials for healthcare, nutrition and cosmetics applications

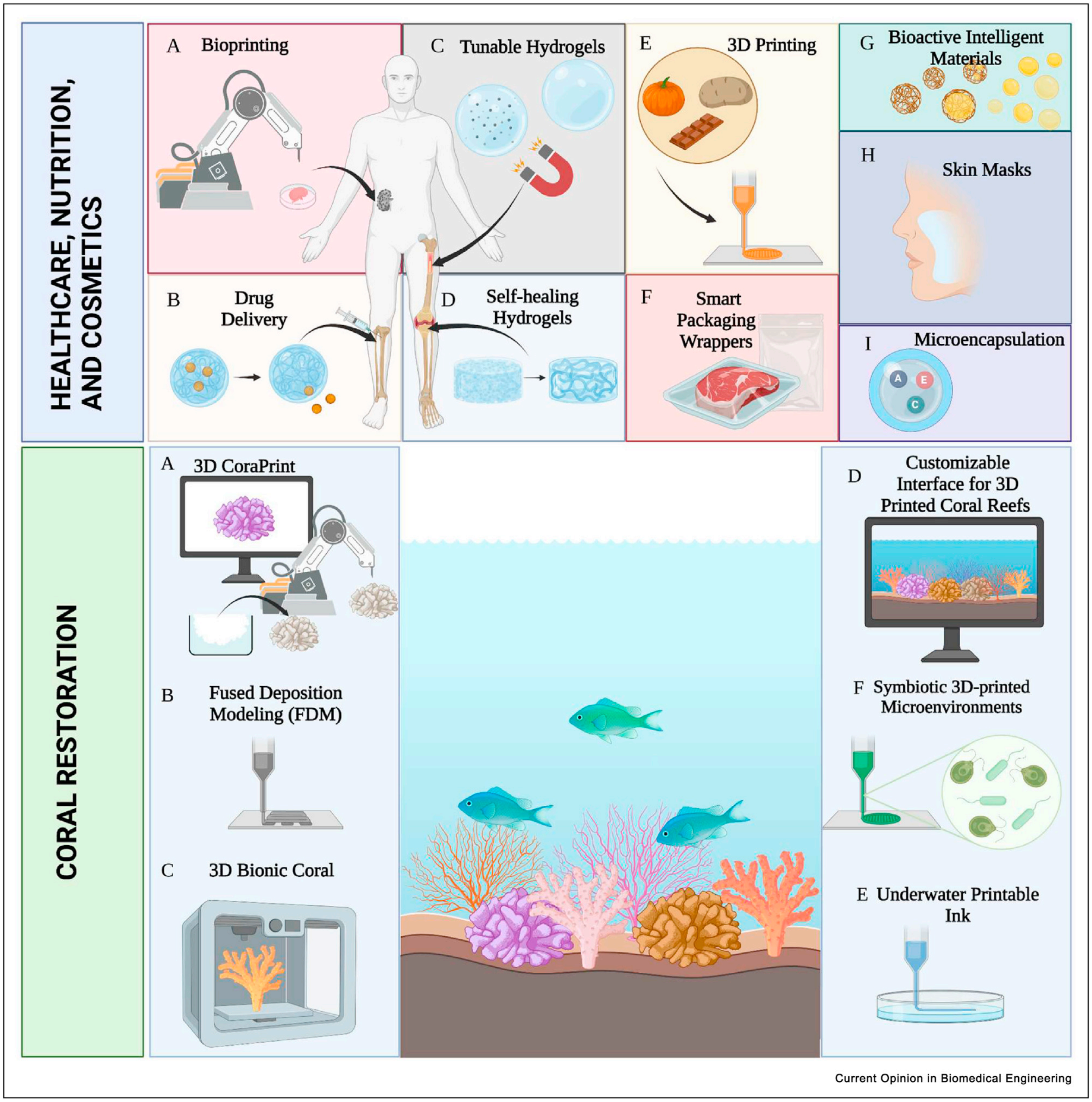
3D printing of tissues

The use of biofabrication technologies is ascending as powerful tools for tissue engineering and regenerative medicine. The continuous development of bioprinting technologies enable the printing of constructs with excellent resolution, visibly refined details, and a consistent thread of gel with no gaps within layers [18]. Present bioprinting and additive manufacturing methods are; extrusion-based techniques, lithographic printing, stereolithography (SLA), and digital light projection printing which uses digital micromirror devices (DLP/DMD), laser-based methods, and melt electro writing. All of these techniques enable the biofabrication of 3D objects in a layer-by-layer process (Figure 2a). Nevertheless, there remains a limitation in the complexity of the type of structures that can be printed [19]. To address this, recent approaches propose the employment of hybrid-bioprinting strategies such as the use of molds and supportive mediums for the biofabrication of more complex structures [20,21]. Therefore, 3D printing presents a monumental potential technology for the design of biocompatible scaffolding microenvironments with high spatial precision [22].

Hydrogels are interesting and efficient smart biomaterials that can be made from natural (like collagen, alginate, and gelatin) or synthetic (such as synthetic fibers, peptides and elastomers) materials. Although hydrogels from natural origin offer advantages like easy recognition of cellular growth factors and biomolecules, as well as natural degradation by the body, synthetic hydrogels are more popularly exploited for 3D bioprinting due to exhibiting enhanced mechanical properties, biocompatibility and having less batch-to-batch variation [23]. Although there is a wide range of synthesis methods for making hydrogels, they can be classified into two main strategies: physical and chemical synthesis. The physical synthesis requires the interaction between the polymer chains resulting in weaker interaction forces (hydrogen bonds, protein interactions, block polymers), while the chemical synthesis exploits cross-linking (crosslinking using enzymes, aldehyde, condensation and addition reactions, free radical polymerization), forming covalent bonds which provide strong mechanical stability to the hydrogel network [24]. Another important characteristic is their porosity, which is crucial for a large range of industrial and medical applications, like 3D bioprinting, drug delivery, tissue engineering, and absorbents [25]. Hydrogels are particularly used in tissue engineering because of their biocompatibility to support cell differentiation and proliferation. It is important to highlight that the chemistry behind the design of smart-materials such as polymer scaffolds is vital, as it greatly influences the physical and biological compatibility properties of the resulting hydrogel. A very recent example of this is shown in the development of magnetically deformable scaffolds for biofabrication [26]. Additionally, the development of jammed microgels with thermosensitive gelatins for shear-induced transition and fast recoverability has also been exploited [27]. On the other hand, conventional 3D printing architectures exploit the advantage of utilizing well-known hydrogel-based scaffolding materials such as alginate, GelMA, and ultrashort peptides to fabricate softer and more delicate tissues, and even stiffer tissues [17,20,28,29]. These key characteristics identify hydrogels as smart biomaterials, which provide suitable microenvironments for a plethora of cells that require specialized culturing environments, such as neurons, chondrocytes, osteoblasts, and stem cells. They can also be used as sacrificial or fugitive inks, as well as smart biocontainment of engineered microorganisms [8,18,22].

The degradation of materials in harsh environments, the increase in fatigue, and other failure mechanisms can be the beginning of microscopic damages that weaken the human body system functionalities. The development of self-healing smart materials can enable intrinsic repair, in which the material itself recovers frequently by healing itself, and extrinsic repair, in which healing agents need to be previously embedded within the materials [30]. If the ability of self-healing is exhibited within the hydrogels, they can turn into remarkable, unique, and smart materials [25,31]. This self-healing attribute in the hydrogel could be achieved, for instance, through the addition of Magnetite (Fe3O4) nanoparticles, a material that is widely used in

Figure 1

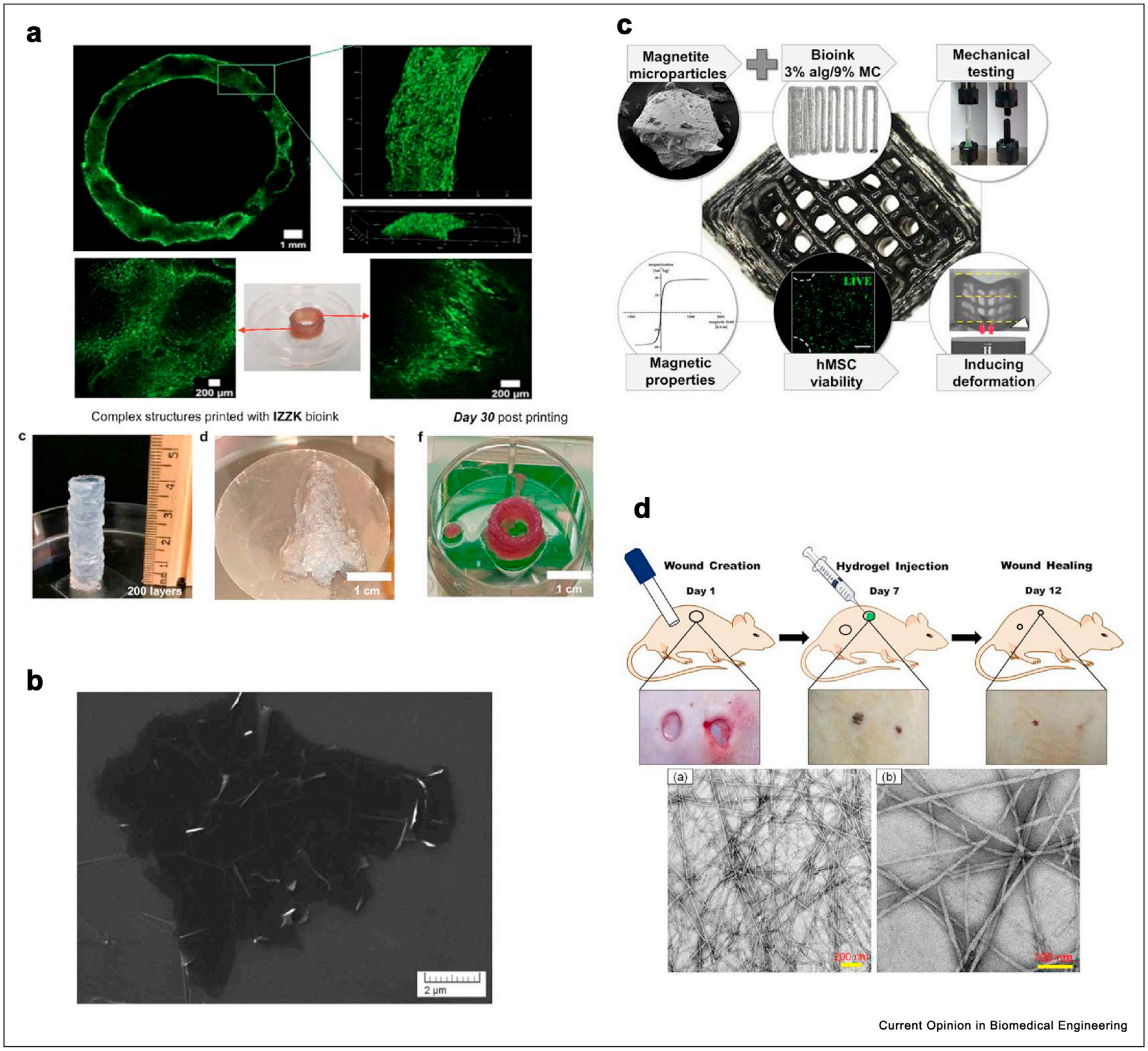


Overview of intelligent and smart biomaterials for sustainable 3D printing applications. A special emphasis is given for healthcare and coral restoration.

biomedical applications with crosslinks between chitosan and oxidized xanthan gum provided through Schiff base linkages (Figure 2c and d). Peptide-based hydrogels also exhibit this type of behavior by displaying thixotropic properties [18,30], thus, keeping a balance between regeneration and breakage [25].

Nanoclay-incorporated double-network (NIDN) hydrogels can be 3D printed into filaments of 2D and 3D constructs and if magnetic microparticles are added, the NIDN hydrogels can be transformed into a new type of magnetic responsive hydrogel for 3D printing [32]. This type of hydrogel also allows the customization and personalization of scaffolds for precision therapy of tissue defects since it improves healing of new bone marrow and the formation of soft tissue. The mechanical stimulation of cells integrated into scaffolds is known to boost cellular performance towards osteogenic or chondrogenic cell differentiation, as well as for the development of tissue. Therefore, magnetic microparticles in

Figure 2



3D bioprinted human bone marrow mesenchymal stem cells with ultra-short peptides for the bioengineering of tissue constructs (a). Adapted from Ref. [18] under a Creative Commons Attribution Noncommercial License (CCC RightsLink). SEM imaging of graphene-laden nanoplates for drug delivery (b). Adapted from Ref. [38] in compliance with Elsevier License (CCC RightsLink). Engineered cell-laden magnetically deformable scaffold for printing (c). Adapted from Ref. [30] under a Creative Commons Attribution Noncommercial License (CCC RightsLink). Coassembled nanofibrous material with thixotropic properties for dermal wound healing (d). Adapted from Ref. [31] under a Creative Commons Attribution Noncommercial License (CC BY 4.0).

bioinks can be used through 3D bioplotting, which is a strategy that allows the definition of a locally adapted presence and concentration of magnetic particles or materials. In this strategy, the adjusted mechanical stimulation is applied to only trigger the cells present in a specific region of the hydrogel with a tunable strength, while the other cells remain unaffected [30]. This piques the interest for the generation of heterogeneous tissue, organs, or even tissue interfaces, and can be further exploited for biofabrication. To illustrate this, a printable magnetic hydrogel that can be successfully used for multi-material direct ink printing of soft actuators was recently developed, while paying special attention to developing bio-nanocomposites that exhibit non-cytotoxicity and good biocompatibility [33]. The use of magnetically responsive hydrogel materials and programmable pattering opens the possibility of applying this technology with the biocompatibility and functionality requirements of soft robotics. Smart materials are essential since their distribution, spatially or by the combination of smart and conventional materials, takes a major role in accomplishing the biofabricated construct functionalities [34].

Material–tissue interfaces

Intelligent materials that can respond to perturbations in the environment in the form of mechanical outputs are particularly valuable as auto-control elements that can deliver drugs, monitor physiological conditions, or modulate embedded cells [7,35]. In the case of bone regeneration, mesoporous bioactive glasses (MBG) are used because of their excellent osteoconductivity, osteo stimulatory effect, and high degradation rate, as well as their highly ordered mesoporous channel structure, and high specific surface area when releasing biologically active ions. These characteristics make them suitable for drug and growth factor delivery, which can be released over time [36]. The use of local biomimetic delivery to heal bone defects provides abundant advantages, due to having an anabolic effect, maintaining local higher concentration, and avoiding side effects. Near-infrared (NIR) reduced graphene oxide loaded chitosan (Cs/rGO) hydrogel was created and applied to accomplish biomimetic pulsatile release of Teriparatide, the only Food and Drug Administration (FDA)-approved anabolic drug for osteoporosis treatment by daily subcutaneous injection [37].

The mechanical stability and conductivity of graphene have been investigated for controlled and tunable drug release with electric or mechanical stimuli. A few layers of graphene can be used as a nanofiller in a hydrogel system with a thermally tunable drug release turning it into a promising tool for thermally triggered drug release in several healthcare scenarios. This hydrogel may also be useful for injectable media, conquering the principal constraints linked to the use of solid-like devices [38]. Graphene scaffold design for NIR photothermal therapy (PTT) is considered a promising alternative for killing cancer cells since it is mediated by an increase in temperature due to NIR light absorbers that are delivered at tumor proximity (Figure 2b). Thus, it has the potential of increasing specificity in comparison to conventional chemotherapy and radiotherapy approaches for cancer treatment [39].

An approach that involves genetically-encoded constructs to precisely and noninvasively manipulate a specific molecular process or cell function by light is known as optogenetics. Optogenetic tools (OTs) reside in photosensitive proteins that are fused with effector domains or peptides, which, when exposed to the light of specific wavelengths, can change shape or even interact with other cellular molecules, and consequently lead to functional changes in the cell [40]. Bacterial biofilms or stand-alone bacterial cells are an application for OTs. These can be programmed to produce engineered living materials that can be used for drug delivery, tissue engineering for regenerative medicine, and the creation of cell-rich bioengineered devices [40].

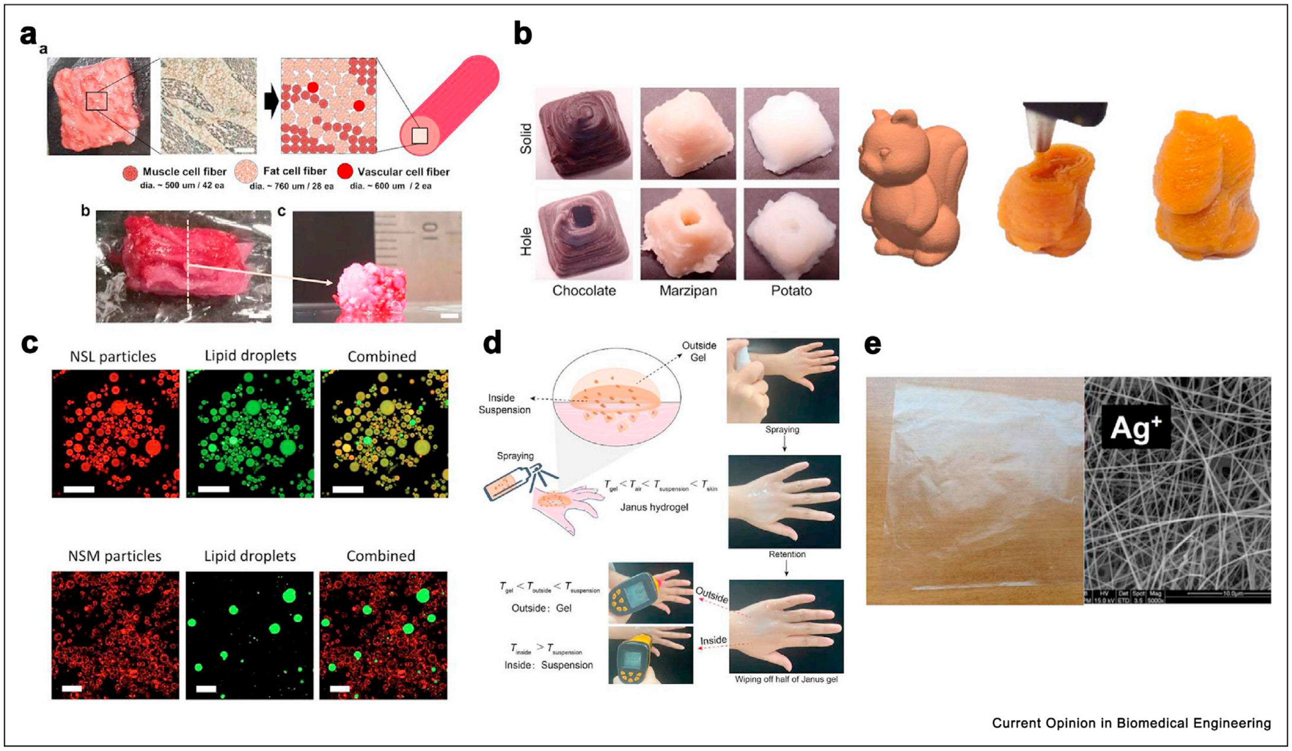
Thermoreversible gels or materials are polymer solutions that can transition to gel upon an increase in temperature above a critical point, and reverse to their original state upon cooling [41]. This type of intelligent biomaterial has enabled ground-breaking discoveries in areas such as protein and peptide delivery, drug and gene delivery, cell culture, tissue engineering, and 3D bioprinting. These gels are beneficial for medicine since they have a low viscosity (below critical temperature), can pass through a syringe, and in their viscous state they can offer enriched retention and prolonged drug delivery at a target location [41].

Nutrition

Edible biomaterials primarily developed from polysaccharides, proteins, and lipids are biodegradable and eco-friendly and present key benefits for the food sector since they can be used as packaging, films, antimicrobials, coatings, and antioxidants, in order to maintain the food freshness [42]. 3D printing can also be applied to food, opening the potential towards personalized nutrition (Figure 3b). In the process of designing the methodology for food printing, different biomaterials (chocolate, marzipan, potato, pumpkin) were printed with basic designs, and cornstarch and guar gum were mixed with the pumpkin ink to upgrade printability and alter the distribution of nutrients [43]. Moreover, 3D bioprinting and the ongoing development of smart and intelligent biomaterials has also been exploited for the in-vitro biomanufacturing of meat (Figure 3a). Recent examples include the assembly of cell fibers by tendon-gel integrated bioprinting to engineer meat-like tissue, and the development of bioactive meat platforms supplemented with naturally derived protein hydrolysates [44,45]. 3D printing also facilitates the utilization of alternative sources of protein, such as insects, for human consumption, since it can tailor the shape, quality, taste, and its nutritional viewpoint, allowing the blossoming of the development of a cost-effective and sustainable alternative protein [46,47]. Precision laser can be used alongside 3D printing in order to cook, boil, cut and even transform food products [48]. A remarkable example in the advances of engineered food is Singapore, which has concentrated efforts in developing technologies for the food industry. In these scenarios, smart and intelligent biomaterials used as bioinks aim to achieve proper cell proliferation and structure formation, while also providing sufficient nutritional requirements from the mimicked food.

To maintain the functional properties of nutraceuticals, biomaterials such as proteins and polysaccharides could

Figure 3



3D bioprinting of meat-like tissue (a). Adapted from Ref. [44] under a Creative Commons Attribution Noncommercial License (CC BY). 3D food printing with pumpkin, chocolate, marzipan and potato-based materials (b). Adapted from Ref. [43] in compliance with ASME original publisher and STM Permission Guidelines. Confocal imaging of nanostructured clay particles (NSL and NSM) supplemented with orlistat to inhibit lipid digestion (c). Adapted from Ref. [52] in compliance with Elsevier License (CCC RightsLink). Development of an intelligent thermosensible paper-free sprayable skin mask (d). Adapted from Ref. [53] in compliance with Elsevier License (CCC RightsLink). Chitin nanofibrils soft film with nanostructured silver particles for cosmetic green carriers and food packaging (e). Adapted from Ref. [54] under a Creative Commons Attribution Noncommercial License (CC BY 4.0).

be used as bioresorbable membranes. The technological advantage of testing natural membranes is the increased extraction capability of valuable biocompounds and the transfer of crucial cations in the final environment of the foods. The extraction is made with supercritical fluids (Superficial Fluid Extraction or SFE), the protective cellulose membranes ionized by plasma affect its efficiency, and with this, the extraction is increased by *22%* [49]. Chitosan (CH)-based hydrogels are unique for intelligent food packaging systems and are used as a passive matrix with simple single indicators, like pH [50,51].

Some of the most promising preclinical and clinical findings regarding the modulation of calorie intake are bioactive intelligent materials that are capable of regulating the fat digestion and absorption process (Figure 3c). The only anti-obesity therapy approved by the FDA that has a localized mechanism of action within the gastrointestinal tract [11]. However, it has its limitations, since it ignores a key role that the glycemic index carbohydrates have in triggering obesity and could lead to nutrient deficiencies. Additionally, biomaterial-based therapies could be explored as alternate obesity management approaches, like preventing weight gain and promoting gut health [11,52].

Cosmetics

The thermogel is an intelligent material that is used for the development of paper-free sprayable skin masks, which undergoes sol—gel—suspension transitions when it is heated (Figure 3d). After the mask is sprayed, a film is formed with a physical gel on the outside and a suspension on the inside. It has been verified that the combination of a thermogel made of biodegradable amphiphilic block copolymers loaded with nicotinamide as a skin mask can decrease pigmentation [53].

Chitin is the second most abundant polymer and can be effortlessly obtained in its nano-size form, chitin nanofibrils (CN), which can be used to make micro-nano particles that encapsulate and protect a diverse range of active ingredients. Figure 3e the micro-nano capsules can be ingrained into fibers of tissues and films to produce antioxidant cosmetics, encapsulate vitamins a, e, and c, or even be used as antiinflammatory, antibacterial and skin-repairing products by encapsulating glycyrrhizic acid or nanostructured silver [54]. The use of nanotechnology can improve the encapsulation efficiency and skin permeability of active ingredients, regulate the release of active substances, boost physical stability, and heal UVB-induced skin damage [12]. 3D Printing can also be used to develop a flexible UV—visible photodetector array that assimilates hybrid organic and inorganic material systems with a portable console that repeatedly monitors broadband irradiance in-situ [55]. This technology is specifically attractive for medical profiling of photosensitive diseases.

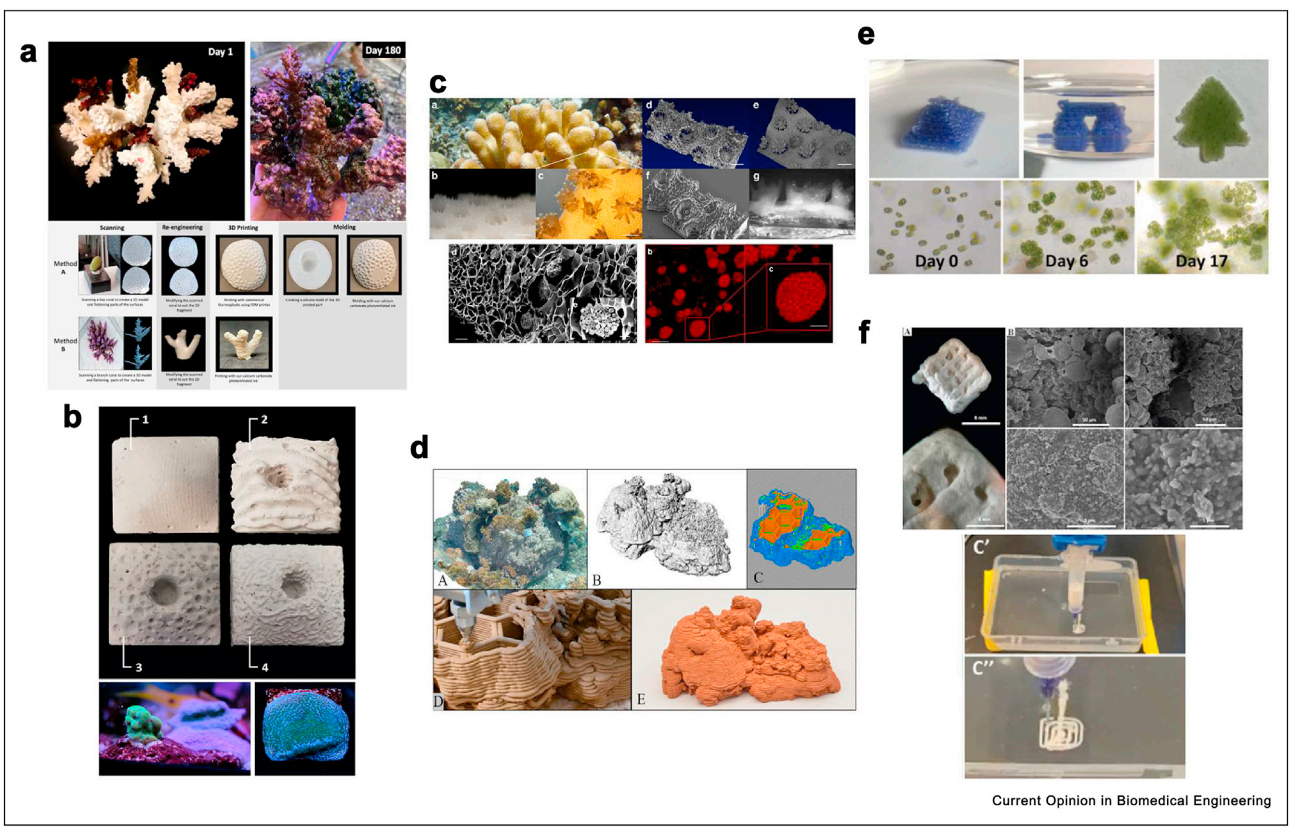
Intelligent and smart biomaterials for environmental applications

Coral restoration

Coral reef degradation is a growing concern, steered by marine heatwaves, the spread of coral diseases, and human impact by overfishing and pollution [14]. Because of the relevance of corals as a key species within marine environments, great efforts have been employed to restore this aquatic ecosystem [56]. Recent studies highlight that the necessary steps to improve the rebuilding of the ecosystem are to increase the complexity, durability, and the enlargement of the 3D structures, with the use of sustainable materials. The design of artificial structures with various roughnesses can play a vital role in species richness, complexity, biodiversity, and the recovery rate in a degraded area [16].

CoraFab is a process developed by the Laboratory for Nanomedicine from King Abdullah University of Science and Technology (KAUST), which uses technology like 3D CoraPrint for coral restoration (Figure 4a). 3D CoraPrint is a method that applies 3D printing technology and smart eco-friendly inks to fabricate artificial natural-based coral skeletons that stimulate the growth rate of coral fragments, making coral reef transplantation faster, while decreasing nursery costs [14]. Figure 4b another study utilizes 3D printing by Fused Deposition

Figure 4



Intelligent and smart materials for the environmental applications. Coral printing strategies (a, b, c). Figure a: adapted from Ref. [14] under a Creative Commons Attribution Noncommercial License (CCC RightsLink). Figure b: adapted from Ref. [56] in compliance with Emerald Publishing Limited and Copyright Clearance Center (CCC RightsLink). Figure c: adapted from Ref. [15] under a Creative Commons Attribution Noncommercial License (CC BY). Scale-up approaches for the 3D printing of coral reefs (d). Adapted from Ref. [58] in compliance with Elsevier License (CCC RightsLink). Development of smart materials: underwater printable ink (e) and engineered symbiotic microenvironments (f). Figure e: adapted from Ref. [60] under a Creative Commons Attribution Noncommercial License (CCC RightsLink). Figure f: adapted from Ref. [59] under a Creative Commons Attribution Noncommercial License (CC BY 4.0).

Modeling (FDM) to generate coral propagation substrates with complex morphologies, cavities, and reliefs for the settlement of coralline algae and coral growth expansion [56].

A 3D printed bionic coral was developed with the capability of growing microalgae [15]. In this research, the morphological features of the bioprinted coral tissue and underlying skeleton were mimicked with hybrid photosynthetic smart biomaterials produced with a 3D printing platform (Figure 4c). In addition, living coral microhabitats can be engineered by applying diverse bioinks for the encapsulation of coral photosynthetic microalgae (Breviolum psygmophilum), and coral mass transfer phenomena are copied by 3D bioprinting coral tissue and skeleton with microscale features [16]. Other research includes the application of 3D printing for the development of 3D biomimetic living materials [57].

A customizable 3D interface is used to produce scalable biomimetic artificial structures, using data collected from coral ecosystems [58]. This interface uses 3D imaging and printing technologies to obtain features from the core of the reef, which could be translated and digitized into a 3D-printed artificial reef (Figure 4d). Figure 4f other studies include the development of underwater printable inks that can be used for 3D printing [59]. 3D bioprinting has also been used for the fabrication of living tissues that grow microorganisms, including single-celled photosynthetic microalgae and bacterial cells [57]. Figure 4e a silk ink with mechanical properties and gelation kinetics, deemed useful for 3D printing, was successfully developed and used for hosting algae [60]. The stability, printability, and long-term functionality are characteristics that support promising environmental utilities. In this way, microalgae and genetically modified microorganisms (GMOs) can facilitate a wide range of important environmental applications, which include sensing and response engineered living materials [8,16,57].

The main difference between conventional and smart materials is the limitation of a conventional material to recognize and respond to stimuli. Although ongoing advances in the development of smart materials enable the generation of stimuli responsive 3D printed structures, there are still limitations related to their utilization for 3D printing in comparison to conventional synthetic and natural materials. For instance, in addition to the inherent rheological and biocompatible characteristics of a conventional material, the 3D printing setup of a smart material should consider avoiding the uncontrolled triggering of a premature response from the smart material during printing. This requires that the selected 3D printing technology and smart material do not share uncontrolled stimuli responses between them. The integration of external stimuli to trigger material response should evaluate the effect on bioprinted cells and microorganisms within the smart material. In addition, changes to the 3D printed cell microenvironment before and after stimuli response (pH, nutrient diffusion, swellability and degradability) must be considered. On the other hand, 3D printed smart biomaterials for health-related applications must consider any potential immune response when intended for human interaction. While the application of smart stimuli responsive 3D printed materials for novel coral restoration strategies in field deployments should consider the degree of required biocontainment for the smart material at a given marine habitat ecosystem. Hence, we have highlighted some of the main bottlenecks to be considered when 3D printing smart materials for healthcare and coral restoration.

Conclusions and future perspectives

Intelligent and smart biomaterials exhibit a wide variety of applications; they enable great versatility to provide solutions in a sustainable and creative way to contemporary health-related and environmental challenges. Because of this, there is genuine interest in the development of these types of biomaterials. For clinical applications, these biomaterials could revolutionize actual treatments given to patients with the help of 3D bioprinting to the smart and specific delivery of biomolecules to target body malfunctions. These biomaterials also demonstrate promising applications for the food industry, as they can be used for the development of smart wrappers and bioactive materials. For the cosmetics industry, intelligent and smart materials contribute to the development of smart skin masks and intelligent microencapsulation strategies. In addition to this, a growing interest has been given to the application of these biomaterials for the environment in combination with 3D bioprinting. Recent examples include 3D CoraPrint, 3D-printed bionic corals and 3D-engineered symbiotic microenvironments which contribute towards the elucidation and potential enhancement of coral reefs against bleaching. The application of 3D printing enables promising novel strategies for a broad spectrum of applications, using it hand by hand with smart and intelligent biomaterials as well as the ongoing development of these technologies is of vital importance to enhance life quality, and mitigate the negative impact of human activities on the environment.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgments

We would like to acknowledge King Abdullah University of Science and Technology (KAUST) baseline funds, KAUST funding 5307RRI, as well as the Computational Bioscience Research Center (CBRC) and Red Sea Research Center (RSRC).

References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest

1. Liu K, Tebyetekerwa M, Ji D, Ramakrishna S: **Intelligent materials**. *Matter* 2020, **3**:590–593.

2. Walther A: **From responsive to adaptive and interactive materials and materials systems: a roadmap**. *Adv Mater* 2020, **32**(20), 1905111.

3. Zhang K, Wang S, Zhou C, Cheng L, Gao X, Xie X, … Xu HH: **Advanced smart biomaterials and constructs for hard tissue engineering and regeneration**. *Bone research* 2018, **6**(1):1–15.

4. Anju MS, Raj DK, Madathil BK, Kasoju N, Anil Kumar PR: **Intelligent biomaterials for tissue engineering and biomedical applications: Current landscape and future prospects**. In *Biomaterials in tissue engineering and regenerative medicine*. Singapore: Springer; 2021:535–560.

5. Kowalski PS, Bhattacharya C, Afewerki S, Langer R: **Smart biomaterials: recent advances and future directions**. *ACS Biomater Sci Eng* 2018, **4**(11):3809–3817.

6. Amukarimi S, Ramakrishna S, Mozafari M: **Smart biomaterials—a proposed definition and overview of the field**. *Current Opinion in Biomedical Engineering* 2021, **19**, 100311.

7. * Tang TC, Tham E, Liu X, Yehl K, Rovner AJ, Yuk H, … Lu TK: **Hydrogel-based biocontainment of bacteria for continuous sensing and computation**. *Nat Chem Biol* 2021, **17**(6): 724–731.

The development of an intelligent biomaterial for the efficient biocontainment of GMOs. Hydrogel-based beads (DEPCOS) restrict GMOs from diffusing out and contain nutrients for cell proliferation, while allowing external metabolites to diffuse inside for interaction. This intelligent biomaterial enables the safe sensing, recording and communication of hydrogel-based biocontained GMOs.

8. Pantoja Angles A, Valle-Pérez AU, Hauser C, Mahfouz MM: **Microbial biocontainment systems for clinical, Agricultural, and industrial applications**. *Front Bioeng Biotechnol* 2022, **28**.

9. Martin N, Bernat T, Dinasquet J, Stofko A, Damon A, Deheyn DD, … Wangpraseurt D: **Synthetic algal-bacteria consortia for space-efficient microalgal growth in a simple hydrogel system**. *J Appl Phycol* 2021, **33**(5):2805–2815.

10. Arab W, Kahin K, Khan Z, Hauser CA: **Exploring nanofibrous self-assembling peptide hydrogels using mouse myoblast cells for three-dimensional bioprinting and tissue engineering applications**. *International Journal of Bioprinting* 2019, **5**.

11. Joyce P, Meola TR, Schultz HB, Prestidge CA: **Biomaterials that regulate fat digestion for the treatment of obesity**. *Trends Food Sci Technol* 2020, **100**:235–245.

12. Zhu JJ, Huang XN, Yang T, Tang CH, Yin SW, Jia XJ, Yang XQ: **An eco-friendly zein nanoparticle as robust cosmetic ingredient ameliorates skin photoaging**. *Ind Crop Prod* 2022, **177**, 114521.

13. Litchfield SG, Schulz KG, Kelaher BP: **The influence of plastic pollution and ocean change on detrital decomposition**. *Mar Pollut Bull* 2020, **158**, 111354.

14. ** Albalawi HI, Khan ZN, Valle-Pérez AU, Kahin KM, Hountondji M, Alwazani H, … Hauser CA: **Sustainable and eco-friendly coral restoration through 3D printing and fabrication**. *ACS Sustainable Chem Eng* 2021, **9**:12634–12645.

The application of 3D extrusion-based printing in combination with a smart eco-friendly calcium carbonate-based ink for the printing of coral skeletons (3D CoraPrint). Then, microfragmentation is applied on the printed skeletons to enable coral growth. This is the first work that applies 3D printing with a calcium carbonate-based smart ink for sustainable coral restoration: CoraFab.

15. ** Wangpraseurt D, You S, Azam F, Jacucci G, Gaidarenko O, Hildebrand M, … Vignolini S: **Bionic 3D printed corals**. *Nat Commun* 2020, **11**(1):1–8.

The application of 3D bioprinting for the development of an intelligent biomaterial for coral restoration. This biomaterial acts as a programmable synthetic microenvironment for coral-algal symbiosis.

16. * Wangpraseurt D, Sun Y, You S, Chua ST, Noel SK, Willard HF, … Chen S: **Bioprinted living coral microenvironments mimicking coral-algal symbiosis**. *Adv Funct Mater* 2022, 2202273.

The development of smart bioinks and their application in additive manufacturing for synthetic corals. The bioinks are used as scaffolding materials for the recreation of coral microhabitats that replicate diffusion phenomena for coral-algal symbiosis.

17. Saadi MASR, Maguire A, Pottackal NT, Thakur MSH, Ikram MM, Hart AJ, … Rahman MM: **Direct ink writing: a 3D printing technology for diverse materials**. *Adv Mater* 2022, 2108855.

18. ** Susapto HH, Alhattab D, Abdelrahman S, Khan Z, Alshehri S, Kahin K, … Hauser CA: **Ultrashort peptide bioinks support automated printing of large-scale constructs assuring long-term survival of printed tissue constructs**. *Nano Lett* 2021, **21**: 2719–2729.

The application of 3D bioprinting in combination with ultra-short peptides and robotic-assisted automation for the engineering of tissue-like 3D printed constructs. The ultra-short peptides exhibit high biocompatibility and stiffness which enables them to act as smart scaffolding materials for 3D organ bioprinting.

19. Bernal PN, Delrot P, Loterie D, Li Y, Malda J, Moser C, Levato R: **Volumetric bioprinting of complex living-tissue constructs within seconds**. *Adv Mater* 2019, **31**, 1904209.

20. Khan ZN, Albalawi HI, Valle-Pérez AU, Aldoukhi A, Hammad N, de León EHP, … Hauser CAE: **From 3D printed molds to bioprinted scaffolds: a hybrid material extrusion and vat polymerization bioprinting approach for soft matter constructs**. *Mater. Sci. Addit. Manuf* 2022, **1**.

21. Zhao J, He N: **A mini-review of embedded 3D printing: supporting media and strategies**. *J Mater Chem B* 2020, **8**: 10474–10486.

22. Chalard A, Mauduit M, Souleille S, Joseph P, Malaquin L, Fitremann J: **3D printing of a biocompatible low molecular weight supramolecular hydrogel by dimethylsulfoxide water solvent exchange**. *Addit Manuf* 2020, **33**, 101162.

23. Mancha Sánchez E, Gómez-Blanco JC, López Nieto E, Casado JG, Macías-García A, Díaz Díez MA, … Pagador JB: **Hydrogels for bioprinting: a systematic review of hydrogels synthesis, bioprinting parameters, and bioprinted structures behavior**. *Front Bioeng Biotechnol* 2020, **8**:776.

24. Akhtar MF, Hanif M, Ranjha NM: **Methods of synthesis of hydrogels… A review**. *Saudi Pharmaceut J* 2016, **24**(5): 554–559.

25. * Sanoh NC, Salazar GM, Penaloza Jr DP: *Magnetic biopolymeric hydrogel composite material with self-healing attribute*. 2021.

Development of a magnetic self-healing and biocompatible smart polymer for medical applications.

26. Spicer CD: **Hydrogel scaffolds for tissue engineering: the importance of polymer choice**. *Polym Chem* 2020, **11**: 184–219.

27. Sheikhi M, Rafiemanzelat F, Ghodsi S, Moroni L, Setayeshmehr M: **3D printing of jammed self-supporting microgels with alternative mechanism for shape Fidelity, crosslinking and conductivity**. *Addit Manuf* 2022, 102997.

28. Wang M, Li W, Hao J, Gonzales A, Zhao Z, Flores RS, … Zhang YS: **Molecularly cleavable bioinks facilitate high-performance digital light processing-based bioprinting of functional volumetric soft tissues**. *Nat Commun* 2022, **13**(1):1–18.

29. Falcone G, Mazzei P, Piccolo A, Esposito T, Mencherini T, Aquino RP, … Russo P: **Advanced printable hydrogels from pre-crosslinked alginate as a new tool in semi solid extrusion 3D printing process**. *Carbohydr Polym* 2022, **276**, 118746.

30. * Spangenberg J, Kilian D, Czichy C, Ahlfeld T, Lode A, Günther S, … Gelinsky M: **Bioprinting of magnetically deformable scaffolds**. *ACS Biomater Sci Eng* 2021, **7**:648–662.
Development of a magnetically deformable intelligent bioink for 3D bioprinting applications.

31. Gavel PK, Kumar N, Parmar HS, Das AK: **Evaluation of a peptide-based coassembled nanofibrous and thixotropic hydrogel for dermal wound healing**. *ACS Appl Bio Mater* 2020, **3**(5):3326–3336.

32. Guo Z, Dong L, Xia J, Mi S, Sun W: **3D printing unique nano-clay-incorporated double-network hydrogels for construction of complex tissue engineering scaffolds**. *Advanced Healthcare Materials* 2021, **10**(11), 2100036.

33. ** Simińska-Stanny J, Nizioł M, Szymczyk-Ziółkowska P, Brożyna M, Junka A, Shavandi A, Podstawczyk D: **4D printing of patterned multimaterial magnetic hydrogel actuators**. *Addit Manuf* 2022, **49**, 102506.
Development of a printable magnetic responsive hydrogel for bioprinting. This intelligent biomaterial can be printed with good resolution, mechanical stability, and exhibits low cytotoxicity.

34. Falahati M, Ahmadvand P, Safaee S, Chang YC, Lyu Z, Chen R, … Lin Y: **Smart polymers and nanocomposites for 3D and 4D printing**. *Mater Today* 2020, **40**:215–245.

35. Clegg JR, Wagner AM, Shin SR, Hassan S, Khademhosseini A, Peppas NA: **Modular fabrication of intelligent material-tissue interfaces for bioinspired and biomimetic devices**. *Prog Mater Sci* 2019, **106**, 100589.

36. Guduric V, Belton N, Richter RF, Bernhardt A, Spangenberg J, Wu C, … Gelinsky M: **Tailorable zinc-substituted mesoporous bioactive glass/alginate-methylcellulose composite bioinks**. *Materials* 2021, **14**(5):1225.

37. Wang X, Guo W, Li L, Yu F, Li J, Liu L, … Xia L: **Photothermally triggered biomimetic drug delivery of Teriparatide via reduced graphene oxide loaded chitosan hydrogel for osteoporotic bone regeneration**. *Chem Eng J* 2021, **413**:127413.

38. Mauri E, Salvati A, Cataldo A, Mozetic P, Basoli F, Abbruzzese F, … Rainer A: **Graphene-laden hydrogels: a strategy for thermally triggered drug delivery**. *Mater Sci Eng C* 2021, **118**, 111353.

39. Palmieri V, Spirito MD, Papi M: **Graphene-based scaffolds for tissue engineering and photothermal therapy**. *Nanomedicine* 2020, **15**:1411–1417.

40. Reshetnikov VV, Smolskaya SV, Feoktistova SG, Verkhusha VV: *Optogenetic approaches in biotechnology and biomaterials.Trends in Biotechnology*. 2022.

41. Cook MT, Haddow P, Kirton SB, McAuley WJ: **Polymers exhibiting lower critical solution temperatures as a route to thermoreversible gelators for healthcare**. *Adv Funct Mater* 2021, **31**, 2008123.

42. Reshmy R, Philip E, Madhavan A, Sindhu R, Pugazhendhi A, Binod P, … Pandey A: **Advanced biomaterials for sustainable applications in the food industry: updates and challenges**. *Environ Pollut* 2021, **283**, 117071.

43. Mahmoud R, Nguyen Q, Christopher G, Egan PF: **3D printed food design and fabrication approach for manufacturability, Rheology, and nutrition Trade-Offs**. In *International design engineering technical conferences and computers and information in engineering conference*, vol. 85383. American Society of Mechanical Engineers (ASME); 2021, August. V03AT03A034.

44. ** Kang DH, Louis F, Liu H, Shimoda H, Nishiyama Y, Nozawa H, … Matsusaki M: **Engineered whole cut meat-like tissue by the assembly of cell fibers using tendon-gel integrated bioprinting**. *Nat Commun* 2021, **12**(1):1–12.
Bath-assisted 3D printing of meat-like constructs with smart bioinks.

45. Dutta SD, Ganguly K, Jeong MS, Patel DK, Patil TV, Cho SJ, Lim KT: **Bioengineered Lab-Grown meat-like constructs through 3D bioprinting of Antioxidative protein hydrolysates**. *ACS Appl Mater Interfaces* 2022, **14**:34513–34526.

46. Sandhu K, Singh S: *Food printing: 3D printing in food industry*. Publisher: Springer; 2022. 2021.

47. Ghazal AF, Zhang M, Mujumdar AS, Ghamry M: **Progress in 4D/5D/6D printing of foods: applications and R&D opportunities**. *Crit Rev Food Sci Nutr* 2022:1–24.

48. Blutinger JD, Tsai A, Storvick E, Seymour G, Liu E, Samarelli N, … Lipson H: **Precision cooking for printed foods via multiwavelength lasers**. *npj Science of Food* 2021, **5**(1):1–9.

49. * Savescu P, Iacobescu F, Poenaru MM: **Study on the use of biomaterials as protective membranes for Certain functional foods**. In *International conference on bio and nanomaterials*. Cham: Springer; 2019, September:178–190.
Application of intelligent materials as bio-resorbable membranes to preserve the functional properties of nutraceuticals.

50. Yang J, Shen M, Luo Y, Wu T, Chen X, Wang Y, Xie J: **Advanced applications of chitosan-based hydrogels: from biosensors to intelligent food packaging system**. *Trends Food Sci Technol* 2021, **110**:822–832.

51. Liu Z, Liu C, Sun X, Zhang S, Yuan Y, Wang D, Xu Y: **Fabrication and characterization of cold-gelation whey protein-chitosan complex hydrogels for the controlled release of curcumin**. *Food Hydrocolloids* 2020, **103**, 105619.

52. * Joyce P, Dening TJ, Meola TR, Gustafsson H, Kovalainen M, Prestidge CA: **Nanostructured clay particles supplement orlistat action in inhibiting lipid digestion: an in vitro evaluation for the treatment of obesity**. *Eur J Pharmaceut Sci* 2019, **135**: 1–11.
Engineering of intelligent nanostructured clay particles intelligent materials for the treatment of obesity.

53. * Cai C, Tang J, Zhang Y, Rao W, Cao D, Guo W, … Ding J: **Intelligent paper-free sprayable skin mask based on an in situ formed Janus hydrogel of an environmentally friendly polymer**. *Advanced Healthcare Materials* 2022, 2102654.
Development of a paper-free intelligent skin mask.

54. Morganti P, Morganti G, Coltelli MB, Yudin WE, Chen HD, Gagliardini A: **Non-woven tissues as novel cosmetic carriers for a green Beauty**. *Advances in Environmental and Engineering Research* 2022, **3**:1. 1.

55. ** Ouyang X, Su R, Ng DWH, Han G, Pearson DR, McAlpine MC: **3D printed skin-Interfaced UV-visible hybrid photodetectors**. *Adv Sci* 2022, 2201275.
Engineering of a 3D printed skin interface for UV–visible photodetection. The intelligent materials are formulated with polymeric photoactive materials and zinc oxide nanoparticles that enhance UV photoresponse and photomultiplciation. The skin interface enables detection of natural irradiance at wavelengths between 310 and 650 nm for 24 h.

56. Matus IV, Alves JL, Gois J, da Rocha AB, Neto R, Mota CDS: **Effect of 3D printer enabled surface morphology and composition on coral growth in artificial reefs**. *Rapid Prototyp J* 2021, **27**:692–706.

57. Wangpraseurt D, You S, Sun Y, Chen S: **Biomimetic 3D living materials powered by microorganisms**. *Trends Biotechnol* 2022.

58. Levy N, Berman O, Yuval M, Loya Y, Treibitz T, Tarazi E, Levy O: **Emerging 3D technologies for future reformation of coral reefs: Enhancing biodiversity using biomimetic structures based on designs by nature**. *Sci Total Environ* 2022, **830**, 154749.

59. * Avila-Ramírez A, Valle-Pérez AU, Susapto HH, Pérez-Pedroza R, Briola GR, Alrashoudi A, … Hauser CA: **Ecologically friendly biofunctional ink for reconstruction of rigid living systems under wet conditions**. *International journal of bioprinting* 2021, **7**.
Development of an underwater 3D printable bioink for coral restoration.

60. ** Zhao S, Guo C, Kumarasena A, Omenetto FG, Kaplan DL: **3D printing of functional microalgal silk structures for environmental applications**. *ACS Biomater Sci Eng* 2019, **5**: 4808–4816.
3D printing of a smart silk-based hydrogel for hosting microalgae. This scaffold enables photosynthetic activity for 90 days, and can potentially be used for oxygen replenishment and carbon dioxide reduction.