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REVIEW

Innovation leading development: a glimpse into three-dimensional bioprinting in Israel

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Abstract

Three-dimensional (3D) printing has attracted increasing research interest as an emerging manufacturing technology for developing sophisticated and exquisite architecture through hierarchical printing. It has also been employed in various advanced industrial areas. The development of intelligent biomedical engineering has raised the requirements for 3D printing, such as flexible manufacturing processes and technologies, biocompatible constituents, and alternative bioproducts. However, state-of-the-art 3D printing mainly involves inorganics or polymers and generally focuses on traditional industrial fields, thus severely limiting applications demanding biocompatibility and biodegradability. In this regard, peptide architectonics, which are self-assembled by programmed amino acid sequences that can be flexibly functionalized, have shown promising potential as bioinspired inks for 3D printing. Therefore, the combination of 3D printing and peptide self-assembly potentially opens up an alternative avenue of 3D bioprinting for diverse advanced applications. Israel, a small but innovative nation, has significantly contributed to 3D bioprinting in terms of scientific studies, marketization, and peptide architectonics, including modulations and applications, and ranks as a leading area in the 3D bioprinting field. This review summarizes the recent progress in 3D bioprinting in Israel, focusing on scientific studies on printable components, soft devices, and tissue engineering. This paper further delves into the manufacture of industrial products, such as artificial meats and bioinspired supramolecular architectures, and the mechanisms, physicochemical properties, and applications of peptide self-assembly. Undoubtedly, Israel contributes significantly to the field of 3D bioprinting and should thus be appropriately recognized.

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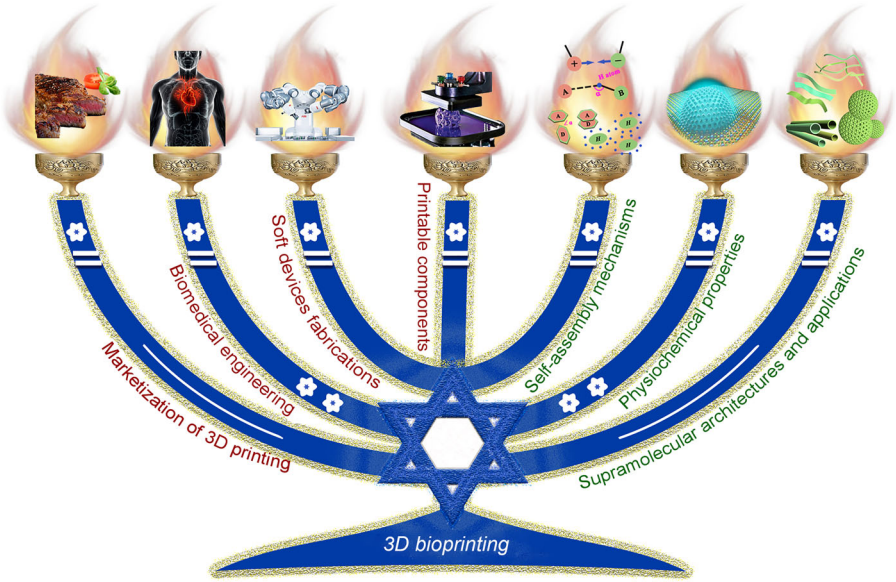
Graphic abstract



Keywords Israel · 3D bioprinting · Biomanufacturing · Peptide self-assembly · Integration of industry, education and research

Introduction

The development of intelligent biomedical engineering [1], sophisticated interface interactions, and artificial organ technology has driven the widespread adoption of implantable and wearable electronic devices [2, 3], such as nerve stimulators [4] and smartwatches [5]. However, significant challenges remain despite the substantial progress achieved in these areas. Some device components are made of rigid materials and are thus non-biocompatible, particularly those that must come in direct contact with the human body, causing discomfort due to rigidity and lack of compliance. Notably, when considering implantation within the human body, the requirements for these devices become more exacting, necessitating enhanced attributes, such as increased flexibility, sensitivity, stability, and biocompatibility. The researchers have previously engineered flexible biomaterials that stand in stark contrast to otherwise biologically unyielding materials, such as steel. Compared with their rigid counterparts, these pliable biomaterials exhibit superior biocompatibility and biodegradability, offering a comfortable adherence to the human skin surface. Simultaneously, the integration of biomaterials has relatively alleviated the problem of adverse reactions triggered by artificial materials and devices interfacing with the human body, thereby contributing significantly to the progression of contemporary medicine and biotechnology.

Three-dimensional (3D) printing [6–8], an extensively investigated form of additive manufacturing, relies on a specialized digital model to create successive layers in a hierarchical fashion, thereby producing neatly aligned complex structures. In contrast to conventional manufacturing techniques, 3D printing eliminates the requirement for bespoke molds and multiple manufacturing steps, resulting in a more efficient, precise, and streamlined production of intricate structures through the direct partitioning of digital models. Consequently, 3D printing has found extensive application in diverse domains, including the biomedical fields [9, 10], such as tissue engineering [10–12] and bionic manufacturing [13–15], and industrial sectors, including the aerospace, smart electronics, and automotive industries.

Conventional 3D printing technologies employ light-cured or nozzle-based printing. Nozzle-based 3D printing incorporates techniques such as fused deposition modeling (FDM) [16], direct ink writing (DIW) [17–26], and inkjet printing [27]. This method relies on material extrusion and facilitates the creation of intricate 3D structures featuring periodic designs and multiple components. Advantageously, this printing process is not restricted by material type or reliant on external factors such as temperature and light. As long as the precursor ink possesses suitable rheological properties, it can be extruded for printing. The structure of the printer is relatively simple, enabling cost-effective adjustments to its components based on the specific requirements of the intended application. Among the array of 3D printing technologies, DIW stands out as a highly versatile additive manufacturing method. It was initially introduced as a technique for crafting ceramics in 1997 by Cesarano

and Grieco [28]. However, the intrinsic reliance of DIW on material extrusion and its dependence on the rheological and shear-thinning properties of the extruded material render it susceptible to restrictions imposed by coordinates and nozzle sizes. Consequently, DIW produces a relatively low print resolution, which, in turn, limits the construction of intricate structures.

In contrast, photopolymerization-based 3D printing achieves higher-resolution object production through localized photopolymerization for curing purposes. Photocurable 3D printing ink typically has three components: a cross-linking agent, an initiator, and a monomer. When exposed to ultraviolet (UV) or visible light, the ink undergoes cross-linking or polymerization, leading to irreversible curing. Light-curing 3D printing primarily includes stereolithography (SLA) [29, 30], digital light processing (DLP) [31–47], and continuous liquid interface production (CLIP) [48]. SLA technology exposes UV-cured ink to a specific laser irradiation intensity, gradually transitioning from point to line and from line to surface, ultimately creating a complex 3D structure layer by layer. Compared with SLA, DLP uses a digital projection system to solidify a layer of photosensitive resin across the entire image, leading to higher printing speeds but slightly low resolution. CLIP technology amalgamates photo curing and continuous liquid interface concepts, enabling the continuous curing of photosensitive resins through photo-induced oxidation reactions, resulting in a more continuous and smoother printing process. However, compared with traditional UV curing technology, CLIP is still in its developmental stage. Therefore, this process will not be discussed further.

In contrast to traditional printing, 3D printing offers a wider array of specific printing forms and the flexibility to employ various raw materials, including metals, ceramics, and polymers. However, the limited biocompatibility and biodegradability of inorganic materials restrict the applications of 3D printing in biomedicine. Nevertheless, 3D bioprinting involving cell and tissue engineering has partly bridged this gap [49]. Three-dimensional bioprinting can be split into two categories: a broader approach involves 3D printing applicable in the biomedical field, and a narrower definition involves 3D printing using bio-ink containing cells to construct active structures. However, the current availability of bio-inks is limited, emphasizing the crucial need to expand the bio-ink repertoire for wider applicability, which would significantly advance the field of 3D bioprinting.

Three-dimensional bioprinting is intimately linked to tissue engineering and regenerative medicine. To achieve the primary goal of organ printing as soon as possible, the adoption of biomaterials, such as peptides, proteins, and amino acids, as printing inks is inevitable. Peptides are noted for their diverse range of raw materials, design flexibility [50, 51], straightforward preparation, and inherent biocompatibility [52]. Through non-covalent bonding, such as intermolecular hydrogen bonding and aromatic, hydrophobic, and electrostatic interactions, short peptide self-assembly initiates the creation of polar one-dimensional (1D) nanostructures [53, 54], such as nanofibers, nanoribbons, and nanotubes [52]. These nanostructures entwine to form a 3D network structure and ultimately produce a supramolecular structural system [52, 55]. Most peptide molecules lack functionalization, prompting the introduction of functionalized molecules (such as enzymes or molecules with optical, electrical, or magnetic properties) to interact synergistically with peptide molecules. This synergistic interaction establishes the functionalization of self-assembled bodies, effectively enhancing system performance and leveraging advantages in structural and functional biomimetics [56]. Owing to the highly adjustable physicochemical properties and innate biocompatibility of short peptide self-assembled supramolecular structures [57–60], they have extensive applications as structural materials in various biomedical domains [61–68], including tissue engineering [69–76], cell culture [77–86], and drug release [87]. Hence, the use of superstructural short peptide systems with various shapes, sizes, and customizable attributes as pioneering inks in 3D printing is an imminent research direction. This trend involves the design and fabrication of intricate 3D structures featuring a blend of micro- and macrostructural arrays.

However, compared with traditional 3D printing materials [88–90], such as ceramics and polymers [91, 92], bioprinting materials are typically soft, posing challenges for the fabrication of intricate structures. This material softness can create unstable layer-by-layer deposition during printing, particularly as the number of layers increases, thereby limiting current biomaterial printing practices. In addition to exploring cutting-edge technologies, investigation of the use of diverse materials as printing inks in 3D printing technology is imperative to bolster the resilience of biological materials. Through the deliberate design of peptide superstructural systems and by harnessing the advantages of 3D printing for creating intricate mechanical structures, the fusion of peptides and 3D printing is highly promising as an area of innovation in the near future.

Israel has earned the moniker “the wellspring of global innovation” and stands out as one of the world’s most innovative and dynamic nations. The nation places significant emphasis on institutional enhancement, investment in research and development, nurturing innovative talents, and fostering of industrial innovation and collaboration. Israel maintains global leadership across several high-value sectors, including the materials engineering, renewable energy, biopharmaceutical, medical device manufacturing, and military industries. This leadership extends to the entire spectrum, including materials production, application, and

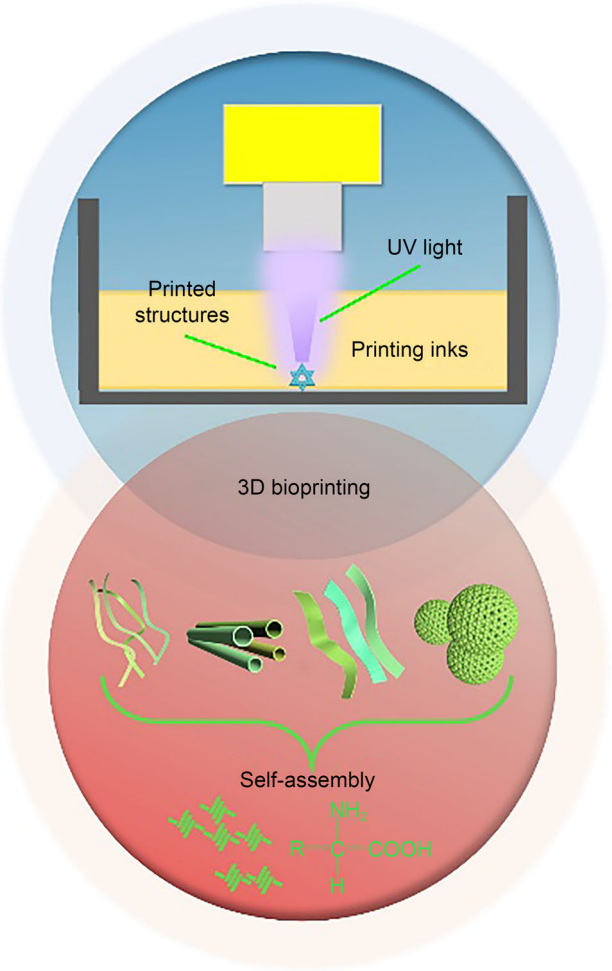


Fig. 1 Schematic diagram of the combination of 3D printing and peptide self-assembly for 3D bioprinting applications. The peptide building blocks can self-assemble to form diverse supramolecular structures through non-covalent interactions. These bioinspired supramolecular systems can behave as bio-inks for 3D bioprinting, enabling the development of bionic constructions with hierarchical structures at both the micro- and macroscopic scales, as well as bioproducts, such as alternative foods and smart biodevices (UV: ultraviolet)

marketization. In this context, we highlight the notable contributions of Israeli scientists in the fields of 3D printing and peptide self-assembly. This review summarizes the advancements of Israeli endeavors in 3D printing and peptide self-assembly, aiming to bridge the two advanced fields to facilitate the development of 3D bioprinting (Fig. 1).

3D printing

Development of 3D printing in Israel

The development of 3D printing has recently made rapid progress; however, relatively speaking, it is still an emerging field. Israel's 3D printing industry has developed rapidly since the 2000s, and now, Israel is the global manufacturer of approximately 40% of 3D printers. Israel's strength lies not only in manufacturing printers, but in fact, also in the clever use of 3D printing technology. The various practical products created that are imaginative and beneficial to humanity have earned Israel's 3D printing technology world renown. Israel's 3D bioprinting advancements have also made significant progress. With the support of top-notch academic and research talents, entrepreneurs, and emerging startups, Israel's achievements in 3D printing are changing the world. A timeline of the development of Israel's 3D printing technology is shown in Fig. 2.

Printable components

Functional hydrogels

Hydrogel, a 3D polymer network dispersed in water, has numerous applications in the assembly of sensors [93], actuators [94, 95], and electronic devices [96] because of its various beneficial characteristics, including biocompatibility, softness, moisture retention, and bioactivity. The mechanical properties of the hydrogels can be adjusted by selecting distinct preparation methods and materials. Furthermore, through structural modifications, dynamic hydrogels with responsive capabilities have been engineered to react to external stimuli, including light [97–99], heat [100], pressure [101], and magnetic fields [102]. Caprioli et al. [103] evaluated a self-healing hydrogel fabricated by DLP 3D printing. Light-curable inks were formulated by blending polyvinyl alcohol with acrylic acid, the cross-linking agent polyethylene glycol diacrylate (PEGDA), and a water-compatible photoinitiator based on diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide (TPO). A commercially available DLP printer was used for printing under a 385-nm light source. After removing residual resin from the printed object using compressed air or a cloth dipped in ethanol, the printed object was post-cured to enhance its strength. Finally, it was stored in a high-humidity, sealed environment. The produced hydrogel achieved rapid self-healing at room temperature without any reactions after cutting (Fig. 3a). The recovered samples quickly resisted deformation, regaining 72% of their initial strength within 12 h. The proposed method successfully fabricated self-healing hydrogel structures via 3D printing, opening avenues for potential applications in soft robotics and energy storage.

Zhou et al. [104] incorporated poly(N-isopropylacrylamide) (PNIPAm) particles into a silica–alumina (Si/Al)-based gel matrix to create a hybrid hydrogel. This hydrogel can be printed layer by layer onto flexible substrates and transparent electrodes using a commercially available 3D printer, all without requiring a curing process. The printed hydrogel demonstrated responsiveness

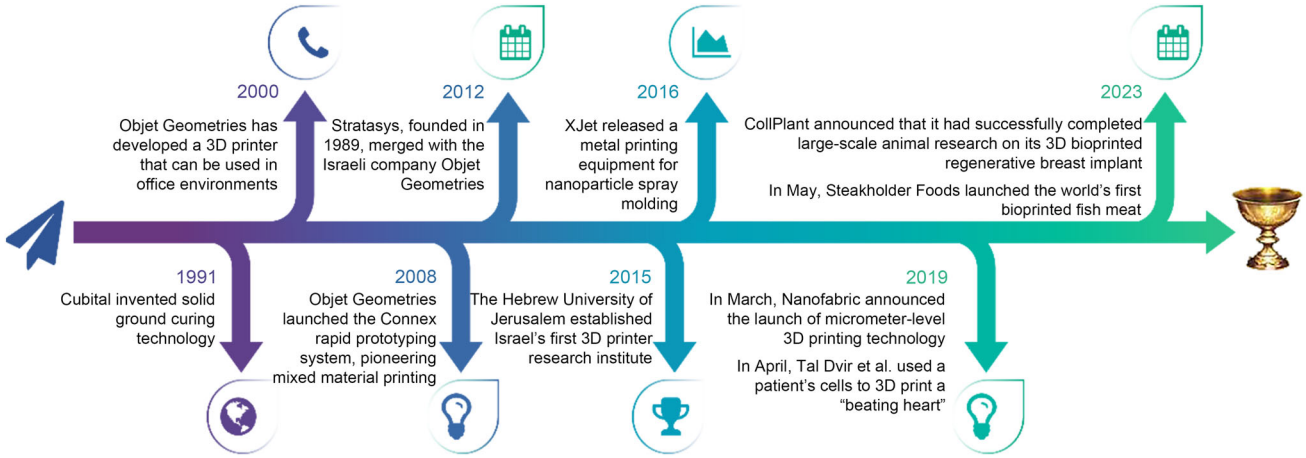


Fig. 2 Flowchart of the development of 3D printing in Israel

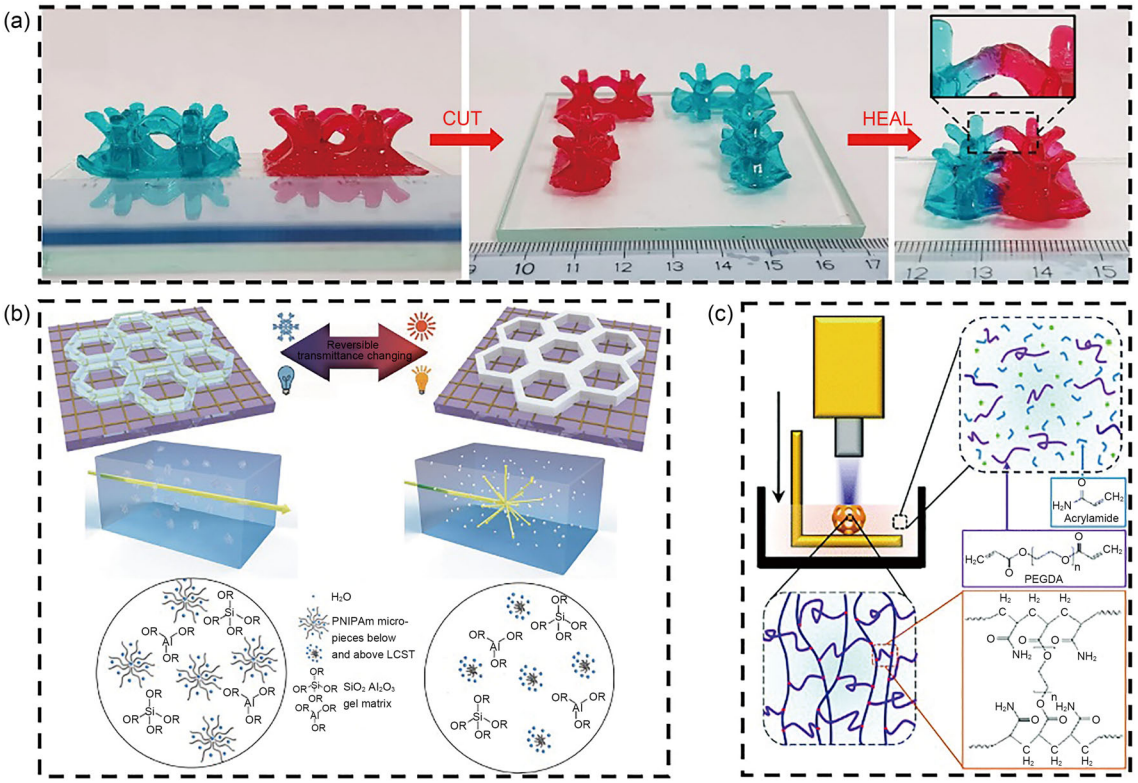


Fig. 3 3D printing using diverse functional hydrogels. **a** Digital light processing (DLP)-printed self-healing hybrid hydrogels consisting of a covalent network of acrylic acid and poly(ethylene glycol) diacrylate with a physical network of poly(vinyl alcohol). Reproduced from Ref. [103], Copyright 2021, with permission from the authors, licensed under a Creative Commons Attribution 4.0 International License. **b** Schematic representation showing the shrinkage of the poly(N-isopropylacrylamide) particles in the printed structures upon release of the trapped water molecules by heating, leading to light scattering. Reproduced from Ref. [104], Copyright 2018, with permission from WILEY–VCH Verlag GmbH & Co. KGaA, Weinheim. **c** Schematic showing the DLP-based 3D printing of acrylamide–polyethylene glycol diacrylate (PEGDA) hydrogel. Reproduced from Ref. [105], Copyright 2018, with permission from The Royal Society of Chemistry. LCST: lower critical solution temperature

to external stimuli and the ability to endure bending angles of up to 180°. The Si/Al matrix is highly water-rich with water retention capabilities. PNIPAm particles serve as functional additives that facilitate the extraction of water molecules from the hydrogel into the Si/Al matrix upon thermal and electrical stimulation. This extraction process results in a

transparency shift that enables thermochromic and optical switching functionality (Fig. 3b). This study provides a robust basis for the fabrication of smart optical devices and other highly water-laden materials by 3D printing.

Zhang et al. [105] created hydrogel solutions by blending hydrogel precursors based on acrylamide–PEGDA (AP) with highly efficient, water-soluble TPO nanoparticle photoinitiators (Fig. 3c). These solutions are compatible with DLP and various UV-curing-based 3D printing technologies. When printing, the double bonds of the acrylic ester functional groups in acrylamide and PEGDA are opened by UV radiation from the digital micromirror device, forming a permanently cross-linked network. Afterwards, the network solidifies layer by layer until the entire printing architecture is completed. The printed hydrogel samples demonstrated exceptional stretchability (exceeding 1300%), remarkable biocompatibility, and optical transparency, demonstrating potential applications in the direct 3D printing of biological structures, tissues, and contact lenses. Furthermore, the ability of the AP hydrogel to establish a robust interfacial bond with commercially 3D-printed elastomers enables the direct use of 3D-printed hybrid hydrogel–elastomer structures for manufacturing flexible electronic boards.

Shape memory polymers

Shape memory polymers (SMPs) [106–108] are polymers with a permanent state and a temporary state. When external stimuli are applied (such as light, heat, or electricity), the material responds by reversibly alternating between permanent and temporary states. SMPs have the advantages of low density, strong resistance to elastic deformation, low cost, and ease of processing. They are widely used in biomedicine, aerospace, and other industries. Extensively studied as a smart material, SMPs [109] can now be produced through various 3D printing techniques, including DIW, FDM, DLP, and SLA. Tao et al. [110] engineered a four-dimensional (4D)-printed origami metamaterial characterized by adaptable compression-twisting behavior. This metamaterial deforms to absorb impact energy, whereas the mechanical properties of the origami material can be customized through parameter design and temperature adjustments.

Ge et al. [61] proposed a multi-material 3D printing technology using a self-built 3D printer based on DLP technology. The UV projector is placed under the printing table, and a horizontally movable glass plate is placed between the projector and printer, which provides different inks for the corresponding layers. This method involves covalently bonding acrylamide, PEGDA, and the photoinitiator TPO in water with various UV-polymerizable polymers, such as elastomers, rigid polymers, acrylonitrile butadiene styrene-like polymers, and SMPs, to create intricate hybrid structures. This multi-material printing technique provides flexibility in adjusting the types and proportions of hydrogel and polymer components, as required. The paper also showcases various applications of this method, including horseshoe-shaped and lattice-reinforced hydrogel composites incorporating rigid polymers (Figs. 4a1–4a5), 4D-printed SMP scaffolds with temperature control and drug delivery capabilities (Figs. 4a6 and 4a7), and flexible electronic devices constructed from 3D ion-conductive hydrogel lattice structures with elastomer protective layers. Zarek et al. [111] created a shape memory resin designed for stereolithography 3D printing. To prepare for printing, the poly(caprolactone) methacrylate (PCLMA) monomer was melted, and photoinitiators, inhibitors as well as dyes were incorporated. After the melt became uniform, it was poured into the monomer bath of the printer and maintained at 90 °C during the printing process. The straightforward ink preparation process allows for the fabrication of thermal shape memory scaffolds in numerous models using SLA technology, including vascular scaffolds with intricate strut designs and numerous voids. To demonstrate one such application, an electrical temperature sensor was created by inkjet printing sinterable ink onto an SMP surface at room temperature (Fig. 4b). This responsive device holds significant potential in the production of wearable electronic devices, soft robots, and minimally invasive medical tools. Keneth et al. [112] also introduced a 3D-printed SMP. They prepared PCLMA monomers using a previously reported methodology [111] and blended them with N-vinyl caprolactam (NVCL) as a diluent and TPO as a photoinitiator to create printable hybrid inks. Of these, PCLMA is used purely as ink (printing temperature, 95 °C), and a mixture of PCLMA and NVCL is used as a mixed ink (printing temperature, 50 °C). A double-lidded box that allowed for its temperature-controlled opening and closing was constructed using these two types of ink (Fig. 4c). Furthermore, stimulation with light can activate the box's switching, enabling remote operation. The results of this study demonstrated the potential for diverse applications, including controlled drug release and the remote actuation of soft brakes.

Other printable inks

The issue of curing printed objects is a recurring major concern in 3D printing research. The ink is susceptible to gravitational and rheological effects, and failure to swiftly secure the printed structure may result in deformation and collapse once it attains a specific height [113]. Combining DIW and photopolymerization offers a viable solution to this challenge. The versatility, cost-effectiveness, straightforward processing, compatibility with various material classes, and capability for simultaneous multi-material printing of DIW have driven its extensive investigation and advancement. Kam et al. [52] employed a dual mechanism that integrated

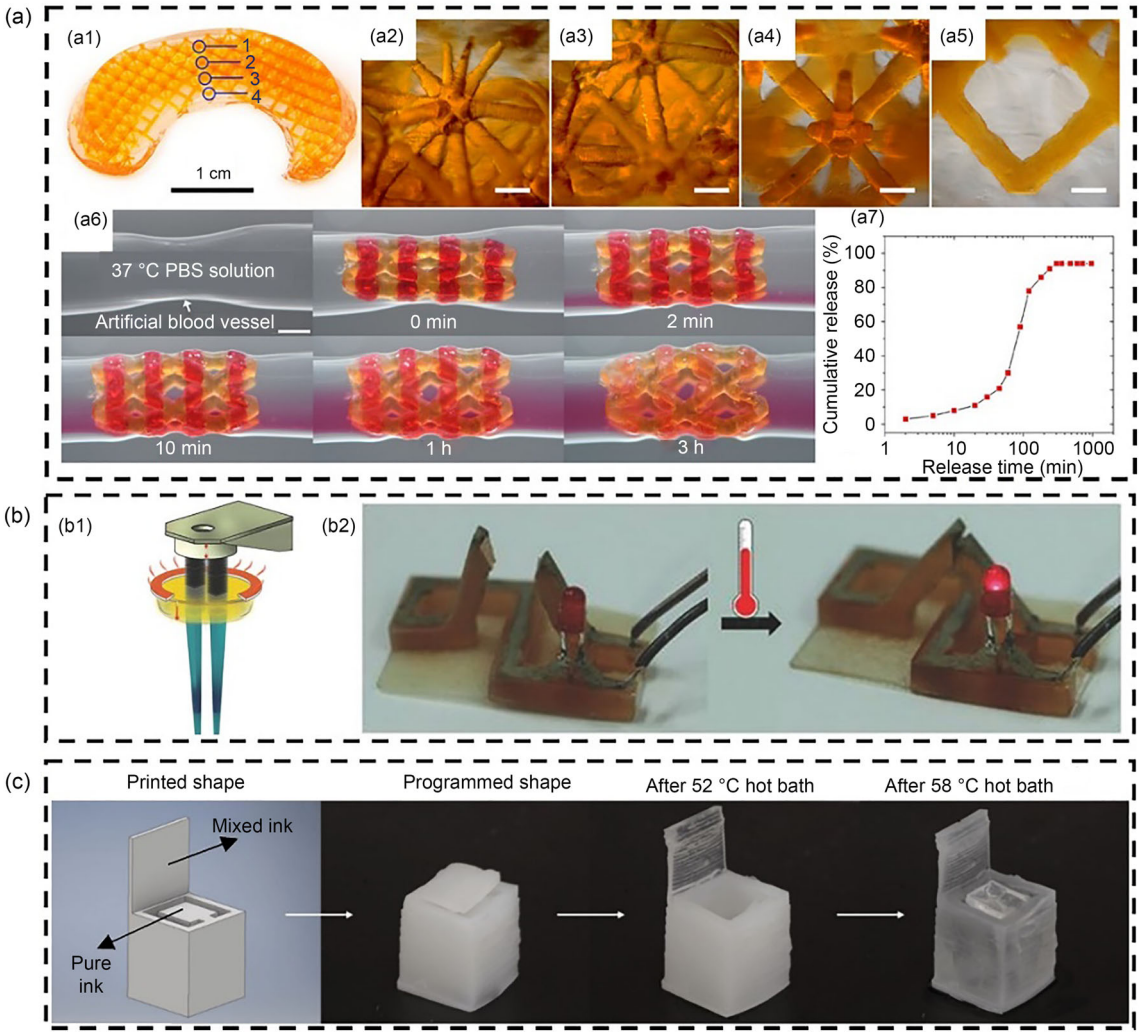


Fig. 4 3D printing using shape memory polymers (SMPs). **a** 3D printing of high-tensile polymers: (a1) snapshot of a printed meniscus made of rigid polymer-doped hydrogel; (a2–a5) corresponding microscopic images (scale bars: 500 μm); (a6) image showing shape memory and drug release (scale bar: 5 mm); (a7) quantitative profile of the drug-release process in artificial blood vessels printed using hydrogels. Reproduced from Ref. [61], Copyright 2021, with permission from the authors, licensed under a Creative Commons Attribution NonCommercial License 4.0 (CC BY-NC). **b** 3D printing of flexible electronic devices using SMPs composed of polycaprolactone: (b1) cartoon illustration of a stereolithography 3D printer for manufacturing SMPs; (b2) image showing a printed temperature sensor in the closed (left) and open (right) states. Reproduced from Ref. [111], Copyright 2015, with permission from WILEY–VCH Verlag GmbH & Co. KGaA, Weinheim. **c** Images depicting thermal and irradiation-stimulated 3D-printed SMPs opening at 52 °C and closing at 58 °C. Reproduced from Ref. [112], Copyright 2020, with permission from the authors, licensed under the terms and conditions of the Creative Commons Attribution (CC BY) license. PBS: phosphate buffered saline

photopolymerization and material rheological properties. They combined an acrylic-based hydrogel enhanced with cellulose nanocrystals with the water-soluble photoinitiator TPO to develop a novel ink suitable for both 3D printing and rapid photopolymerization (Figs. 5a1–5a3). An extrusion printer installed with 365-nm light-emitting diode (LED) lights was used for printing. The printing structure not only breaks through height limitations but also has a high aspect ratio and can solidify objects under visible light at 405 nm (Figs. 5a4 and 5a5), thereby maintaining bio-ink activity.

Two-photon polymerization (TPP) [114] is a laser-based 3D printing method similar to SLA. This method relies on the convergence of two laser beams to solidify the resin, enabling the fabrication of intricate micro- and nanoscale structures. Cooperstein et al. [115] introduced an innovative ink for creating transparent, microscale ceramic structures by TPP 3D printing (Figs. 5b1–5b4). Transparent polycrystalline yttrium

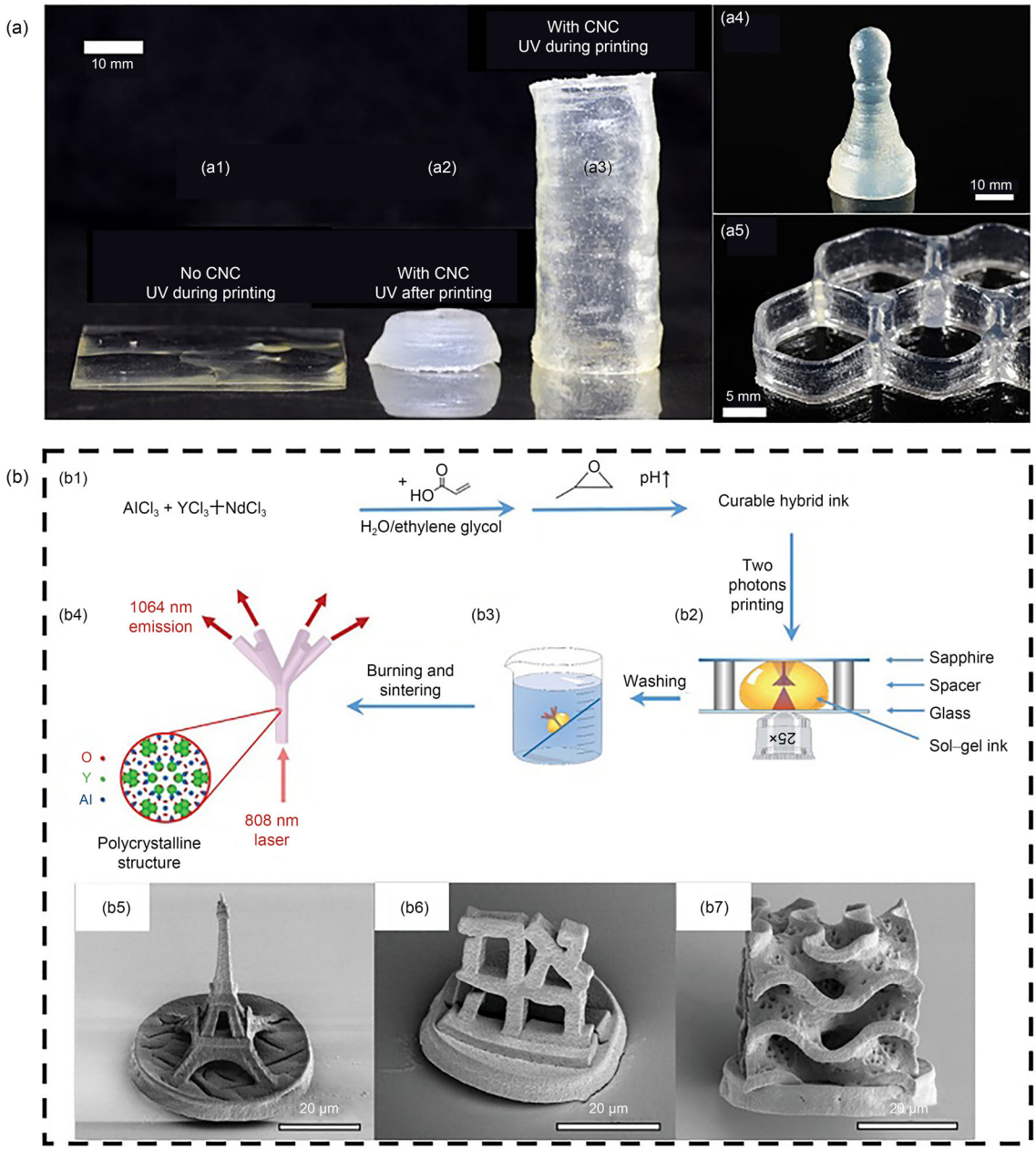


Fig. 5 3D-printed structures using diverse inks. **a** Tubular object with 20 mm in diameter printed by direct ink writing using different hydrogel compositions: (a1) no cellulose nanocrystals (CNCs) or ultraviolet (UV) during printing; (a2) tubular object abortively printed with CNC and UV-cured after printing; (a3) tubular object successfully printed with CNC and UV-cured during printing; (a4) UV-cured chess set; (a5) photocured honeycomb-shaped object. Reproduced from Ref. [52], Copyright 2021, with permission from American Chemical Society. **b** Flowchart of doped yttrium aluminum garnet (YAG) 3D structure printed using ceramic ink: (b1) preparation of transparent ceramic inks; (b2) printed with a two-photon printer; (b3) finishing the printed 3D objects by washing; (b4) high temperature heating to form single-phase Nd:YAG; (b5–b7) diverse polycrystalline structures printed after heating to 1500 °C. Reproduced from Ref. [115], Copyright 2020, with permission from WILEY–VCH Verlag GmbH & Co. KGaA, Weinheim

aluminum garnet (YAG: $Y_3Al_5O_{12}$), a commonly used optical material, was selected as a component of the printing ink. It was doped with rare earth metal elements to function as a laser medium. Unlike the YAG structures described elsewhere [116], the precursor of the printed structure discussed here is devoid of particles, allowing printing via TPP. The dense polycrystalline YAG structure was achieved through a post-print thermal process using relatively low temperatures (Figs. 5b5–5b7). This ink preparation method is anticipated to streamline the production of optical devices with high

damage thresholds. Furthermore, printed objects have the potential for extensive use in micro- and nanoscale lasers and light sources.

Fabrication of the soft devices

Printed electronics

Printed electronics refers to the technology of manufacturing electronic devices using 3D printing techniques, especially in combination with flexible materials to prepare flexible and stretchable electronics. Conductive materials employed in the fabrication of flexible electronics include metal nanoparticles (e.g., Ag [117], Cu [118], and Ni [119]), carbon materials (such as graphene and carbon nanotubes), conductive polymers, and reactive inks utilizing metal compounds and complexes as precursors. In parallel, materials suitable for flexible substrate printing include polyurethane, silicone, and hydrogels [120].

Inkjet 3D printing is a highly effective method for producing flexible electronic products with intricate patterns, such as circuits [121] and sensors [122]. Layani et al. [123] introduced a novel ink designed for the fabrication of conductive 3D structures via inkjet printing. This specialized ink is formulated with a UV-reactive oil phase and silver nanoparticles, printed layer by layer through continuous inkjet printing to produce a 3D structure. Subsequently, the printed 3D structure is submerged in a sodium chloride solution to undergo sintering to confer conductivity through the formation of a conductive pattern. The resulting structure consists of a dual network created by sintered silver nanoparticles for conductivity and organic polymers for mechanical integrity.

Taking it a step further, Agarwala et al. [124] proposed a new approach to bioprinting (Fig. 6a). The bioprinter was fitted with a printhead capable of extruding a hydrogel bio-ink consisting of gelatin methacryloyl (GelMA) [125], sodium chloride, and a photoinducer, in addition to a microvalve for dispensing the silver ink. Consistent with prior findings, silver nanoparticles lose stability upon contact with oppositely charged polyelectrolytes, such as chloride ions, leading to spontaneous agglomeration even at room temperature [126]. Consequently, when silver-based circuits are printed onto a GelMA layer, the silver nanoparticles undergo rapid self-sintering, resulting in the acquisition of electrical conductivity by the printed structure.

Zhou et al. [127] have successfully produced fully DIW 3D-printed, stretchable piezoelectric nanogenerators (Fig. 6b), which incorporate a non-protruding kirigami structure. This development offers a promising approach for manufacturing energy harvesters intended for integration into wearable devices. In this study, they used a printer equipped with a printhead that can extrude ink and a movable heating platform that was maintained at 70 °C during the printing process to achieve rapid solvent evaporation and curing of composite materials. Piezoelectric materials were created by printing $BaTiO_3$ nanoparticles and P(VDF-TrFE) powders, with silver-based conductive layers serving as electrodes on both sides of the piezoelectric materials. To impart stretchability to the piezoelectric device, a non-protruding kirigami structure with fractal cuts was engineered into the two-dimensional planes of the flexible material, thereby enhancing its flexibility while maintaining its structural integrity. This structure can withstand strains of up to 300% without diminishing the output voltage of the device. The stretchable piezoelectric nanogenerator exhibits an open-circuit voltage output of approximately 6 V, a current density of 2 $\mu A/cm^2$, and a maximum power density of 1.4 $\mu W/cm^2$ at a load resistance of 107 Ω. Furthermore, this device can be affixed as an energy harvester to wearable textiles, such as those used for the sensing of gait information.

Soft actuators

Robotics is becoming pervasive in contemporary society and is profoundly transforming human production and daily life. Conventional robots, characterized by rigid arms and intricate mechanical systems, face limitations when tasked with delicately grasping soft, easily deformable objects. They are unable to effectively perform this task without adjusting the force and grasping angle according to the specific situation. In contrast to traditional robots, which rely on complex computational programs to execute such commands, soft robots inspired by biological systems can be built using materials with diverse mechanical properties [128]. Their unique material composition enables soft robots to achieve a remarkable level of continuous deformability and a modulus of elasticity akin to that of biological systems, thereby facilitating adaptation to various shapes. Soft robots offer broader applications because of their intrinsic qualities, including lightweight construction, cost-effectiveness, pliability, and ease of manipulation. The actuator within a soft robot plays a pivotal role in generating mechanical motion. It can be activated by diverse stimuli, including pneumatic, electrical, magnetic, and thermal forces, to induce reversible deformations and propel the robot.

Additive manufacturing enables the fabrication of soft actuators using elastomeric materials. Patel et al. [129] developed highly stretchable UV-cured elastomer systems using a typical "top-down" DLP printer equipped with digital mirror devices and UV LED light sources (385 nm). The elastomeric resin was developed by blending a monofunctional ethylene acrylic acid copolymer monomer with a bifunctional aliphatic urethane diacrylate crosslinker. The resulting elastomers had mechanical properties that could be varied by adjusting the ratio of these components and exhibited an impressive stretchability of up to 1100%, surpassing the

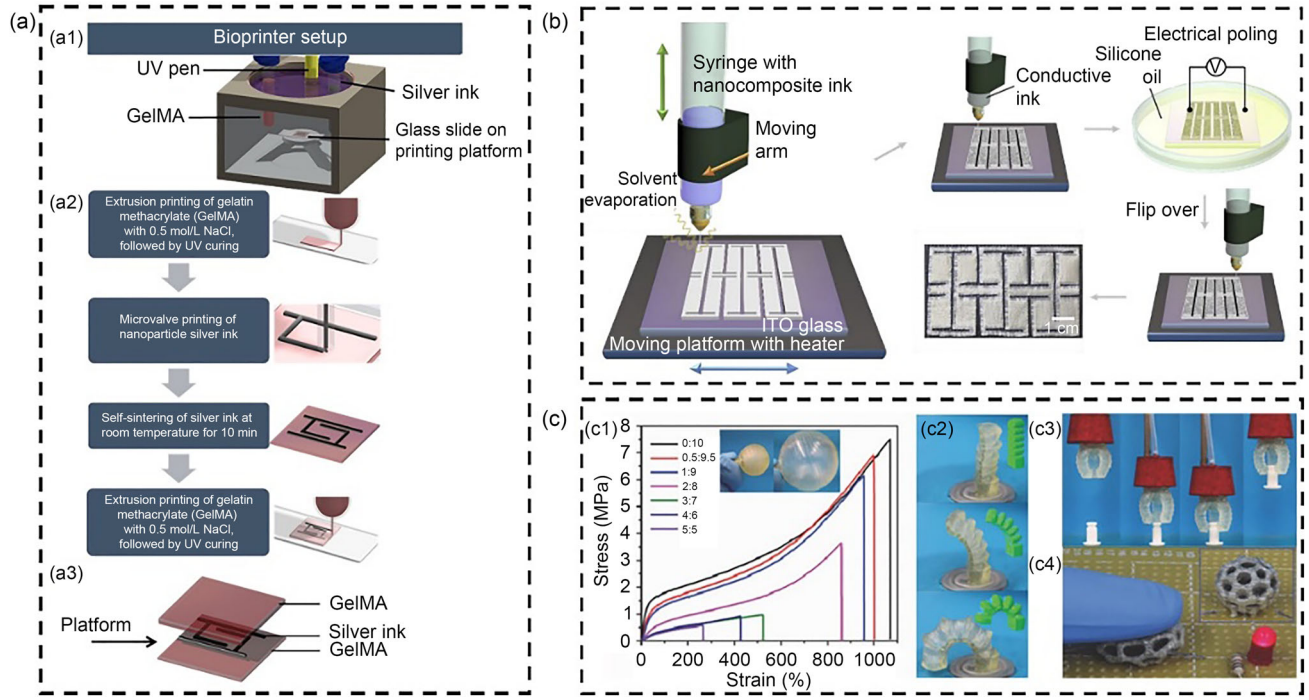


Fig. 6 Manufacturing of soft devices by 3D printing. **a** Schematic illustrating the bioelectronics printing platform: (a1) configurational structure of the 3D bioprinter; (a2) flowchart of the printing process for bioelectronic devices; (a3) schematic diagram of the sandwich-like biodevice. Reproduced from Ref. [124], Copyright 2017, with permission from Elsevier. **b** Schematic diagram showing the 3D printing process of a stretchable piezoelectric nanogenerator. Reproduced from Ref. [127], Copyright 2020, with permission from the authors, licensed under CC BY-NC-ND. **c** 3D-printed, high-tensile, and UV-cured hybrid elastomers consisting of EAAs and an AUD containing cross-linker: (c1) stress–strain behavior of stretchable and UV-cured elastomers with different EAA/AUD ratios; (c2) 3D-printed pneumatic soft actuator; (c3) 3D-printed gripper; (c4) printed conductive bucky balls used as electrical switches. Reproduced from Ref. [129], Copyright 2017, with permission from WILEY–VCH Verlag GmbH & Co. KGaA, Weinheim. UV: ultraviolet; GelMA: gelatin methacryloyl; ITO: indium tin oxide; EAAs: ethylene acrylic acid copolymer monomers; AUD: aliphatic urethane diacrylate

elongation at break of numerous commercially available elastomers by more than fivefold (Fig. 6c1). These elastomer compositions are augmented with TPO to increase compatibility with UV-curing-based 3D printing technology. This study synergized the remarkable attributes of highly stretchable super-elastomers with DLP 3D printing, thereby enhancing the capacity to craft intricate, deformable 3D structures and devices (Figs. 6c2–6c4). The results also indicate various applications, including soft robotics, flexible electronics, and acoustic metamaterials.

Tissue engineering

Heart failure is a significant health challenge in adults, particularly the elderly. It is caused by various factors and is currently the leading cause of morbidity and mortality worldwide. Heart failure is an advanced manifestation of heart disease that progresses in stages. In cases of severe heart failure, the sole viable medical recourse is a heart transplant. However, issues, such as rejection, procedural complexity, and a scarcity of heart donor resources, have left numerous patients without prospects for survival [130].

Tissue engineering primarily involves the fabrication of biocompatible scaffolds that can be populated with cells to produce functional tissues in vitro. Once these tissues reach an appropriate level of maturation, they can be transplanted into the body to execute their intended functions. The advancement of cardiac tissue engineering [131] has opened up a therapeutic option for patients with heart failure [132]. Nonetheless, organ transplantation requires intricately structured, highly complex functional tissues with diverse materials tailored for specific roles, which has posed limitations on their production.

As a subset of 3D printing, 3D bioprinting has undergone rapid advancements in recent years, although the 3D bioprinting of transplantable organs remains a distant goal [133, 134]. A key aspect of 3D bioprinting is the development and study of appropriate bio-inks for the process. The bio-ink must meet various prerequisites, including robustness to support subsequent cell culture, excellent biocompatibility and biodegradability to facilitate cell growth and prevent

immune reactions upon implantation, and, fundamentally, it must meet the printing requirements. Consequently, bio-inks consist entirely of cells or are encased in hydrogels, enabling the creation and printing of intricate structures incorporating multiple materials.

Three-dimensional bioprinting techniques can be categorized by their underlying printing principles and inks, such as extrusion-based, light-curing-based, and droplet-based printing methods. Among these, extrusion-based 3D printing is the most commonly used method. Furthermore, extrusion-based printing accommodates the simultaneous printing of multiple materials, making it the preferred technique for constructing structures with exceptional mechanical properties. Notably, researchers in Israel have achieved significant advancements in extrusion-based 3D printing, particularly in the field of cardiac tissue engineering.

Noor et al. [135] pioneered 3D bioprinting of a substantial vascularized cardiac patch (Fig. 7a). To prevent an immune response, the omental tissue was directly sourced from the patient, and the tissue matrix was isolated from the cells. The cytoplasmic matrix was then transformed into a personalized, thermoresponsive hydrogel. Cells isolated from omental tissue were reprogrammed into induced pluripotent stem cells (iPSCs). These iPSCs later differentiated into cardiomyocytes, which form the main structure of the heart, and endothelial cells, which make up the blood vessels. Subsequently, the cells were enclosed and cultivated within the hydrogel to serve as the foundational bio-inks for printing. An extrusion-based printer was used to extrude the bio-ink according to the designed geometric shape, forming a supporting wall and vascular network. Finally, the printed patches were incubated and cultured.

Furthermore, to facilitate the monitoring of the functions of the engineered tissues of the customized 3D-printed heart, Asulin et al. [136] successfully integrated electronic systems with biomaterials in the 3D printing of a heart patch with incorporated soft and stretchable electronics (Fig. 7b). In essence, electronic systems were integrated with cells within the field of tissue engineering to create controllable tissues. These electronic components can monitor heart tissue function during contractions, providing essential data for controlling heart tissue function.

The mechanical properties of biomaterials limit their applications, necessitating the development of methods for bolstering the mechanical properties of engineered tissues. Silberman et al. [137] proposed a method for reinforcing cardiac tissue during a subsequent stage of fabrication based on previously developed extracellular matrix hydrogels. This advancement facilitates the 3D printing of cardiac tissues for potential transplantation into the human body. In the post-assembly maturation phase of the tissue, polyaldehyde SO_x was introduced to enhance its mechanical strength. This was achieved by employing a Schiff base "click" chemical reaction with the amine portion within the natural extracellular matrix (Fig. 7c). However, substantial challenges remain in 3D bioprinting, and only rudimentary heart functionality has been achieved using this technology. Regardless, these are significant endeavors in cardiac tissue engineering and provide a robust foundation for and in addressing notable obstacles to biomedical initiatives, such as organ transplants.

Marketization of 3D printing

As the global population soars and resources become scarcer, meat prices are predicted to rise in the near future. Given this context, redefining meat could provide a solution to future shortages in meat resources [138]. Israel, known for its strong support for research and development, has nurtured numerous startups dedicated to commercializing advanced technologies.

In June 2020, the Israeli startup "Redefine Meat" introduced a 3D-printed plant-based steak to Israeli and European markets [139] (Fig. 8a). This artificial beef not only faithfully recreated the visual and organoleptic characteristics of traditional beef, but also boasted an efficient, low-cost production process. The additive manufacturing approach meets the level of structural sophistication required for the mimicking of whole muscle cuts, while allowing mass customization for tailoring steak attributes, such as fat marbling, to the demands of different markets and customers. This approach forms the basis of Redefine Meat's plant-based tissue engineering technology that regards meat as a collection of tissues and addresses each element separately via the conventional food technology approach. The meat fabrication process involves two-step component manufacturing via mixing and whole-cut manufacturing via 3D printing and advanced assembly methods [140]. Legumes and grain proteins substitute for muscle tissue, while plant fats replace animal fats. Juiciness in the 3D-printed steak is achieved by adjusting the aqueous phase structure and supplementation with natural flavors, colors, and other plant-based ingredients (Fig. 8b). In the same year, the company expanded its offerings to include various artificial beef products, including hamburgers, ground beef, and pulled beef. Their aspiration is to become the world's leading alt-meat company, capable of replicating every meat product derived from cattle.

According to media reports, the Israeli-based startup "Steakholder Foods" has produced the world's first ready-to-eat fish using 3D printing [141]. They conducted an experiment on cultivating grouper cells to grow muscle and fat, which were then used as bio-ink for printing. Subsequently, these bio-ink materials were placed in a Petri dish for further cultivation to eventually produce artificial meat. Notably, the taste of the 3D-printed fish was indistinguishable from that of the real fish after cooking.

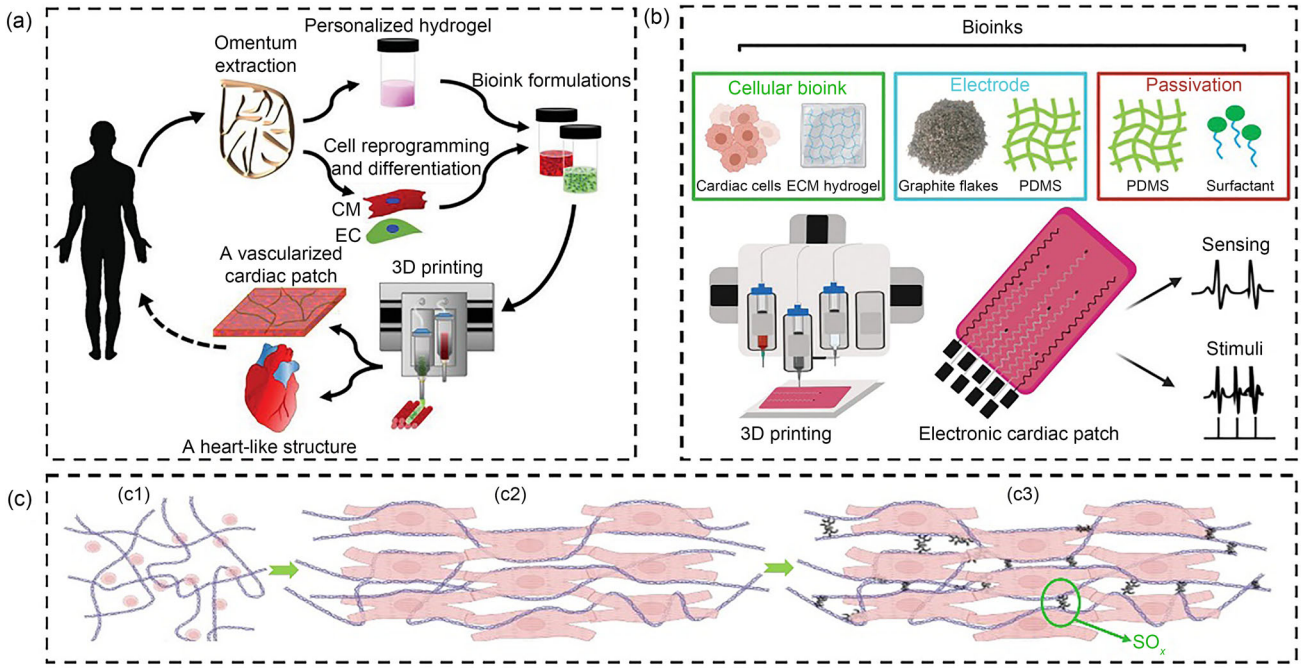


Fig. 7 Biomedical engineering applications of 3D printing. **a** Conceptual scheme showing a heart patch and 3D printing of the heart. Reproduced from Ref. [135], Copyright 2019, with permission from the authors, licensed under the terms of the Creative Commons Attribution License. **b** 3D printing of heart patches using built-in electronic devices. Reproduced from Ref. [136], Copyright 2021, with permission from the authors, licensed under the terms of the Creative Commons Attribution License. **c** Schematic showing the manufacturing procedure of reinforced heart tissue: (c1) 3D printing of cardiac tissue; (c2) propagation and culture of cells used to construct tissues; (c3) SO_x is added to enhance the mechanical rigidity. Reproduced from Ref. [137], Copyright 2023, with permission from the authors, licensed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License. CM: cardiomyocyte; EC: endothelial cell; ECM: extracellular matrix; PDMS: polydimethylsiloxane

Eshchar Ben-Shitrit, co-founder and CEO of Redefine Meat, stated that 3D-printed meat offers significant ecological benefits to humanity [142]. 3D-printed meat is presently in its scale-up stage and may not currently offer substantial cost advantages compared with livestock meat. However, ongoing improvements in the 3D-printing process are facilitating the wide-scale adoption of the next generation of plant-based meats produced through advanced manufacturing methods and 3D printing. This development in meat alternatives can address the challenges posed by the need to significantly increase the production of protein-rich foods while considering the highly inefficient methods of making them via existing processes, such as industrial animal farming.

Collagen [143] is the primary component of human skin, bones, and connective tissue. As the most abundant structural protein in mammals, collagen has been widely used as a building block for recombinant collagen materials in various fields, such as food packaging, medical aesthetics, and wound accessories. CollPlant [144], an Israeli company specializing in 3D bioprinting and regenerative medicine, relies on independently developed technology to develop substitute collagen implants in medical aesthetics. Using the tobacco plant expression technology developed at the Hebrew University in Israel [145], recombinant human type I collagen (rhCollagen) produced and extracted from recombinant plants can be modified and crosslinked by irradiation at different wavelengths using a photoinitiator. Seror et al. [146] introduced the potential applications of light-cured rhCollagen in two major cosmetic medical treatments, namely, skin filling/facial modification, and augmentation/reconstruction of breast tissue (Fig. 8c). Another study demonstrated the efficacy of rhCollagen flowable gel in animal wound models to shorten the healing time of human wounds [147].

Israel is a hub for the 3D printing industry. Since the inception of 3D printing, the country has manufactured over 40% of the world's 3D printers. Beyond companies specializing in bioprinting, Israel hosts numerous other 3D printing companies spanning various industries and sectors. These firms employ 3D printing technology across a spectrum of applications, including industrial manufacturing, aerospace, healthcare, consumer goods, design, education, and construction. These entities play distinct roles within Israel's 3D printing landscape in tackling specific needs and challenges within their respective domains. The collective diversity and innovation of these companies propel Israel's advancements

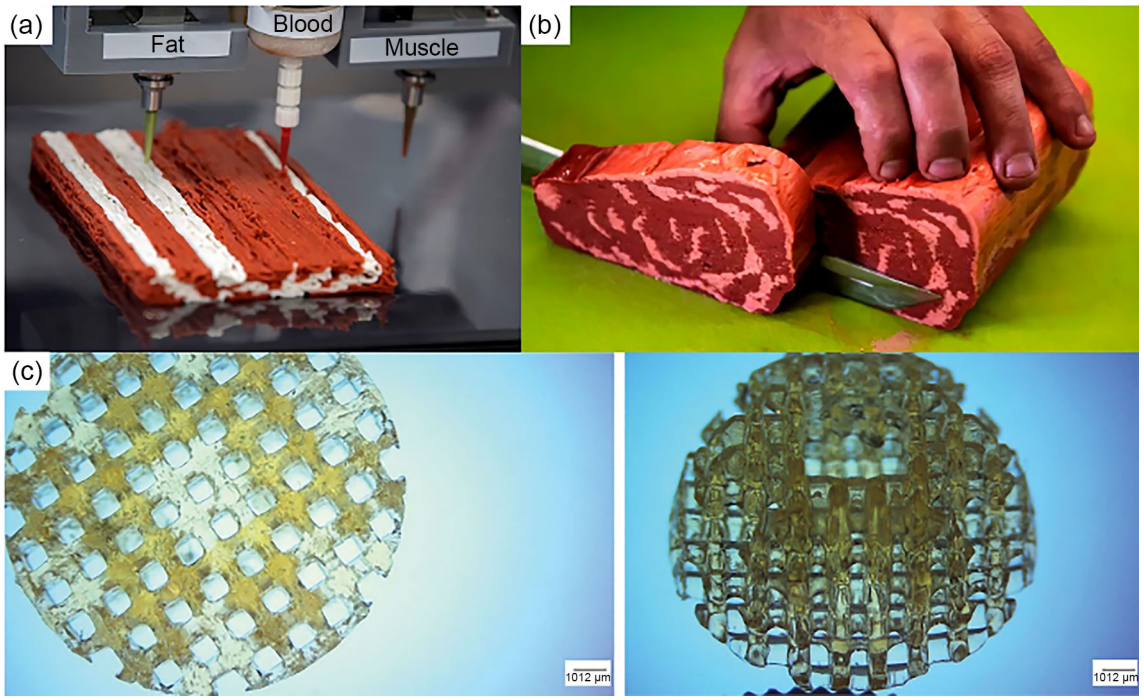


Fig. 8 Artificial food manufactured by 3D printing. **a** Fabrication of a plant-based steak by Redefine Meat Co. **b** The 3D-printed plant-based steak can be trimmed for frying. Reproduced with permission from Ref. [148]. **c** Miniature breast implant prototype printed using a DLP printer. The bio-ink is composed of synthetic polymers and modified rhCollagen. Reproduced from Ref. [146], Copyright 2021, with permission from American Society of Plastic Surgeons. DLP: digital light processing

Table 1 Summary of the 3D bioprinting companies in Israel

Company	Established time	Chief researchers	Representative products	References
Redefine Meat	2018	Eshchar Ben-Shitrit, Oshri Reuven, and Sagi Cohen	Using 3D printing technology to manufacture plant-based meat substitutes	[139]
Steakholder Foods	2017	Arik Kaufman	3D printing of beef and fish meat	–
CollPlant	2004	Yehiel Tal and Oded Shoseyov	Biomedical and medical 3D printing materials	[146, 147]
Aleph Farms	2017	Didier Toubia, Shulamit Levenberg, and Amir Ilan	Using biological 3D printing technology to produce cultivated beef	[149, 150]
Believer Meats	2018	Yaakov Nahmias	Producing meat products through biotechnology and cell culture techniques	[151]
Matricelf	2021	Nissim Darvish and Avner Yayon	Autologous regenerative medicine	[152]
MASSIVit 3D	2013	Gershon Miler, Igor Yakubov, and Moshe Uzan	Focusing on large-scale 3D printing technology	[153]
MeaTech	2018	Sharon Fima and Ronen Tzur	Using 3D bioprinting technology to manufacture and cultivate meat	–
XJet	2005	Hanan Gothait and Dr. Shachar Richter	Nanoparticle jetting technology	[154]
Nano Dimension	2012	Amir Shulman	Focused on electronic 3D printing and developed the DragonFly Pro system	[155, 156]
Stratasys	1989	Scott Crump and Jack Gump	Produced various types of 3D printers and materials	[157–159]

in 3D printing technology. Table 1 presents a selection of Israeli 3D printing companies.

Peptide self-assembly

To broaden the applications of 3D printing, access to a range of new materials suitable for use as bio-inks is essential. Most 3D printing inks currently consist of polymers [160] or conventional materials such as metals and ceramics [161, 162]. However, these materials lack the necessary functionalities required for diverse potential applications, such as electrical conductivity, thermal conductivity, self-healing, luminescence, and magnetism. Thus, a notable interest has arisen in the discovery of new functional materials and the integration of composites with appropriate functionalities to be used as 3D printing inks. In the biomedical field, biomaterials to be used as 3D printing inks should be carefully chosen. Natural biological building blocks, such as nucleic acids and peptides, for biomaterials can be used to design different, materially suitable sequences according to the needs and to build complex structures through self-assembly under various non-covalent forces, including the formation of stimulus-responsive molecules with different functions [163–165]. Driven by the requirements for intelligent material development, these assemblies have been extensively explored. Israel has played a pivotal role in the development of peptide-based self-assembly to explore materials for 3D printing inks. The nation has nurtured numerous scientists who have been instrumental in advancing the application of peptides in various domains, including peptide drugs, peptide biosensors, and peptide materials.

Self-assembly mechanism

Diphenylalanine (FF) peptides play significant roles in self-assembly and molecular recognition. This is particularly noteworthy because Reches and Gazit [166] observed in 2003 that FF peptides serve as a core recognition sequence for amyloid proteins, which is implicated in various neurodegenerative diseases. Subsequent research into the self-assembly of short peptides was based on this foundational work. In a span of two decades, scientists have acquired the capability to control the self-assembly processes of various short peptides and their derivatives by influencing the structure and function of self-assembled materials by manipulating the external assembly conditions. This achievement has significantly expanded the knowledge of the mechanisms governing short peptide assembly and broadened the potential applications of short peptide materials. The FF motif, one of the most extensively studied short peptide sequences, has demonstrated the ability to undergo structural modifications caused by changes in the preparation methods or solvent conditions and subsequently produce diverse nanostructures. Nevertheless, further tailoring of the FF structure is required to produce functional nanomaterials and materials with versatile responsiveness. Ji et al. [167] successfully engineered multi-responsive, supramolecular, two-component hydrogels by employing a co-assembly strategy that mixed various bipyridine derivatives with three distinct N-terminally capped FF peptides (ZFF, BocFF, and AcFF) to generate nanostructures with diverse morphologies (Fig. 9a). Furthermore, this study elucidated the mechanism underlying the multilevel self-assembly process using molecular dynamics simulations.

Molecular self-assembly is a common occurrence, for which hydrogels have been extensively studied in the biomedical and biotechnological fields. Peptide self-assembly processes can modulate assembly morphology by altering factors, such as solution concentration, pH, solvent type, and the addition of small molecules. These processes create hydrogels, crystals, and other product states. Hydrogels with a 3D network structure are a common outcome of peptide self-assembly, and scientists have attempted to prepare hydrogel agents with low critical micelle concentrations. Chakraborty et al. [168] reported a novel dipeptide gel agent, FmocLys(Fmoc)-Asp, a hydrogel based on lysine and aspartic acid (Fig. 9b1). In contrast to the assembly routes of other gelling agents, FmocLys(Fmoc)-Asp undergoes a unique two-step assembly process (Fig. 9b3). Initially, it forms microsized spherical aggregate gels at a low concentration of only 0.002% (mass fraction). Subsequently, these spherical aggregates self-assemble into nanofiber cross-linked networks. Building on this, we prepared polyaniline–dipeptide composite gels and investigated their potential use as 3D cell culture scaffolds. The fluorenylmethoxycarbonyl (Fmoc) moiety, a common N-terminal-protective group, contributes to π-π stacking and hydrophobic interactions to facilitate peptide self-assembly into hydrogels in aqueous solutions. Tikhonova et al. [169] developed a defrost sensor based on the self-assembly of Fmoc-FF peptides. This sensor employs the turbidity of the hydrogel to indicate temperature changes and can irreversibly determine if a product has been defrosted, making it suitable for the transportation and preservation of medical products, among other applications.

Israeli researchers have made significant strides in the preparation and application of peptide materials. They have harnessed the self-assembling capability of peptides to create and investigate the mechanical and optical properties of innovative nanomaterials. These endeavors have significantly contributed to the advancement of novel nanomaterials and biomaterials.

Characterization of the physicochemical properties

Small-molecule metabolites possess distinct physicochemical properties. Guerin et al. [170] found that β-glycine

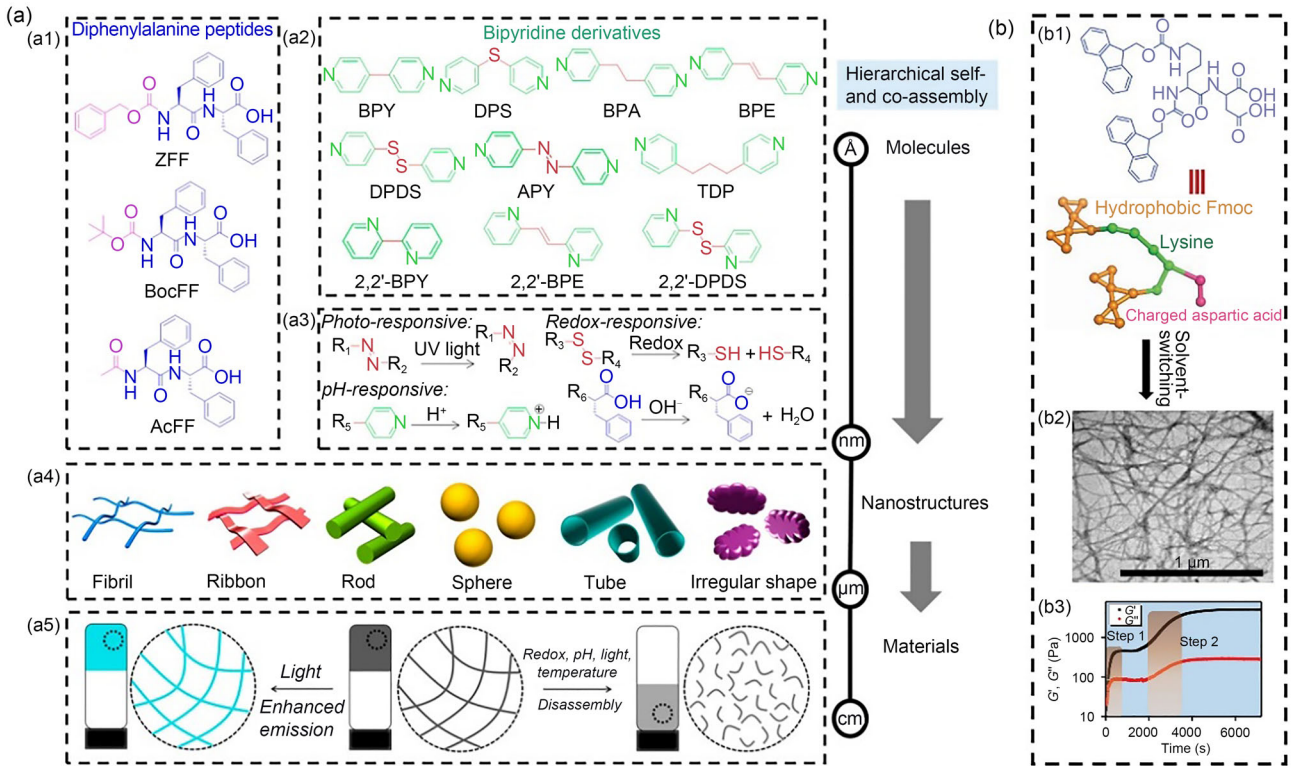


Fig. 9 Analysis of mechanisms underlying peptide self-assembly. **a** Bioinspired multi-response hydrogels co-assembled from FF and bipyridine derivatives: molecular structures of (a1) FF derivative peptides and (a2) bipyridine derivatives; (a3) stimulus–response mechanisms of the bipyridine derivatives; (a4) morphological diversity of the individual supramolecular structures and (a5) crosslinked multi-response hydrogels. Reproduced from Ref. [167], Copyright 2021, with permission from American Chemical Society. **b** Fmoc-Lys(Fmoc)-Asp dipeptide can self-assemble into nanofibrillar hydrogels at a low concentration of 0.002% (mass fraction): (b1) chemical structure of Fmoc-Lys(Fmoc)-Asp; (b2) transmission electron microscopy image of the self-assembled nanofibers; (b3) the two-step assembly process of the Fmoc-Lys(Fmoc)-Asp hydrogel. Reproduced from Ref. [168], Copyright 2020, with permission from WILEY–VCH Verlag GmbH & Co. KGaA, Weinheim. 1 Å = 10^{-10} m. FF: diphenylalanine; UV: ultraviolet

crystals exhibit exceptional high-voltage electrical properties, exceeding those of ceramics and polymers. Extensive research on individual amino acids is essential to uncover superior traits that could significantly impact diverse fields. Aromatic amino acids tend to form well-organized self-assembled supramolecular structures because of their limited solubility in water. A research initiative led by Gazit's group examined the characteristics of distinct amino acids, including *L*-Phe, *L*-Tyr, and *L*-DOPA (Fig. 10) [171]. They found that, compared with other amino acids, *L*-Tyr crystals formed an intricate 3D stacking network that significantly decreased their solubility (Fig. 10c). *L*-Tyr, while being the least soluble in water, exhibits the highest thermal stability and mechanical properties with the statistical Young's modulus and point stiffness up to (177.03±54.39) GPa and (632.77±220.44) N/m, respectively (Figs. 10e and 10f). Moreover, non-centrosymmetric dimer structures in *L*-Tyr crystals confer piezoelectric properties. This study also demonstrated the mechanical responsiveness of *L*-Tyr crystal/polydimethylsiloxane composites in bending applications. Furthermore, *L*-Tyr crystalline needles doped with the rhodamine B dye exhibited active guidance of light waves, emphasizing the substantial potential of amino acid crystals in the development of flexible electronic materials, optical waveguide materials, and energy harvesting applications.

Fabrication and applications of peptide supramolecular structures

Enzymes are highly efficient catalysts for specific chemical reactions in living organisms. Their myriad advantages have driven research development in the food, cosmetics, agriculture, and energy sectors, among others. However, their practical applications are impeded by their structural complexity, limited stability, stringent reaction conditions, and recycling challenges. Research dedicated to designing biocatalysts with improved stability and simplified structures is ongoing. Makam et al. [172] showed that supramolecular assemblies composed of single amino acid residues

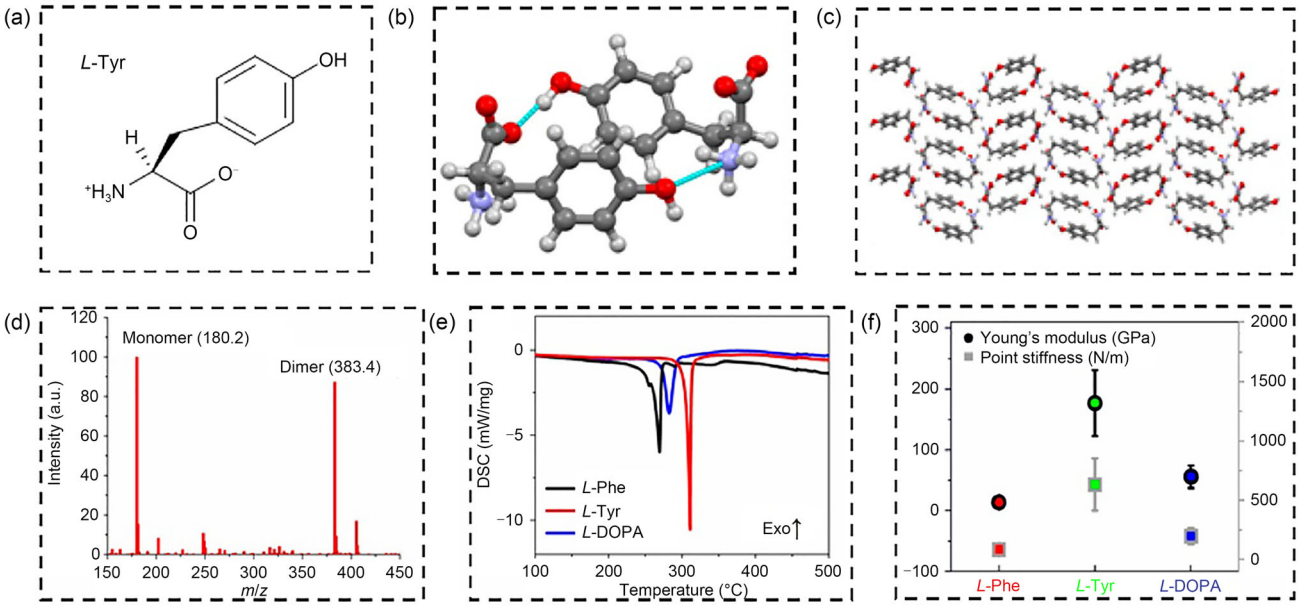


Fig. 10 Sustainability of the bioinspired supramolecular structures: **a** molecular structure of *L*-Tyr; **b** chemical structure of hydrogen-bonded dimeric structures; **c** crystal stacking of the *L*-Tyr crystals; **d** mass spectrometry spectrum showing the monomeric and dimeric molecular weights of *L*-Tyr crystals (*m*/*z*: mass-to-charge ratio); **e** differential scanning calorimetry (DSC) profile and **f** statistical Young's moduli along with point stiffness, demonstrating the significantly higher thermal and mechanical rigidity of *L*-Tyr self-assemblies compared with controls. Reproduced from Ref. [171], Copyright 2019, with permission from American Chemical Society

can function as highly effective hydrolysis catalysts. They employed Zn(II) ions as cofactors to craft F-Zn(II) single crystals, which replicate carbonic anhydrase hydrolase. The amyloid-like supramolecular structure of F-Zn(II) crystals, along with densely ordered zinc ion arrays on their surface, facilitates substrate access to Zn(II) catalytic centers, enabling F-Zn(II) to perform two distinct catalytic functions: serving as *p*-nitrophenyl acetate (pNPA) esterase for substrates and as a hydratase for CO_2 (Fig. 11a). Subsequently, Makam et al. [173] developed a straightforward laccase constructed from a single phenylalanine chain and redox-active divalent copper ions (Cu^{2+}) to mimic biological nanoenzymes.

Melanin is widely distributed in animals, plants, fungi, and bacteria, representing a diverse group of high-molecular-weight amorphous polymers with shared characteristics [174]. Melanin plays a multifaceted role, as it can capture energy from radiation and serves as an effective UV protectant [175]. Melanin is also present in camouflage (e.g., in chameleons) and contributes to skin coloration. Nevertheless, because of the intrinsically disordered structure of melanin and the absence of a direct correlation between structure and function, scientists have encountered challenges in attempting to replicate melanin in laboratory settings. Drawing inspiration from the multifaceted nature of melanin and the principles of bioinspiration, Lampel et al. [176] proposed the use of peptide building blocks to develop supramolecular materials that can dynamically alter the fiber structure through various non-covalent interactions and mimic the characteristics of melanin (Fig. 11b). Reddy et al. [177] further synthesized a series of melanin-inspired materials using tripeptides. They modified the photoelectric properties of the resulting polymers by altering the peptide sequence order. The resulting peptide precursors with different amino acid sequences were systematically transformed into polymer pigments with various functionalities. Building on previous studies, Lampel et al. [178] selected a self-assembled peptide precursor, lysine-tyrosine-tyrosine (KYY), to produce melanin-like supramolecular fibers capable of conducting electricity through enzymatic oxidation. This tripeptide self-assembly approach, with its structural simplicity and capacity to confer melanin-like functional traits via oxidation, has various potential bioelectronic applications. Furthermore, a reactive scaffold, the tripeptide Lys-Tyr-Phe (KYF), was developed. The optical properties of this scaffold were modulated by the introduction of amino acids with different side chains. Oxidative doping of amino acids with diverse side chains in pre-organized self-assemblies produced polymeric chromophores (Fig. 11c). This method is significant for the synthesis of melanin materials with tunable photonic properties.

Neocoronavirus pneumonia, caused by a novel coronavirus infection not previously identified in humans, emerged

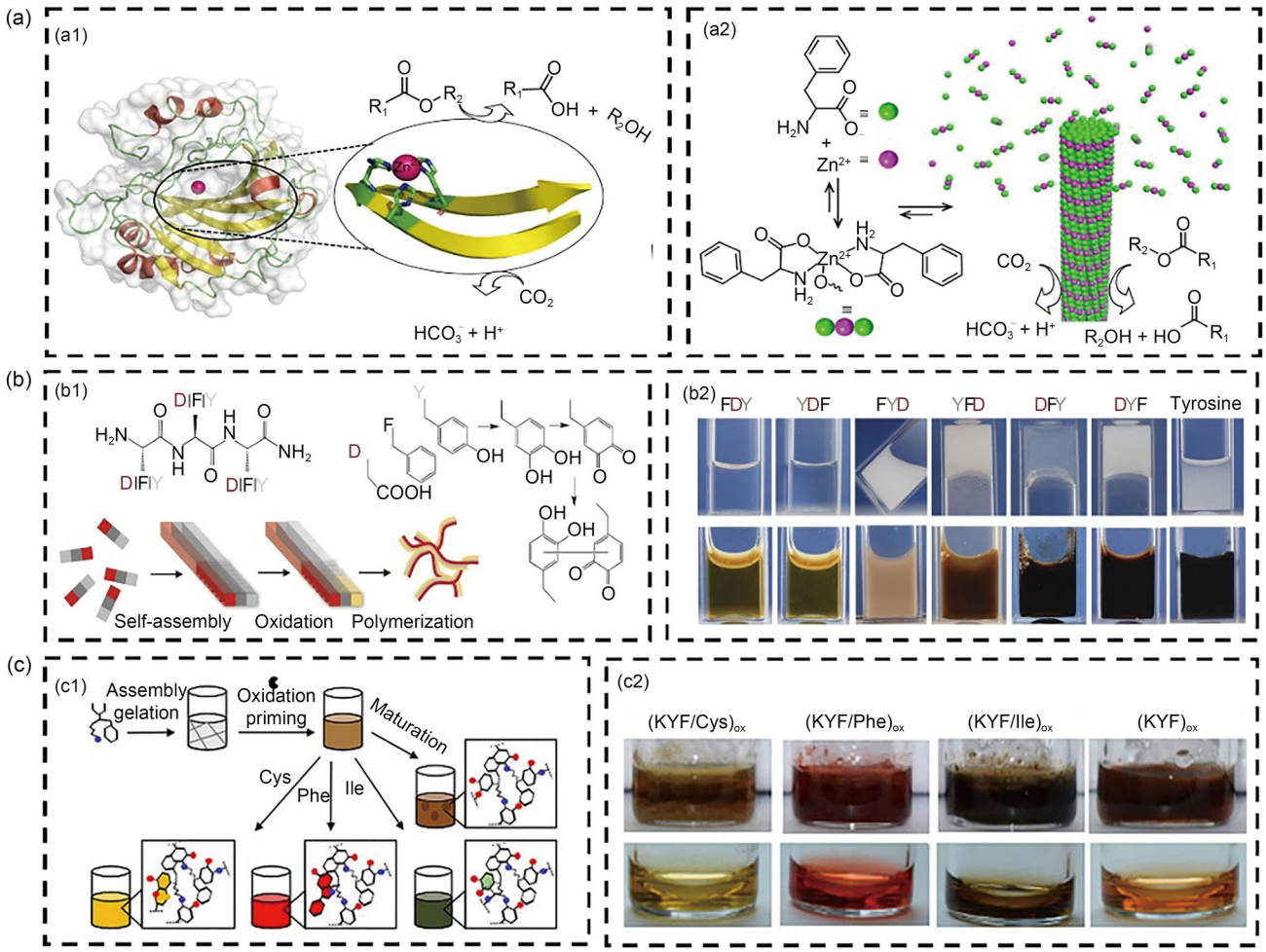


Fig. 11 Diverse properties and applications of self-assembling peptide structures. **a** F-Zn(II) co-assembled carbonic anhydrases (CA) II mimic nanozyme: (a1) chemical structures of the active core inside CA and (a2) F-Zn(II) co-assembled biocatalyst. Reproduced from Ref. [172], Copyright 2019, with permission from the authors, licensed under exclusive license to Springer Nature Limited. **b** (b1) Schematic depiction of Tyr containing peptides-based supramolecular pigments produced by enzymatic oxidation and subsequent polymerization; (b2) macroscopic images of the material formed by the self-assembly of tripeptides before (top) and after (bottom) enzymatic oxidation. Reproduced from Ref. [176], Copyright 2017, with permission from American Association for the Advancement of Science. **c** (c1) Schematic depiction showing introduction of other amino acids (Cys, Phe, and Ile) during KYF self-assembly modulates photoactivity; (c2) macroscopic images of the reaction mixtures (top) and supernatants (bottom). Reproduced from Ref. [178], Copyright 2021, with permission from Wiley–VCH GmbH

in 2019. Since its onset, this virus has exhibited high morbidity and mortality rates, posing a significant global threat to human lives and health. Notably, the novel coronavirus can be transmitted through various surfaces, significantly increasing the scope and speed of transmission. Self-assembling peptides have demonstrated the ability to inhibit viral activity [179], rendering them notable candidates for developing functional coatings, such as anti-biofouling in organic solvents [180]. Hu et al. [181] sought to diminish viral transmission rates by devising an innovative antiviral surface and coating and found that two peptides, DOPA-Phe(4F)-Phe(4F)-OMe and DOPA-Phe-Phe-OMe, can self-assemble into spherical structures to form supramolecular entities with antiviral activity (Fig. 12). The activities of phenylalanine and its fluorinated derivatives are crucial within this peptide, which agrees with previous studies demonstrating its antiviral and antifungal properties [182, 183].

Overall, Israeli researchers have made significant strides in understanding the mechanisms of peptide self-assembly and characterizing their physicochemical attributes. These contributions not only advance current peptide applications but also facilitate the development of novel peptide-based drugs, biosensors, and material.

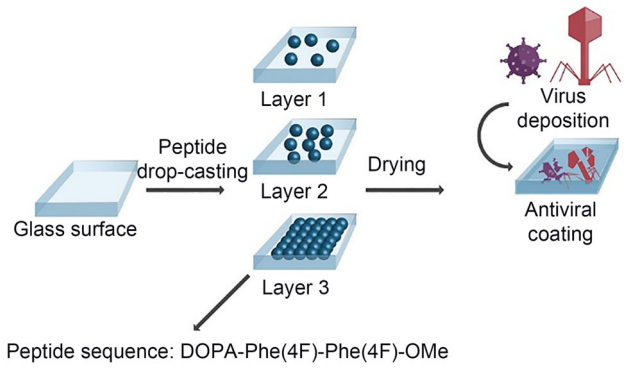


Fig. 12 Schematic cartoon depicting the development of antiviral coatings based on peptide self-assembly. Reproduced from Ref. [181], Copyright 2021, with permission from American Chemical Society

Peptide-based 3D printing materials

Peptide-based materials serve as intelligent building modules for nanobiological devices. Their properties can be programmed by tweaking their molecular arrangement or composition, thereby enabling the development of materials with variable morphology, mechanical properties, and excellent biocompatibility. These advantages make peptide self-assembly materials candidate components of intricate 3D printing structures with extensive potential applications as sensors, actuators, electronic devices, and other biomedical materials.

Adler-Abramovich and Gazit [184] described the application of inkjet technology in the construction of peptide nanostructures on non-biological surfaces. Three aromatic dipeptide nanotubes (ADNTs) were engineered for facile self-assembly in solution: FF and two N-terminally modified analogs (Fmoc-FF and Boc-FF). ADNTs served as the "ink" in the inkjet printing, which employed a basic computer-based inkjet printer to compose images on transparent foil and indium tin oxide-coated plastic surfaces. The volatility of the solution ensured the precise and swift spraying of nanostructures onto predetermined positions, effectively mapping them into pre-designed patterns. Additionally, the proven ability to fill or coat peptide nanotubes with metal materials indicates their potential application in nanoelectronic devices. Similarly, Mohanraj et al. [185] utilized inkjet technology to mix artificial antimicrobial peptides with the photoreactive compound benzophenone. They deposited and fixed the photoreactive peptides onto an ultrafiltration membrane using an inkjet printer equipped with a UV lamp.

Yang et al. [186] described a study at the University of Hong Kong on a 3D printing method for FF microstructures that enabled free-shape creation with crystal properties. Initially, the amorphous FF of a meniscus-guided material was 3D printed and rapid solvent evaporation was applied. Subsequently, through thermally induced self-assembly, the printed amorphous FF transitioned into rhombic crystals (Fig. 13a), resulting in the acquisition of a free-surface 3D structure of FF (Fig. 13b). Characterization revealed substantial post-annealing morphological changes that led to the formation of a crystal structure with piezoelectric properties (Fig. 13c). Notably, the piezoelectric characteristics of multi-layer FF structures demonstrated consistent performance irrespective of thickness, which would potentially increase the design flexibility in device manufacturing. Moreover, precise control over the FF concentration facilitated high-resolution additive manufacturing. Importantly, both processes were conducted on the same construction platform, thereby streamlining the manufacturing process.

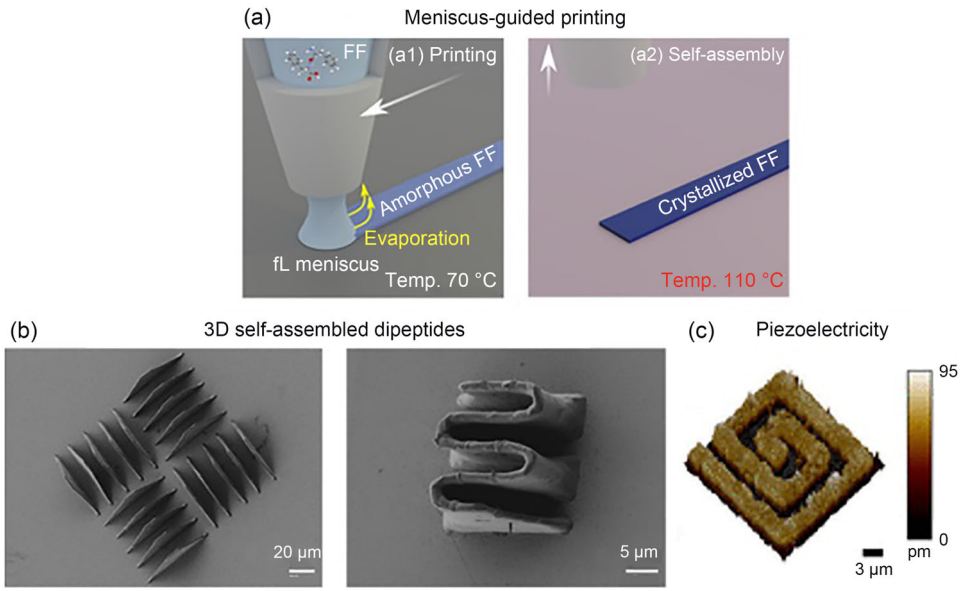


Fig. 13 3D printing of FF dipeptides. **a** Schematics illustrating the two-step 3D printing process of FF: (a1) femtoliter meniscus-guided 3D printing of amorphous FF under rapid solvent evaporation at 70 °C; (a2) the self-assembly process (i.e., crystallization) of FF with the aid of thermal treatment at 110 °C. **b** Arrays of microwalls with an isosceles trapezoid shape and a zigzag wall. **c** A 3D vertical piezoresponse force microscopy image of spiral patterns of FF after annealing. Reproduced from Ref. [186], Copyright 2021, with permission from American Chemical Society. FF: diphenylalanine

The use of peptides in 3D printing has significant potential applications, particularly in 3D bioprinting, owing to their exceptional design flexibility, molecular structure, and adaptable shape characteristics. These attributes indicate the potential applications of 3D printing in the biomedical field, particularly in tissue engineering. However, the use of peptide self-assembly in 3D printing is still in its early stages, with only a limited availability of peptide bio-inks, signifying the need for further exploration and development. Nevertheless, Israel has shown exceptional progress in both realms of peptide self-assembly and 3D printing, encouraging scholars and startups to initiate interdisciplinary collaborations in peptide and 3D printing research. Consequently, Israel's nurturing research environment has made it a fertile ground for advancing the application of peptide self-assembly in 3D printing.

Conclusions and future perspectives

Israel is well-known worldwide for its innovation and has achieved substantial advancements in 3D printing and peptide self-assembly. It has successfully advanced and promoted 3D printing from research to commercialization. Unsurprisingly, Israel has gained eminence in peptide self-assembly with its intimate involvement in unraveling the underlying mechanisms, characterizing the physicochemical properties, and modulating supramolecular morphologies.

The introduction of bioinspired resources as printing inks is a promising approach that would expand the applications of 3D printing in the biomedical and bio-machine interface fields, with peptide self-assemblies as strong candidates for 3D printing bio-inks. Their advantages, such as ease of modification and intrinsic biocompatibility, endow them with the ability to adjust their physicochemical properties.

However, peptide-based 3D bioprinting is still in its infancy, and many challenges need to be resolved before its extensive applications can be realized. Specifically, the viscoelasticity of the peptide self-assembling hydrogels is inherently weak, which may cause the printed structures to collapse. Therefore, the peptides need to be reasonably designed, and their self-assembly should be precisely regulated to achieve the required mechanical properties. The processing technologies and corresponding parameters also need to be thoroughly analyzed and optimized for 3D printing of peptide self-assemblies. Furthermore, commercial exploration should be prioritized in the advancement of peptides-based 3D printing to accelerate the incorporation of this technology as a pivotal contributor to the improvement of human lives. All of these challenges require further efforts to advance 3D bioprinting to the next stage. Israel, albeit a small nation, is a critical game player in the 3D printing field. Extensive international collaborations should be fostered between such a high-tech area and large-market nations to promote the application of 3D bioprinting in various fields, thereby achieving a win–win situation. This extensive review offers a detailed overview of Israel's progress in 3D bioprinting and provides a material basis for further development of 3D-printed bioproducts.

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Declarations

Conflict of interest KT is an academic editor for *Bio-Design and Manufacturing* and was 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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