Bio-Design and Manufacturing (2024) 7:857–888
https://doi.org/10.1007/s42242-024-00317-y

REVIEW

3D bioprinting of tumor models and potential applications

Huaixu Li[1] · Yang Qiao[1] · Xingliang Dai[1,2] · Haotian Tian[1] · Zhenyu Han[3] · Sheng Cheng[3] · Peng Gao[1,4] · Hongwei Cheng[1]

Received: 10 October 2023 / Accepted: 10 September 2024 / Published online: 14 November 2024

Abstract

Cancer is the most common cause of human mortality and has created an unbridgeable health gap due to its unrestrained aberrant proliferation, rapid growth, metastasis, and high heterogeneity. Conventional two-dimensional cell culture and animal models for tumor diagnostic and therapeutic studies have extremely low clinical translation rates due to their intrinsic limitations. Appropriate tumor models are therefore required for cancer research. Engineered human three-dimensional (3D) cancer models stand out for their ability to better replicate the spatial organization, cellular resources, and microenvironmental features (e.g., hypoxia, necrosis, and delayed proliferation) of actual human tumors. Further, the fabrication of these models can be achieved by an emerging technology known as 3D bioprinting, which allows for the fabrication of living structures by precisely regulating the spatial distribution of cells, biomolecules, and matrix components. The aim of this paper is to review the current technologies and bioinks associated with 3D bioprinted cancer models for glioma, breast, liver, intestinal, cervical, ovarian, and neuroblastoma, as well as, advances in the applications of 3D bioprinted-based tumor models in the fields of tumor microenvironment, tumor vascularization, tumor stem cells, tumor resistance and therapeutic drug screening, tumorimmunotherapy, and precision medicine.

Huaixu Li and Yang Qiao have contributed equally to this work.

✉ Xingliang Dai
daixingliang@ahmu.edu.cn

✉ Peng Gao
gaopeng@ahmu.edu.cn

✉ Hongwei Cheng
hongwei.cheng@ahmu.edu.cn

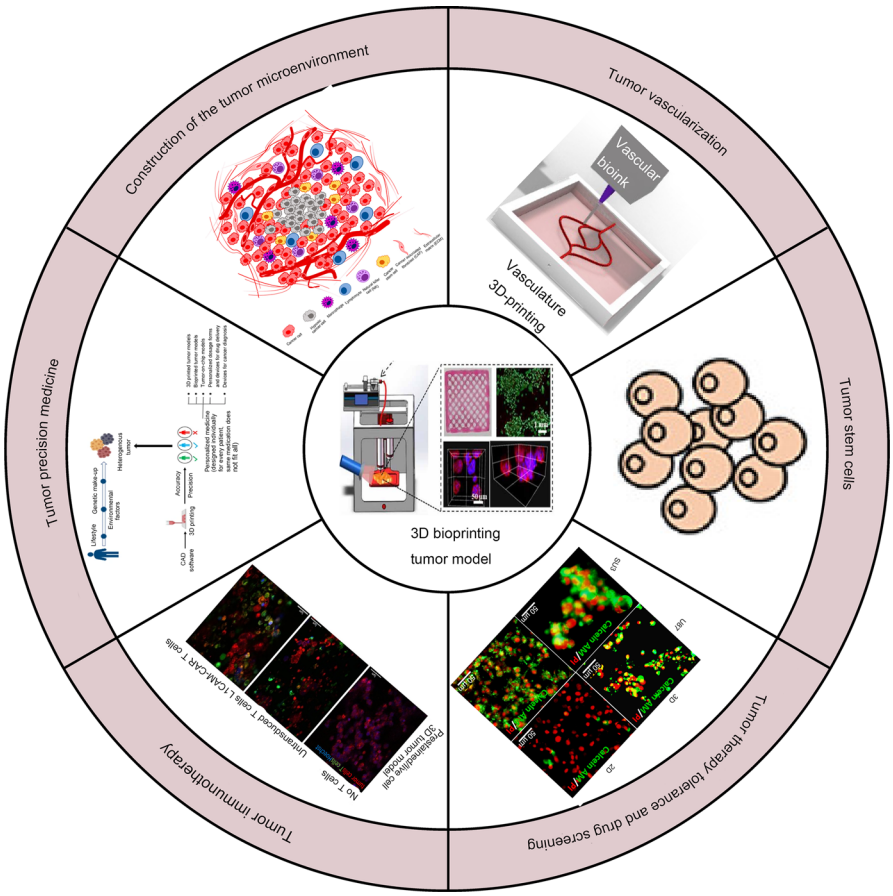
[1] Department of Neurosurgery, The First Affiliated Hospital of Anhui Medical University, Hefei 230001, China

[2] Department of Research and Development, East China Institute of Digital Medical Engineering, Shangrao 334000, China

[3] Department of Medical Imaging Technology, The First Clinical College of Anhui Medical University, Hefei 230032, China

[4] Department of Neurosurgery, Affiliated Jinling Hospital, Medical School of Nanjing University, Nanjing 210002, China

Graphic abstract



Keywords Bioprinting · Tumor micro-environment (TME) · Cancer model · Application

Introduction

An innovative technique called three-dimensional (3D) bioprinting enables the rapid, precise, and quantitative deposition of biologically active components, including living cells, biomaterials, drugs, growth hormones, and genomes, to create active tissues with highly complex spatial structures [1–4]. Bioprinting has been used to fabricate scaffold material-containing and scaffold material-free tissue/organ-like structures [5], microtissues [3], and organ cores [6–9]. Progress in this field has even reached the demonstration of alternative human organ functions, including cardiac, hepatic, and renal tissues, which shows the potential application for bioprinted materials to act as in vitro organoids [1]. Nevertheless, mimicking cell–cell and cell–tissue microenvironments, histological structures, and functions is not an easy task due to the difficulty of vascularization and the complexity of heterogeneity within tissues. On the other hand, although biomaterials can be bioprinted to promote cell growth and proliferation with a certain degree of decay and biomimicry, it is still not feasible to use these bioprinted tissues/organs to truly replace human organs on a large scale and completely [2]. Despite additional challenges, 3D bioprinting has started to gain widespread acceptance and is being used for a greater number of applications. For example, 3D-printed tissue models are beginning to replace two-dimensional (2D) models and animal models for drug testing, since 2D cell culture models cannot replicate 3D tissue microenvironments [10–13] and animal models do not reliably predict toxicological and pathophysiological responses in humans [14]. More specifically, to aid in the healing and recovery of skeletal muscle injuries, biological engineering and regenerative healthcare have been used to develop bioprinted bone and cartilage [2, 3, 15, 16]. Furthermore, in situ bioprinting has been used to directly print at the surgical site, enabling the regeneration of complex larger tissues via body-driven cardiovascular regeneration [4, 17, 18]. Due to the rise of artificial intelligence, some studies have proposed to combine 3D

printing with artificial intelligence to print tissue organs [19]. Compared to conventional 2D models, 3D-based bioprinted tumor models exhibit vastly different molecular features, gene expression, and drug sensitivity, and have shown great potential for both basic and applied oncology research. This potential is demonstrated by the ability of bioprinted tumor models to better mimic complicated 3D cell–cell and cell—matrix connections that have been crucial to understanding cancer physiopathology [20].

Tumor models are important tools necessary for studying various aspects of tumorigenesis, diagnosis, and treatment [21]. The traditional use of flat dish cultured cell models and xenogeneic animal models yields inherent and unavoidable natural defects that reduce the clinical translation rate of research results [22], thereby limiting the pace of fighting tumor development. Therefore, the task of developing new and appropriate models to be applied in tumor research has become imminent. Indeed, the in vitro reconstruction of human tumors faces many challenges that arise from the in vitro construction methods, the support material systems, and the culture systems used to maintain nutrients, oxygen, and eliminate metabolic wastes. However, the in vitro reconstruction of 3D tumors replicating the in vivo tumor microenvironment has improved thanks to advancements in 3D bioprinting technology. Common methods used for the 3D bioprinting of tumor models include extrusion bioprinting [23], inkjet bioprinting [24], light-curing bioprinting [25], and laser-assisted bioprinting [26], among others. Materials used for bioprintability include synthetic and natural hydrogels such as polyethylene glycol (PEG), Planitronic F-127, sodium alginate, gelatin and its derivatives, and hyaluronic acid and its derivatives [27–29]. Applications of 3D bioprinted tumor models using bioprinted materials include research on the construction of the tumor microenvironment, tumor stem cells, tumor vascularization, tumor therapy tolerance and drug screening, tumor immunotherapy, and precision medicine. Moreover, 3D bioprinting has been used to create a variety of tumor models, including neurological tumors, breast cancer tumors, reproductive system tumors, digestive system tumors, bone tumors, and skin tumors, among others.

Here, the working principle of the 3D bioprinted tumor model is extensively presented, as a broad understanding of its working principle will facilitate its application to oncology. For readers interested in fundamental and translational research on 3D bioprinted tumor models, this paper also offers a critical analysis of them and a discussion of their drawbacks.

3D bioprinting technology

Currently, there are four main 3D bioprinting technologies for tumor models. These include droplet-based bioprinting (DBB) [30] (Fig. 1a), extrusion-based bioprinting (EBB) [23] (Fig. 1b), laser-assisted bioprinting (LAB) [31] (Fig. 1c), and stereolithography bioprinting/digital light bioprinting (SLB/DLB) [32] (Fig. 1d). Each bioprinting method has been thoroughly explained in the citations above. As a result, we will list below the benefits and drawbacks of the four bioprinting methods.

DBB [30], also known as "drop-by-drop" printing, is a non-contact printing technology that includes inkjet, piezoelectric, acoustic and microwave bioprinting techniques [35–37]. Currently, droplet bioprinting has been successfully applied to many different types of tumors, including breast, colorectal, and liver cancers [38–40]. Using this technique, comprehensively controlling the deposition pattern offers several benefits, including rapidity, flexibility, and ease of usage. Regulating the quantity of bioink deposited in a preset area makes it possible to print living cells and makes it easier to clearly localize cells [3]. Moreover, this method currently encounters difficulties such as the limited selection of bioink materials that can be used for printing, heterogeneous droplet sizes and nozzle clogging, bioprinting-induced cell death, the fact that bioprinted constructions often lack integrity and mechanical strength, and that a lack of vascularization and porousness restricts the size of printed structures [35, 41].

EBB, also known as "layer-by-layer" printing, is an extremely popular and inexpensive 3D printing method that can be used for both biological and non-biological materials. In this method, the desired 3D spatial structure is created by extruding a fluid ink from a specific inner diameter (ID) needle using layer-by-layer stacking of 2D structures by pneumatic, piston, or screw power [23, 42]. Currently, EBB has been successfully used to study a variety of tumors, including breast, liver, and colorectal cancers [43–45]. It can create tissue at extremely high cell densities while printing vertically along cell spheroids with biological inks that have hyper-viscosity like clay substrates and complicated polymers [46, 47]. However, this method can lead to cellular structure deformation and viability loss, and is therefore only ideal for printing thick liquids [46, 47]. DBB is analogous to LAB, an indirect manufacturing technology that prints using a laser-induced transfer of energy [31, 48–50]. In recent years, LAB has been used to construct a variety of tumors models for research purposes, including breast cancer, glioblastoma, and pancreatic cancer [51–53]. As a bioprinting protocol, LAB does not require a printhead, a modification that provides benefits, including high throughput, high resolution, and high speed [54, 55]. Thus, LAB avoids issues like printhead failure or clogging and also

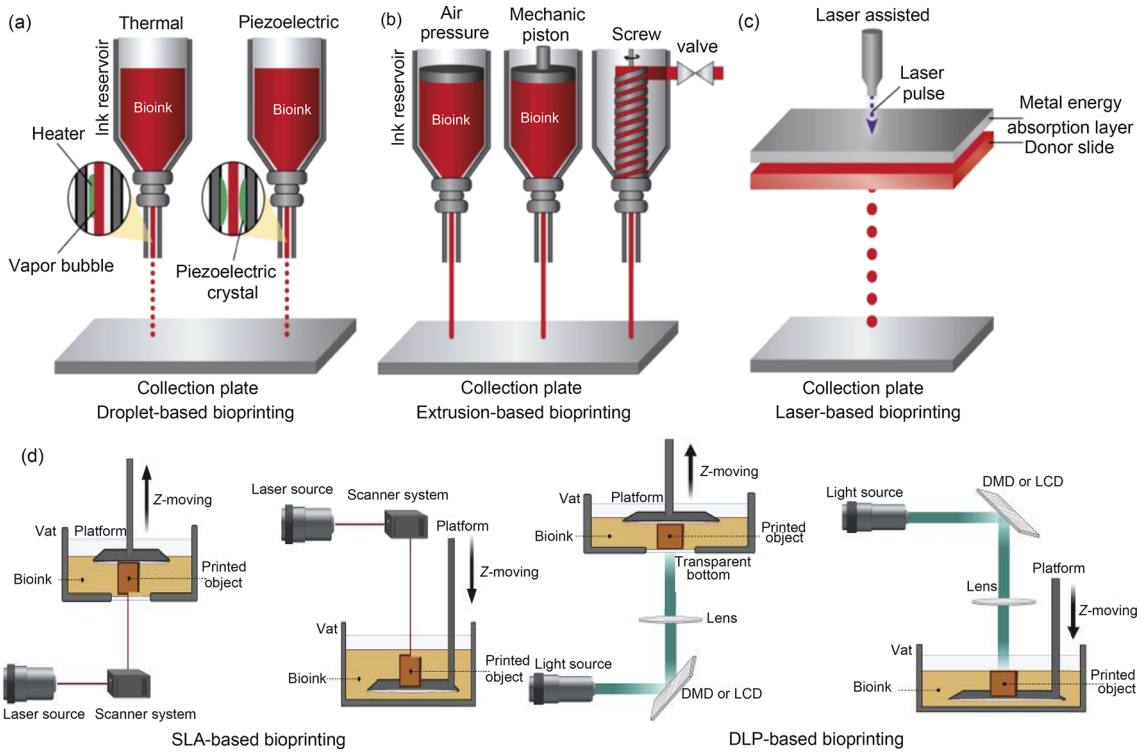


Fig. 1 Five methods of bioprinting: **a** droplet-based bioprinting; **b** extrusion-based bioprinting; **c** laser-based bioprinting (adapted and modified from Ref. [33], Copyright 2023, with permission from The Royal Society of Chemistry); **d** SLA/DLP-based bioprinting (adapted and modified from Ref. [34], Copyright 2023, with permission from the authors, licensed under CC BY-NC-ND 4.0). SLA: stereolithography apparatus; DLP: digital light processing

enhances the compatibility of printed materials while extending the range of viscosities that can be used for printable material applications [56]. However, during laser transfer, live cells may be subjected to high thermal and/or mechanical stresses. If these exceed cell-specific tolerances, irreparable damage to the cells may result [57–59]. SLB /DLB is a bioprinting method that utilizes micromirror arrays to photopolymerize polymer resins in the existence of cells [32]. Since it is not prone to alignment problems associated with single-nozzle extruders, it permits the rapid printing of biological cells at high resolution and without the need for additional support materials, and printed cells have shown extremely high viability (>85%) [60–62]. SLB/DLB technology has been applied in the research of multiple types of tumors, such as breast cancer, liver cancer, and glioma [63–65]. However, SLB/DLB also has numerous drawbacks, including the absence of biodegradable and biocompatible polymers, adverse impacts of harmful light-curing components on cells, the inability to completely remove the framework, and the inability to generate horizontal variations in the design [46, 66]. These problems need to be addressed during future refinement of this technique.

No single bioprinting approach has yet been able to produce synthetic tissues or organs that are perfect in all respects. Thus, the suitable bioprinting approach used for a desired tissue should reflect considerations of the relevant guidelines, material needs, and benefits and drawbacks of each of the candidate techniques [67]. Moreover, the development of 3D bioprinting within the medical industry has had a considerable impact on both the production of medical equipment and the development of numerous therapies. Finally, we also note that these techniques can be combined to produce necessary tissues since 3D bioprinting has been divided into several categories based on its functions.

Bioinks

Bioink is a key material for 3D bioprinting technologies, and consists of cells, matrices, and other biomaterials that are used to 3D print a variety of biological tissues characterized by complex structures and specific functions [68]. Bioinks can be categorized into natural and synthetic ones based on their source. Currently used bioinks are listed in Table 1. Since different 3D bioprinting technologies have different requirements, the selection of bioinks must take into account their characteristics such as biocompatibility, mechanical properties, hydrophilicity, porosity, acid–base neutralization,

Table 1 The advantages and disadvantages of natural and synthetic bioinks currently in use

	Advantages	Disadvantages
Natural bioinks		
Agarose	Good biocompatibility; form stable gels; degradable	Lower plasticity
Alginate	Easy to prepare; chemically biocompatible; high plasticity	Fairly biocompatible; not precise enough
Dextran	Good biocompatibility; can form static gels; easy to process and modify	Not malleable; faster solidification
Hyaluronic acid	Highly cytocompatible and biocompatible; good water absorption and water retention; aid in cell migration and proliferation	Expensive; not suitable for trauma
Silk	Biological structure similar to human tissue; good biocompatibility and plasticity; can be customized via genetic engineering	Expensive; require chemical modification
Fibrin	Biocompatible; promote growth and regeneration; can form strong gels	Easily degradable; require the addition of blood during use
Collagen	Biologically similar to human tissue; promote cell attachment and growth; can be customized via genetic engineering	Easily degradable
Decellularized extracellular matrix (dECM)	Wide range of sources; natural fiber arrangement suitable for applications for muscle, bone, and other tissues	Create pollution; high production costs
Matrigel	A variety of substances such as collagen, ovalbumin and whey proteins contribute to a complex three-dimensional (3D) environment; compatible with a wide range of cell types	Significantly reduce the size of the cell patch, making it difficult to use for large tissue repairs
Cellulose	Soluble cellulose is easy to process and modify; non-toxic; biodegradable; assimilable in the human body	Low plasticity
Gelatin	Easy to handle and 3D print; good biocompatibility	Possible adverse reactions
Chitosan	Good biocompatibility and bioactivity; easy to process and modify	Fragile, breakable; slow to solidify
Natural gums	Biodegradable; can be modified to produce many different bioinks	Less precise; variable plasticity
Synthetic bioinks		
Polyethylene glycol	Biocompatible; form highly controllable carriers; prevent protein inactivation	Possible effect on growth factors
Poly-glycolic acid	Biodegradable; biocompatible; can form strong templates	Rapid dissolution; susceptible to heat and free acid damage during dissolution, leading to protein inactivation
Polycaprolactone	Biodegradable; good plasticity; biocompatible	Slow degradation; low expansion
Polyvinylpyrrolidone	Easy to prepare; good biocompatibility; properties can be adjusted by controlling molecular weight	Unstable and easily affected by light, heat, and other factors
Poly(L-lactic) acid	Biodegradable; good biocompatibility; good bioabsorbability	Slow degradation; potential for tissue irritation
Polylactic-co-glycolic acid	Biodegradable; high strength; good biocompatibility; degradation rate can be adjusted by controlling the mixture ratio	Imprecise degradation rate; potential for tissue irritation
Pluronic acid	Easy to prepare and process; form stable gels; good biocompatibility	Low gel strength; susceptible to temperature and pH

Table 1 (continued)

	Advantages	Disadvantages
Polydimethylsiloxane	Good plasticity; good biocompatibility	React easily with other substances and lose stability
Acrylonitrile butadiene styrene	Strong, wear-resistant; organ structures can be fabricated by 3D printing	May cause tissue irritation; not degradable
Polyether ether ketone	Excellent biocompatibility; high stability and plasticity; biodegradable	High production costs
Polyvinyl alcohol	Easy to prepare and process; good biocompatibility	Low solubility and difficult to degrade
Polyurethane	High plasticity; good biocompatibility; high strength; various organ structures can be fabricated by 3D printing	May cause tissue irritation; not degradable

and biodegradability [69–71]. In most scientific literature, many kinds of bioinks and the printing techniques that are the most appropriate have been described in depth [72, 73]. This review will focus on an overview of natural and synthetic bioinks and their applications in tumor models.

Most natural bioinks have been applied for tumor models. These include gelatin, hyaluronic acid, fibronectin, filipin, dextran, sodium alginate, chitosan, collagen, cellulose, decellularized extracellular matrix (dECM), matrix gels, junction cold gels, cellular aggregates, and konjac gum [74]. For example, Hedegaard et al. used peptide amphiphiles (PAs) to coassemble with and organize extracellular matrix (ECM) proteins, producing tunable 3D models of the tumor microenvironment [75]. In addition, Gebeyehu and colleagues created several polysaccharide-based bioinks to create durable and shape-retaining 3D-printed tumor models that imitate the tumor microenvironment (TME) for chemotherapeutic drug screening of triple-negative breast cancer and lung adenocarcinoma [76]. It is worth mentioning that the extracellular matrix microenvironment of tumors can be accurately represented by a dECM that is itself made from tissues. Thus, a variety of dECM bioinks have been employed for the 3D bioprinting of tumor models. These include glioblastoma microarray bioprinting, which uses dECM bioinks produced from healthy pig skin or brain, as well as bioprinting of hepatic cancer, which uses hepatic dECM bioinks [64, 77, 78]. Although the dECM has the benefit of closely resembling the original tumor stroma, it also lacks certain crucial elements, including glycosaminoglycans [79], and has poor mechanical properties [64]. Moreover, since the complexity of stromal gels is equivalent to the make-up of in vivo cells, they are frequently used as a foundation for 3D carcinoma modeling. The repeatability and precise regulation of the chemical and mechanical characteristics of organic bioinks during bioprinting, however, are sometimes hampered by batch-to-batch fluctuation in matrix gel composition and poorly specified composition [80]. Compared to natural bioinks, synthetic bioinks are tunable, simple to prepare, have higher mechanical properties and immunogenicity, and more easily meet different printing requirements [81]. Polyethylene glycol, polycaprolactone, polyvinylpyrrolidone, poly(L-lactic) acid, and poly(lactic-go-glycolic) acid are a few examples of synthetic bioinks that are often used [82]. For example, Anseth et al. [83] used a multi-arm PEG system to model the interaction between stromal cells and melanoma cells [84, 85]. Shi et al. [86] used poly(lactic-co-glycolic acid) (PLGA) hydrogels to print drug-loaded scaffolds, and their study showed that doing so dramatically reduced breast cancer development and recurrence. However, synthetic bioinks continue to face difficulties such as the use of harmful or radiotoxic solvents that induces cellular damage and the limited cell compatibility of the synthetic bioinks including the lack of adhesion sites for embedding in the cells [82]. These issues [82], have limited their use in some tumor models.

To guarantee that bioprinted tissues and organs operate properly, it is vital to use bioinks that have the required arbitrary, rheological, and physiological features of specific tissues [87]. Therefore, there is an urgent need for standardized bioink formulations that can be used for different bioprinting applications.

3D bioprinting tumor models

Due to ethical and safety constraints and limitations, research on tumors and antitumor drugs cannot be directly studied in the clinic. Given this limitation, and relative to 2D models and animal xenograft tumor models, 3D tumor models have become the most promising tumor models for their ability to better simulate the microenvironment of human tumor tissues [88, 89]. Various cell types embedded in hydrogel materials through precise colonization can be used to simulate the tumor microenvironment, which can be used to

study the characteristics of tumorigenesis, tumor heterogeneity, invasion and migration, and anticancer drug sensitivity [90]. Currently, 3D bioprinting has been carried out in a variety of tumors, including glioma, breast cancer, hepatocellular carcinoma, colorectal cancer, cervical cancer, ovarian cancer, pancreatic cancer, intestinal cancer, pituitary tumor, neuroblastoma, and lung cancer. These studies lay the foundation for the practical use of bioprinted tumor models for precision medicine [11, 22, 91–93].

Glioma

Glioma remains the greatest prevalent carcinomas located in the adolescent nerve system, and shows a high degree of malignancy, extremely high rates of recurrence and mortality, an average prognosis period of even less than one year, and a very low five-year survival rate. Since there are currently very few effective treatments for glioma, it is urgently necessary to develop new medications and therapies for clinical use [94–97]. The biological tumor model serves as a useful tool for researching carcinogenesis and evaluating the impact of radiation treatment. It is hypothesized that the creation of 3D glioma models that capable of simulating the in vivo milieu would present an opportunity to explore the process of glioma genesis, thereby improving the sensitivity and prognosis of glioma radiotherapy. Overall, it is still the absence of appropriate tumor models that has impeded research into brain malignant glioma.

Our team created an in vitro 3D model of glioma using 3D bioprinting to overcome the obstacles arising from the lack of suitable tumor models. In doing so, we uncovered a glioma stem cell enrichment effect and transdifferentiated vascular endothelial potential [98–100], as well as fusion phenomenon between glioma stem cells and bone marrow mesenchymal stem cells [101, 102]. All these findings confirmed that the 3D glioma model had stronger invasive and temozolomide-resistant characteristics [103] (Fig. 2a). Furthermore, studies have demonstrated that 3D bioprinted glioma models can more faithfully replicate the human tumor microenvironment [65, 104]. For example, Haring et al. proposed a biomimetic hydrogel with Herschel–Bulkley fluid rheological properties for the biomanufacturing of micro-physiological brain structures that could be used in pharmaceutical evaluation and disease simulation [105] (Fig. 2b). With the in-depth study of glioblastoma (GBM), DePalma et al. offered a method for creating complex, multicomponent in vitro cancer models, which promises to create more accurate tumor models that more closely resemble the in vivo tumor microenvironment [106] (Fig. 2c). On the other hand, Tang et al. proposed a bioprinting strategy to address the difficulty of crossing the blood–brain barrier for most chemotherapeutic drugs, which mimics relevant biomaterials in natural tissues to create models for more reliable mechanistic studies and preclinical drug screening that may ultimately accelerate drug development for GBM [107]. In addition, Heinrich et al. used 3D bioprinted glioblastoma models in which a macrophage component was added to study the interaction between macrophages and GBM [108] (Fig. 2d). They found that glioblastoma cells actively recruit macrophages and polarize them into a glioblastoma-associated macrophage (GAM)-specific phenotype. Further, macrophages were found to play a role in inducing the development and intrusiveness of brain tumors. In addition to the above valuable findings that tumor models have brought to the study of glioblastoma, another study reported that patient-derived tumor stereo models more accurately capture the biological, biochemical, and bodily characteristics associated with them in real tumors [109], and that the discovery of these features may improve cancer treatment plan effectiveness. Moreover, by simultaneously generating perfused arteries using sacrificial biomaterials consisting of pericytes and endothelial cells, it is possible to demonstrate parallels between gene expression in cells cultivated in vivo and those produced by 3D bioprinting systems [110] (Fig. 2e). Furthermore, to study interactions between cancer stem cells (CSCs) in proliferation and hypoxia conditions, a new ex vivo model called patient-derived glioblastoma-like organs has been developed [111]. In future, these organs have the potential to be used for many applications, including individualized drug screening.

The 3D bioprinting of glioma models is an exciting field and holds tremendous potential for the advancement of glioma research and treatment. Yet, some challenges need to be overcome. For instance, the complexity and cost of bioprinting tumor models may limit their widespread clinical application. In addition, the biological similarity and sustainability of the models still require further improvement to better reflect the characteristics of real tumors. However, through continued research and technological advancement, these models can be further developed to improve glioma research and treatment, ultimately providing effective personalized medicine for patients.

Breast cancer

The latest statistics from the World Health Organization show that for the first time, breast cancer cases surpassed lung cancer as the most threatening cancer to human health [112]. One of the best ways to systemically treat clinical malignancies is chemotherapy, since there are too few bionic tumor models for drug testing. These treatments have rarely received Food and Drug Administration approval for clinical trials [113, 114]. As we know, in addition to the large number of cancer cells that make-up breast tumors, cellular activity is involved in the process of breast cancer development and progression, and the extracellular matrix (ECM) is able to regulate the microenvironment of malignant tumors thus becoming a

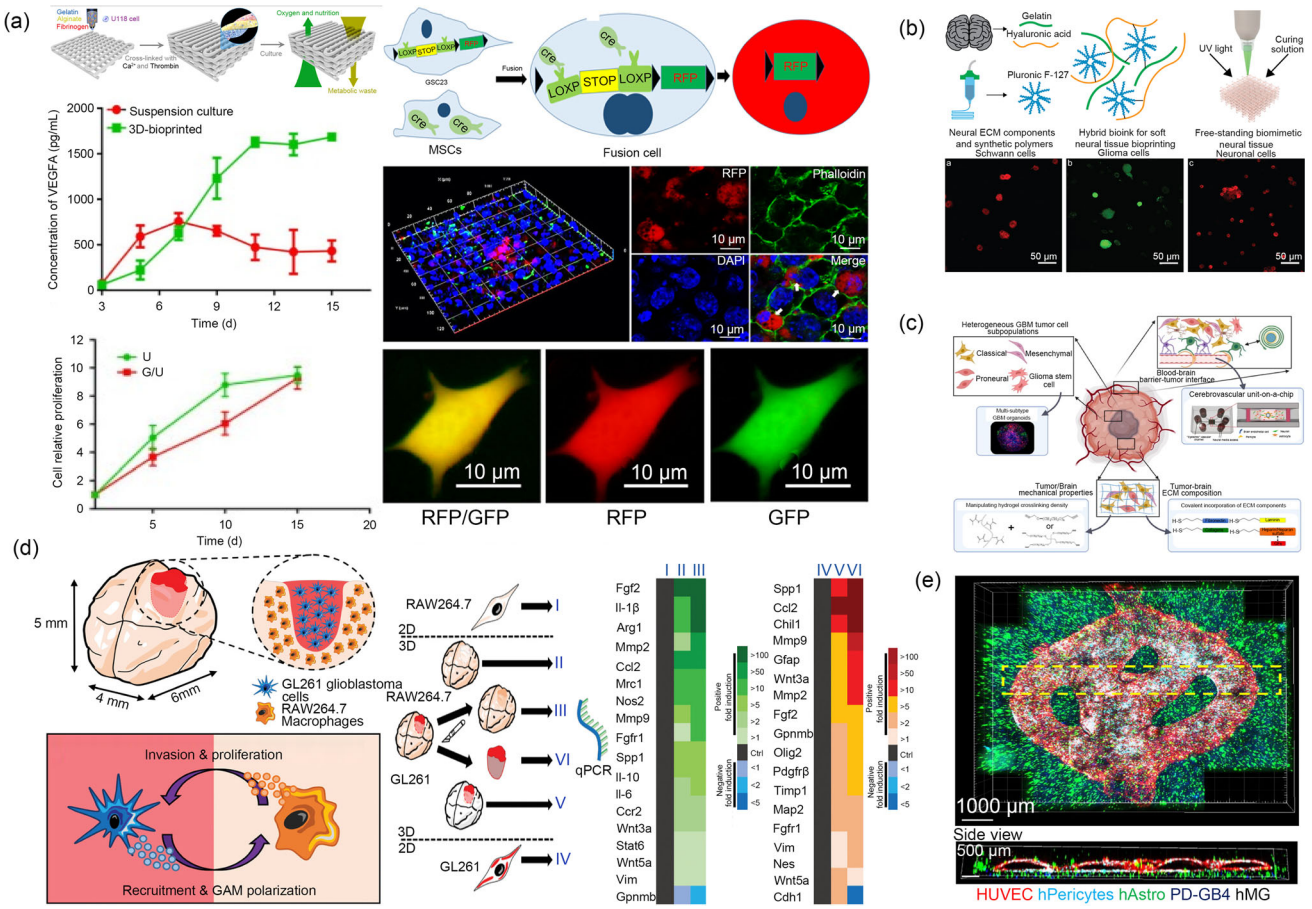


Fig. 2 3D bioprinting of brain glioma models. **a** 3D bioprinting technology to create in vitro 3D models of gliomas and to study glioma stem cell properties and medical applications (adapted and modified from Ref. [98], Copyright 2018, with permission from Elsevier B.V.; adapted and modified from Ref. [99], Copyright 2018, with permission from Wiley Periodicals, Inc.; adapted and modified from Ref. [101], Copyright 2017, with permission from the authors, licensed under CC BY 4.0; adapted and modified from Ref. [102], Copyright 2022, with permission from the American Chemical Society; adapted and modified from Ref. [103], Copyright 2018, with permission from Elsevier B.V.). **b** A biomimetic hydrogel bioprinted glioma model with Herschel–Bulkley fluid rheological properties (adapted and modified from Ref. [105], Copyright 2019, with permission from IOP Publishing Ltd). **c** A strategy for developing complex multicomponent in vitro glioma models (adapted and modified from Ref. [106], Copyright 2021, with permission from Elsevier B.V.). **d** Macrophage-GBM interactions in a 3D bioprinted glioblastoma model (adapted and modified from Ref. [108], Copyright 2019, with permission from WILEY–VCH Verlag GmbH & Co. KGaA, Weinheim). **e** Creating perfusable blood vessels using sacrificial bioinks containing pericytes and endothelial cells to study differences in cellular gene expression (adapted and modified from Ref. [110], Copyright 2021, with permission from the authors, licensed under CC BY-NC 4.0). GBM: glioblastoma

key factor influencing cellular activity [115–117]. Therefore, efforts are being made to add tumor stromal components to biomaterials to improve their biocompatibility and heterogeneity to better mimic the tumor matrix environment [118].

Epithelial-adipose interactions are a critical step in the development of the lethal metastasis of breast cancer cells. In one study, Chaji et al. [119] investigated adipocyte-breast cancer cell interactions by using 3D bioprinted breast cancer tumor models to simulate breast cancer tumors (Fig. 3a). In addition, Vinson et al. [120] used laser direct-write bioprinting to load a hydrogel matrix containing differentiated adipocytes with breast cancer cells into a breast cancer model, which was biologically fabricated from microbeads to mimic the phenomenon of breast cancer cell invasion into adipose tissues and specifically the model allowed tracking of MCF-7 and MDA-MB-231 breast cancer cell invasion for more than two weeks in an optically transparent hydrogel scaffold (Fig. 3b). In addition, Blanco-Fernandez et al. [121] (Fig. 3c) developed a decellularized tissue- and organ-derived matrices (TDM) bioink based on decellularized porcine breast tissue combined with type I collagen. This bioink is a good biomaterial for creating breast cancer models, which not only allowed for the tight reconstruction of breast tumors in vitro, but also promoted the proliferation of breast cancer cells in order to form cell clusters and spheroids, and increased the resistance of the model. Alternatively, decellularized human

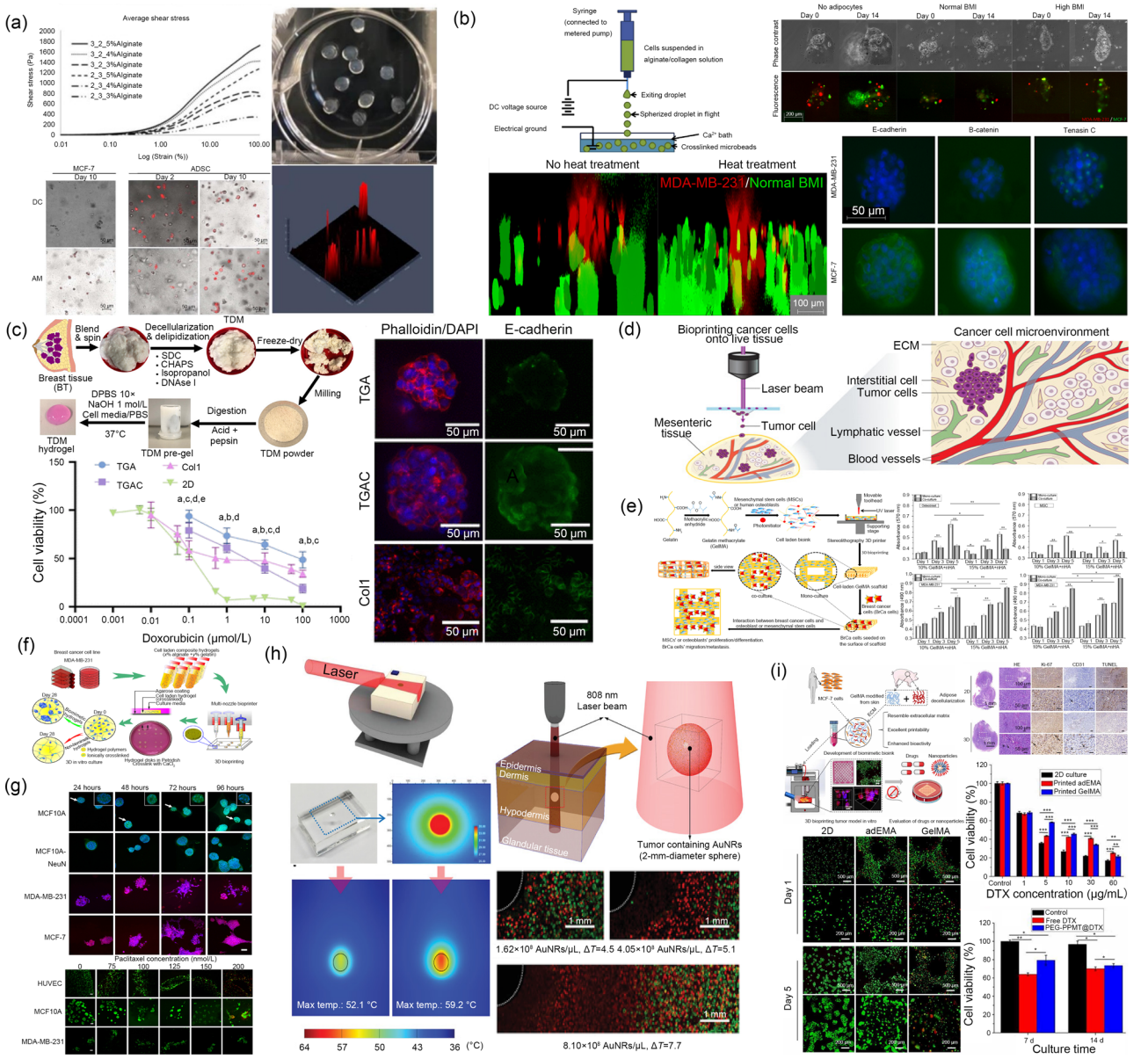


Fig. 3 3D bioprinting of breast cancer tumor models. **a** 3D bioprinted breast cancer tumor model for the study of adipocyte-breast cancer cell interactions (adapted and modified from Ref. [119], Copyright 2020, with permission from the authors, licensed under CC BY 4.0). **b** Laser direct writing bioprinted breast cancer models to study tumor invasiveness and drug resistance (adapted and modified from Ref. [120], Copyright 2017, with permission from IOP Publishing Ltd). **c** Development of a TDM bioink based on decellularized porcine udder tissue combined with type I collagen and a corresponding cell viability study (adapted and modified from Ref. [121], Copyright 2022, with permission from the authors, licensed under CC BY 4.0). **d** Bioprinting cancer cells onto live tissue to create an ex vivo model for the study of cell migration (adapted and modified from Ref. [127], Copyright 2016, with permission from Wiley Periodicals, Inc.). **e** Schematic diagram of a direct, 3D bioprinted, cell-laden bone matrix as a biomimetic model for a breast cancer metastasis study (adapted and modified from Ref. [128], Copyright 2016, with permission from the American Chemical Society). **f** Schematic depicting the generation of composite gels, the bioprinting process, and the subsequent generation of MCTS of breast cancer cells in bioprinted alginate/gelatin hydrogels (adapted and modified from Ref. [130], Copyright 2019, with permission from IOP Publishing Ltd). **g** Bioprinted 3D breast epithelial spheroids maintained a typical spheroid morphology for 96 h in a collagen/alginate bioink and representative live/dead images from co-culture experiments showing HUVEC, MCF10A, or MDA-MB-231 bioprinted grid areas (adapted and modified from Ref. [131], Copyright 2019, with permission from IOP Publishing Ltd). **h** Quantitative photothermal characterization using bioprinted 3D tissue constructs using gold nanorods for early-stage breast cancer therapy (adapted and modified from Ref. [133], Copyright 2021, with permission from the authors, licensed under CC BY-NC-ND). **i** 3D bioprinted tumor model using extracellular matrix enhanced bioinks for nanoparticle evaluation (adapted and modified from Ref. [134], Copyright 2022, with permission from IOP Publishing Ltd). TDM: tissue- and organ-derived matrix; MCTS: multicellular tumor spheroid; HUVEC: human umbilical vein endothelial cell

or rat mammary tissues can also be used to construct hydrogels [122]. These ECM hydrogels are able to retain their unique structures and signaling profiles to construct breast cancer-like organs with tissue-specific matrices. In addition, researchers have created hydrogel-based models, including the shell and core structures of hydrogel-encapsulated breast cancer printed by laser direct writing [123], scaffold-free 3D breast cancer tumor structure [124], as well as models filled with breast cancer cells in 3D vascularized breast cancer structures and mimicked breast duct-like structures [125, 126]. It has been shown that 3D tumor models are important for studying cancer treatment as well as the interactions between tissue-specific ECMs and cancer cells. For example, Burks et al. used laser direct-write bioprinting of breast cancer cells onto ex vivo microvascular networks containing vasculature, lymphatic vessels, and mesenchymal cell populations to quantify cancer cell migration and the effects of the migration on angiogenesis and lymphangiogenesis in an intact network that should resemble the full complexity of the tumor microenvironment [127] (Fig. 3d).

Breast cancer metastasis can lead to fatal consequences, and the currently existing 3D bionic models are insufficient to similarize this procedure in vitro. Thus, to study the interactions among breast cancer (BrCa) cells and bone tissue cells, Zhou et al. [128] developed a hydrogel with a bionic bone matrix using stereolithography 3D bioprinting (Fig. 3e). They discovered that BrCa cells had been boosted in the presence of bone marrow and mesenchymal stem cells (MSCs), while bone marrow and MSC proliferation were blocked in the existing of BrCa cells. 3D bioprinted BrCa cells and bone stromal metastatic cancer models provide an opportunity to study the mechanisms of bone metastases in breast cancer and the oncogenesis of MSCs. Further, it was discovered that the presence of osteoblasts and MSCs promoted the growth of BrCa cells while inhibiting their proliferation. All in all, a useful technique for researching the mechanisms involved in breast cancer bone metastasis and developing targeted treatments is the 3D bioprinting of BrCa cells and skeletal tissue metastatic cancer models.

The real tumor milieu in vivo is more closely resembled by 3D cancer models than by traditional 2D cultures, and 3D bioprinting-based cancer models enable rapid replication of the cancer microenvironment, which can allow high-throughput screening of drugs [129]. For example, during the creation of an in vitro breast tumor model, Jiang et al. [130] reported using an engineered composite hydrogel made of gelatin and alginate components to create multicellular tumor spheroids from 3D bioprinted breast cancer cells (Fig. 3f). Further, to produce tumor tissue models that are able to be employed immediately, Swaminathan et al. [131] proposed a method for bioprinting pre-formed 3D spheres of breast cancer directly using alginate-based bioinks. Specifically individual breast epithelial cell lineages have been bioprinted as single cells or spheres that had already been produced and retained their viability, structure, and function (Fig. 3g). Yet another study has shown that the antitumor medications camptothecin and paclitaxel did not have the same effect on independently printed breast cells as they did on the bioprinted breast spheroids [132]. In addition, Nam et al. [133] built 3D complex tissue structures by bioprinting, using processed gels obtained from porcine skin and human decellularized adipose tissue. Based on this model, they utilized plasma photothermal therapy (PPTT) with gold nanoparticles (AuNPs), demonstrating its potential for treating breast tumors (Fig. 3h). In recent years, there has been a general upsurge in nanomedicine research for tumor therapy. However, the conventional methods for evaluating nanoparticles (NPs) have mainly relied on two-dimensional cell culture and animal models, which generally do not comprehensively explore the complicated movement of NPs and have difficulty adequately simulating the human tumor microenvironment; therefore, this evaluating method restricts the application of nanomedicine formulations in clinical research. Consequently, Chen et al. [134] used fat-dECM-enhanced hybrid bioinks to fabricate tumor models via 3D bioprinting. These not only more closely resembled real tumors in terms of tumor proteins, gene expression, and tumorigenicity, thereby demonstrating ECM reconstruction and transition from epithelial to mesenchymal features, but also exhibited greater resistance to nanomedicines. Taken together, this model is expected to provide greater precision platforms for pharmaceutical development and design prior to entry into animal and clinical trials (Fig. 3i).

Consequently, the 3D bioprinting of breast cancer models is an important technology in the field of breast cancer research and treatment. By using more realistic, comparable, and user-friendly breast cancer models, we can better understand the mechanisms involved in breast cancer development, better evaluate the effectiveness of different treatment strategies, and conduct better drug screenings. However, some challenges must still be overcome. For instance, bioprinting breast cancer models require high-precision techniques and complex equipment, and this can be costly and time-consuming. Furthermore, there is still room for improvement in terms of the biological similarity and reproducibility of bioprinted models, particularly in simulating the interactions between cancerous and normal cells in a 3D environment. Although the 3D bioprinting technology for breast cancer models has the abovementioned challenges, it still has a bright future. Through continuous improvement of the technology and in-depth research, we can enhance the clinical application of bioprinted models and provide better medical services to patients.

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is now the fifth most common cancer worldwide and the second leading cause of cancer-related deaths [135]. The stiffness of the hepatic extracellular matrix has a significant impact on the onset and progression of HCC, and the development of HCC is associated with greater stiffness values of the background liver parenchyma [136, 137]. In addition, HCC progression includes the invasion of the fibrous septum by tumor tissue [138]. The traditional approach to studying HCC progression involves simply adjusting the stiffness of the 2D substrate. However, this model does not accurately represent the 3D mechanical environment seen in the natural liver, which may cause results to differ from those obtained using 3D methods [139–142].

Ma et al. [64] developed a photocrosslinkable liver dECM and a quick 3D bioprinting process based on light curing and used it as a platform for the study of the progression of HCC (Fig. 4a). Cirrhotic liver tissue might be securely encapsulated in 3D bioprinted liver dECM scaffolds, and its mechanical properties are also preserved by encapsulation. HepG2 cells showed decreased proliferation and an increase in invasive markers when enclosed in dECM scaffolds with cirrhotic stiffness as opposed to unaffected controls. Moreover, Li et al. [143] integrated 3D bioprinting, co-culture, and microfluidics to build a 3D co-culture microfluidic model of a controllable hepatoma cluster size. They then applied this model to perform a pharmacodynamic test of a novel anti-CD147 monoclonal antibody, Metuzumab, and found that hepatocellular carcinoma cells proliferated faster in the new model, which had less impact on the migratory properties and proliferation of hepatocellular carcinoma cells, compared to a common in vitro 3D model made only by cell printing (Fig. 4b). The findings are in line with those of comparable animal studies and anti-CD147 clinical trials, and offer an invaluable frame of reference for the investigation of intricate in vitro liver cancer models. On the other hand, Sun et al. [44] created 3D models with HepG2 cells using extruded 3D bioprinting, revealing dramatic differences in gene transcription between 3D and 2D cell cultures, especially in mutations associated with hepatocyte function. They also compared antitumor drug sensitivity, and hypothesized that this difference may lead to differences in drug pharmacodynamics (Fig. 4c). Hwang et al. [144] first proposed an integrated digital light processing based (DLP-based) 3D bioprinting platform that enables the printing of liver cancer cell models on conventional porous cell culture plates, leading to the rapid generation of in vitro 3D tissue models for high-throughput preclinical drug screening and disease modeling (Fig. 4d). It is important to mention that the choice of bioink is as important as the printing technique. Ying et al. [145] developed a novel bioink formulation based on a two-phase aqueous emulsion of gelatin methacryloyl (GelMA) solution and polyethylene oxide (PEO) solution, through the use of which printed tumor cells showed enhanced cell viability, spreading, and proliferation (Fig. 4e). Moreover, Polez et al. [146] first proposed the printing hepatocellular carcinoma tumor models by using a plant-derived hydrogel as a bioink, and the results of subsequent in vitro cell viability testing (Fig. 4f) showed that the scaffolds printed with this bioink were able to promote the proliferation of hepatocellular carcinoma HepG2 cells. Xie et al. [147] constructed a hydrogel consisting of 2,2,6,6-tetramethylpiperidine 1-aryloxy oxidized cellulose nanofibers (TOCNFs) and chitosan nanofibers (CsNFs), into which cells were able to be injected to better mimic the cellular microenvironment and to show the potential of biologically adaptive 3D cell cultures for biomedical applications (Fig. 4g). In another study, Mao et al. [148] bioprinted intrahepatic cholangiocarcinoma cells isolated from patients into pre-designed hydrogel grid structures using a gelatin–alginate–Matrigel^{TM} composite hydrogel system. Subsequently, it was observed that intrahepatic cholangiocarcinoma cells were characterized by high viability and the cells were also more capable of forming active proliferative colonies. The tumor microenvironment of the aggressive and metastatic phenotype of intrahepatic cholangiocarcinoma cells was confirmed by assessments of the expression levels of tumor markers, cancer stem cell markers, matrix metalloproteinase proteins, the tumor fibrosis index, the liver function index, and the epithelial-mesenchymal transition regulatory protein levels recorded in the 3D prints. Furthermore, the team also used clinical specimens from hepatocellular carcinoma patients for bioprinting to successfully construct 3D models of patient-derived hepatocellular carcinoma tissues and achieve longer-term in vitro cultures. These retained the characteristics of parental hepatocellular carcinomas, including stable biomarker expression, tumor-specific genetic alterations, and the stable maintenance of expression profiles, and are expected to be able to predict patient-specific medications for the development of personalized therapies [147].

Overall, the 3D bioprinting of liver cancer models is an important technology in the field of liver cancer research and treatment. However, similar to breast cancer models, 3D bioprinting of liver cancer models faces some challenges. For example, this technique still requires high-precision printing techniques and complex equipment, and there is room for improvement in terms of the biological similarity and reproducibility of the models. In addition, the liver is structurally and functionally complex, and the completeness and authenticity of the models for this feature are crucial factors to consider. In conclusion, we believe that 3D bioprinting of liver cancer models is a promising field that can bring significant advancements to liver cancer research and treatment.

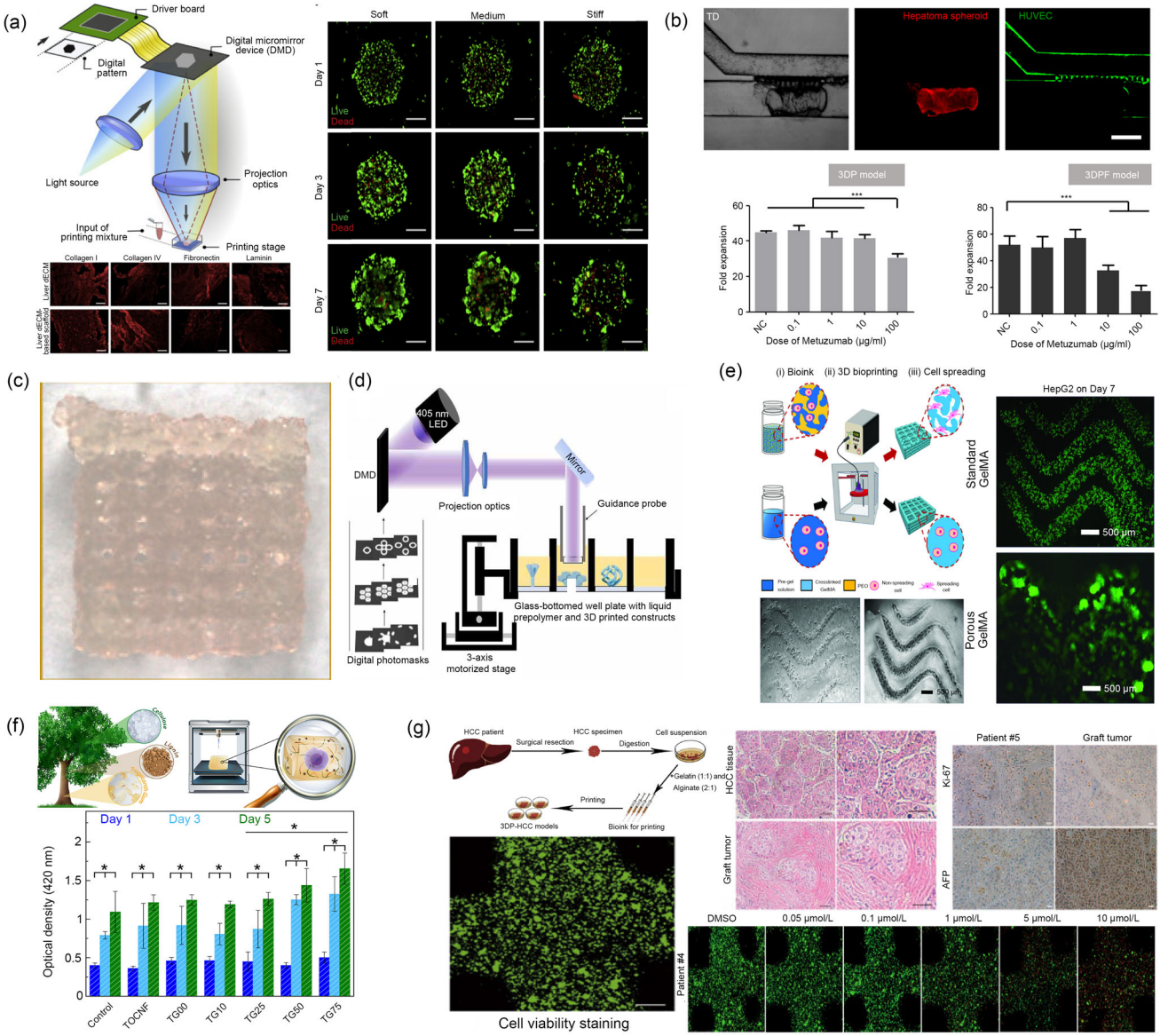


Fig. 4 3D bioprinting of HCC tumor models. **a** Schematic diagram showing the bioprinting of dECM-based hexagonal scaffolds and the characterization of HCC growth and invasion potential in dECM-based scaffolds with varied stiffness (adapted and modified from Ref. [64], Copyright 2018, with permission from Elsevier Ltd). **b** 3D bioprinting of HCC cells and microfluidic applications involved in the pharmacodynamic testing of Metuzumab (adapted and modified from Ref. [143], Copyright 2019, with permission from IOP Publishing Ltd). **c** 3D bioprinting of HCC cell models in antitumor drug research (adapted and modified from Ref. [44], Copyright 2020, with permission from the authors, licensed under CC BY). **d** DLP-based integrated 3D bioprinting platform prints of liver cancer cell models for high-throughput preclinical drug screening and disease modeling (adapted and modified from Ref. [144], Copyright 2021, with permission from IOP Publishing Ltd). **e** Novel bioink formulation based on gelatin methacryloyl and polyethylene oxide solutions for the printing of tumor cells, to study their cell viability, spreading, and proliferative capacity (adapted and modified from Ref. [145], Copyright 2018, with permission from WILEY–VCH Verlag GmbH & Co. KGaA, Weinheim). **f** Printing of HCC tumor models using plant-derived hydrogels (adapted and modified from Ref. [146], Copyright 2022, with permission from the authors, licensed under CC BY 4.0). **g** Patient-derived 3D bioprinted HCC (3DP-HCC) model and a study of its characteristics (adapted and modified from Ref. [147], Copyright 2020, with permission from Elsevier Ltd). HCC: hepatocellular carcinoma; dECM: decellularized extracellular matrix; DLP: digital light processing

By continuously improving the technology and conducting further research, we can enhance the clinical applications of liver cancer models and provide better treatment options for liver cancer patients.

Colorectal cancer

Currently, colorectal cancer is recognized as a serious disease that may affect human beings [112, 149]. Fibroblasts and endothelial cells enlisted from neighboring tissues comprise a complicated mesenchymal extracellular matrix that makes up the solid tumor microenvironment [150–152]. Tumor-associated endothelial cells are associated with tumor malignancy and metastasis [153], and in addition, tumor-associated endothelial cells (TECs) influence not only tumor metabolism [154] but also their tumor drug resistance [155]. Therefore, co-culturing of cancerous cells with TME-related cells is a unique method for analyzing different TME characteristics. TME-associated cells produced from normal cells can evolve into tumor-specific stromal cells under the control of tumor signaling. Due to their innate flexibility, TME-associated cells can be used to create in vitro 3D tumor models. For example, Chen et al. [156] developed a method for obtaining tumor-associated stromal cells and constructed a reproducible 3D colon cancer tissue model (3DT) using 3D printing, which constructed a scaffold that accommodated the three cellular components and allowed for straightforward direct cell-to-cell interactions and the formation of tissue network structures (Fig. 5a). Similar results were obtained using a coaxial bioprinted intestinal-like tissue body constructed by Han et al. [157] (Fig. 5b). In another study, Cadamuro et al. developed a protocol for the 3D bioprinting of colorectal cancer (CRC) models based on hyaluronic acid and signaling glycans, and demonstrated that these glycosylated hydrogels showed good 3D printability, biocompatibility, and long-term stability [158] (Fig. 5c). Furthermore, a 3D multicellular model consisting of SW480 cells, tumor-associated macrophages, and endothelial cells was constructed by 3D bioprinting, and biological activity was evaluated by immunofluorescence, hematoxylin and eosin staining of frozen pathological sections, and transcriptome sequencing, followed by the further application of the model to antitumor drug screening experiments based on the above results. It was found that the 3D printed-M group was significantly more resistant to chemotherapy as compared with the 3D printed-S group [159] (Fig. 5d). In another example, Sbirkov et al. constructed an affordable, flexible, and highly replicable 3D bioprinted CRC model that can be used for disease modeling and drug testing and in their work, this experimental platform was tested with three of the most commonly used chemotherapeutic drugs (i.e., 5-fluorouracil, oxaliplatin, and irinotecan), and the results suggested that it could provide innovative opportunities for personalized treatment screening [45] (Fig. 5e). The 3D tumor model exhibited a physiological state similar to that in vivo, in addition to being highly degree of drug resistance, enabling continuous long-term culture for monitoring and functional assessment. Burkholder-Wenger et al. [160] used hybrid nano-inks composed of alginate, GelMA, and cellulose nanocrystals (CNCs) which were thought to possess superior rheological and mechanical properties applied to fabricate complex multicellular in vitro intestinal cancer tumor models (Fig. 5f). Bowel CSCs are the root cause of tumor recurrence and metastasis, so therapies targeting tumor stem cells are the highest priority of treating related cancers. However, in vitro expansion and stemness maintenance of bowel CSCs remain relatively limited. To address this issue, Zhang et al. [161] found that hydrogels based on GelMA-nanoclay hybrid were capable of inducing and enriching colorectal CSCs in 3D bioprintable materials (Fig. 5g). However, it is still believed that the in vitro rebuilding of organoids from patient-derived tumor tissues may be the most effective method for simulating the genuine tumor microenvironment. With this in mind, Chen et al. [39] precisely aligned patient-derived colorectal tumors and healthy organoids via acoustic bioprinting methods and re-encapsulated the structure of primary tissues (Fig. 5h). These tumor-like organs can be generated efficiently and can present histological, genomic, and phenotypic primary tumor features, allowing physiologically relevant in vitro drug (5-fluorouracil) screening and thus prediction of response to patient-matched chemotherapy. These results illustrate the potential for precision and personalized medicine through the creation of 3D bioprinted bowel cancer tumor models of colorectal cancer. Briefly, this study created models using patient-derived colorectal cancer tumors via acoustic bioprinting, which enabled accurate reconstruction of the primary tumor microenvironment, and could therefore serve as an adjunctive diagnostic tool to guide clinical practice.

The 3D bioprinting of colorectal cancer models, as an important technology in the field of colorectal cancer research and treatment, can provide more realistic and accurate environments for colorectal cancer cells, thereby helping us to better understand the mechanisms of the disease and to evaluate the effectiveness of different treatment strategies. However, this technology also faces several challenges. First, producing colorectal cancer models requires high-precision printing techniques and sophisticated equipment. Second, further improvements in printing materials and processes are needed to improve the biological similarity and reproducibility of these models. In addition, the heterogeneity and individual differences of colorectal cancer increase the complexity of model design. Despite these challenges, 3D bioprinting of colorectal cancer models still holds tremendous potential. Through continuous research and technological advancement, we can use 3D bioprinting

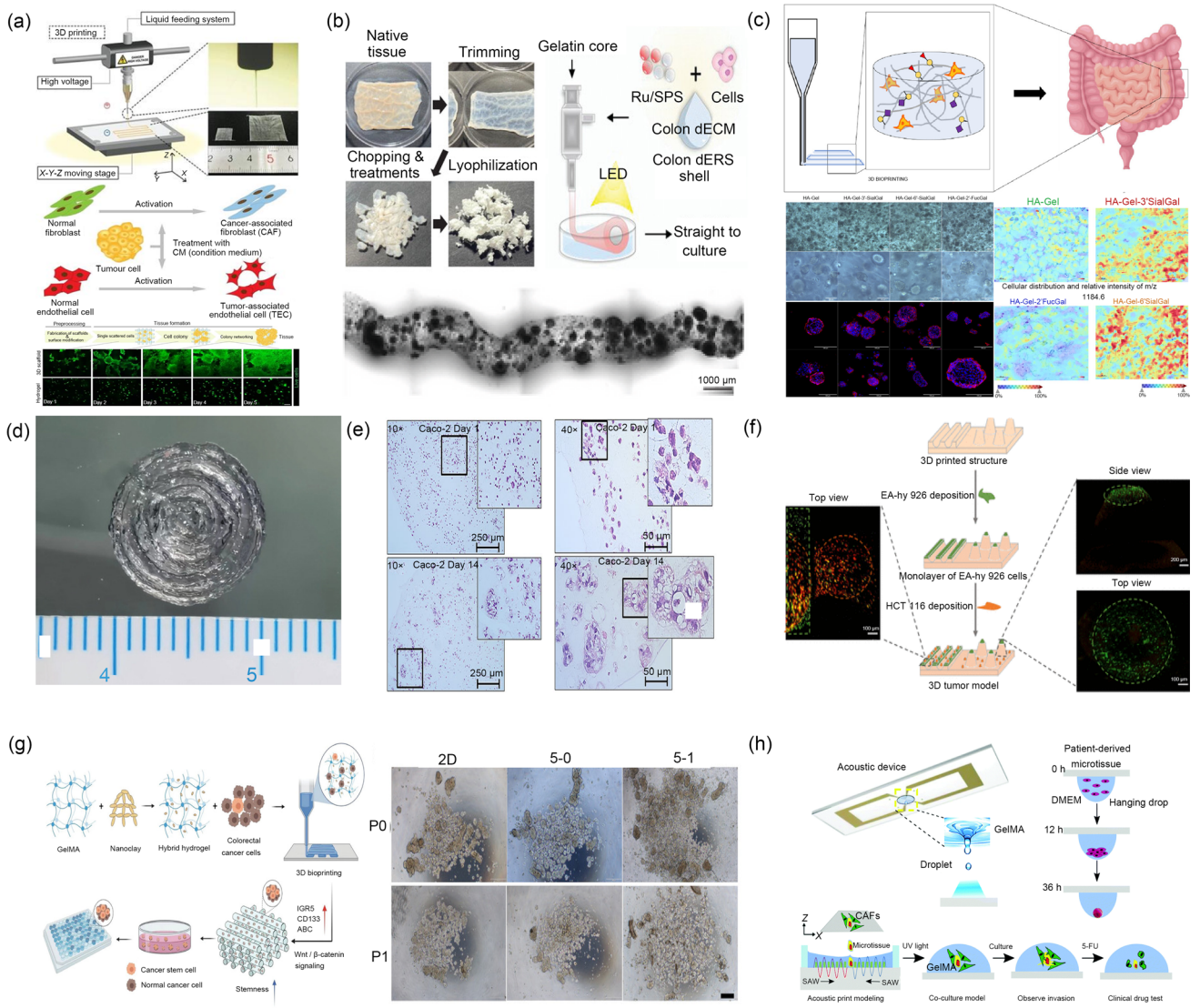


Fig. 5 3D bioprinting of colorectal cancer tumor models. **a** Flowchart of 3D printed colon cancer models and mechanisms of promoting cell function network formation (adapted and modified from Ref. [156], Copyright 2020, with permission from the authors, licensed under CC BY 4.0). **b** Bioprinted tubular bowel model using colon-specific extracellular matrix bioinks (adapted and modified from Ref. [157], Copyright 2021, with permission from Wiley–VCH GmbH). **c** 3D bioprinted colorectal cancer model based on hyaluronic acid and signaling glycans (adapted and modified from Ref. [158], Copyright 2022, with permission from the authors, licensed under CC BY-NC-ND 4.0). **d** Experimental results of antitumor drug screening using a 3D multicellular model (adapted and modified from Ref. [159], Copyright 2023, with permission from the authors, licensed under CC BY 4.0). **e** Drug testing results of a 3D printed CRC model using three of the most commonly used chemotherapeutic drugs (adapted and modified from Ref. [45], Copyright 2021, with permission from the authors, licensed under CC BY). **f** An illustration of hybrid nano-inks for multi-nozzle micro-extrusion 3D printing of tumor models (adapted and modified from Ref. [160], Copyright 2022, with permission from the American Chemical Society). **g** GelMA-nanoclay hybridized hydrogels induce and enrich colorectal CSCs (adapted and modified from Ref. [161], Copyright 2022, with permission from Wiley–VCH GmbH). **h** Acoustic bioprinting of patient-derived colorectal tumors and healthy organoids (adapted and modified from Ref. [39], Copyright 2022, with permission from The Royal Society of Chemistry). CRC: colorectal cancer; GelMA: gelatin methacryloyl; CSCs: cancer stem cells

of colorectal cancer models to gain a better understanding of the development process of colorectal cancer and provide more accurate and personalized treatment plans. This will lead to improved treatment outcomes and survival rates for patients with colorectal cancer.

Cervical cancer

The 3D bioprinted cervical cancer model is one of the earlier 3D bioprinted tumor models that have been investigated. In 2014, Sun's team at Tsinghua University [162] reported an extruded 3D bioprinting to construct an in vitro model of cervical cancer, which used Hela cells and a gelatin/alginate/fibrinogen hydrogel. The results showed that the cell viability was up to 90%, and the cells maintained a high proliferative activity with a tendency to form cell spheroids. The results also showed a significant increase in the secretion of matrix metalloproteinase (MMP)-2 and MMP-9 matrix metalloproteinases, which are associated with tumor invasive migration, compared to the 2D model (Fig. 6a). In addition, after treatment with the chemotherapeutic drug, a large number of apoptotic cells, irregular cell morphology, a loose cytoskeletal pattern, a significant decrease in the average diameter of cell spheroids, and significantly lower metabolic activity than that of the 2D control group could be observed in the 3D tumor model. This result was then validated by Gospodinova et al., who showed that Hela cells biofabricated by extruded 3D bioprinting of highly viscous and thixotropic hydroxyethyl cellulose-based hydrogel mixed with sodium alginate [163] performed similarly (Fig. 6b). In 2018, Sun's team [164] again reported a 3D bioprinted tumor sphere model based on gelatin, sodium alginate, matrix gel, and cervical cancer cells, which successfully induced the epithelial-mesenchymal transition (EMT) process in Hela cells via transforming growth factor β (TGF-β) (Fig. 6c). Moreover, they found that Smad2/3 was activated by the TGF-β treatment pathway and promoted the expression of the transcription factor Snail, which inhibits the expression of E-cadherin but induces the expression of vimentin and N-cadherin. In contrast, the use of disulfiram (DSF) and the EMT pathway inhibitor C19, which encloses TGF-β, can successfully inhibit the EMT of 3D bioprinted cervical cancer cells. Moreover, the EMT outcomes of 2D cultivated cells have been shown to differ from those of 3D bioprinting-based cervical cancer models, which are a novel model for assessing the efficacy of chemotherapeutic drugs used to treat cervical cancer. Recently, Becconi et al. [165] used platinum nano-electrodes and scanning electrochemical microscopy at high spatial resolution to characterize oxygen concentration in a tumor model, a crucial aspect of the cellular microenvironment (Fig. 6d). They also quantitatively measured drug molecule diffusion over time in a tumor model, which can be used in the future to evaluate the penetration and distribution of drugs in the body.

The 3D bioprinting of cervical cancer models also holds great potential in terms of application. Compared to traditional 2D cell culture models, 3D bioprinted models can better simulate the three-dimensional morphology and microenvironment of tumors, and therefore present more realistic biological characteristics. As a result, they can more effectively evaluate the efficacy of different treatment strategies. Similar to 3D bioprinting of colorectal cancer models, creating 3D bioprinted cervical cancer models requires high-precision printing techniques and complex equipment. Suitable printing materials and processes are necessary to simulate the in vivo environment of cervical cancer cells, which enhances the biological similarity and reproducibility of the models. Additionally, cervical cancer exhibits heterogeneity and individual differences, and this requires more detailed and personalized model designs. Overall, the research and application of 3D bioprinted cervical cancer models have broad prospects. They can help us better understand the mechanisms behind disease development and can help us to evaluate the effectiveness of different treatment strategies, ultimately providing more accurate and personalized treatment plans for patients.

Ovarian cancer

High-throughput automated 3D ovarian cancer model production is made possible by combining extracellular matrix and ovarian cancer cells using 3D bioprinting. Interestingly, the biofabrication of ovarian cancer models has been accomplished using droplet bioprinting techniques. For example, Xu et al. [166] used a droplet-based system to print OVCAR-5 (an epithelial human ovarian cancer cell line) ovarian cancer cells and MRC-5 (a normal human fibroblast cell line) normal fibroblasts in a controlled spatial distribution on Matrigel gel scaffolds to construct ovarian cancer microtissue organoid in order to study the feedback mechanisms between tumor and stromal cells and to provide a high-throughput drug screening tool (Fig. 7a). Wu et al. [167] used an extrusion bioprinting platform to biofabricate 3D ovaries (Fig. 7b). While the focus of that study was on isolated oocyte maturation, ovarian cancer cell lines were used in the process of optimizing the biocompatibility of the bioinks, and they showed high cell viability both during and after the extrusion process. In another study, Baka et al. optimized the bioinks while investigating a variety of biological characterizations of ovarian cancer, including viability and proliferation assays, histology, and immunological staining, which laid the groundwork for studies such as drug screening [168] (Fig. 7c). Lucà et al. [169] used extrusion bioprinting to demonstrate that murine double minute 4 (MDM4) was able to reduce the ability of ovarian cancer cells to migrate and disseminate, as

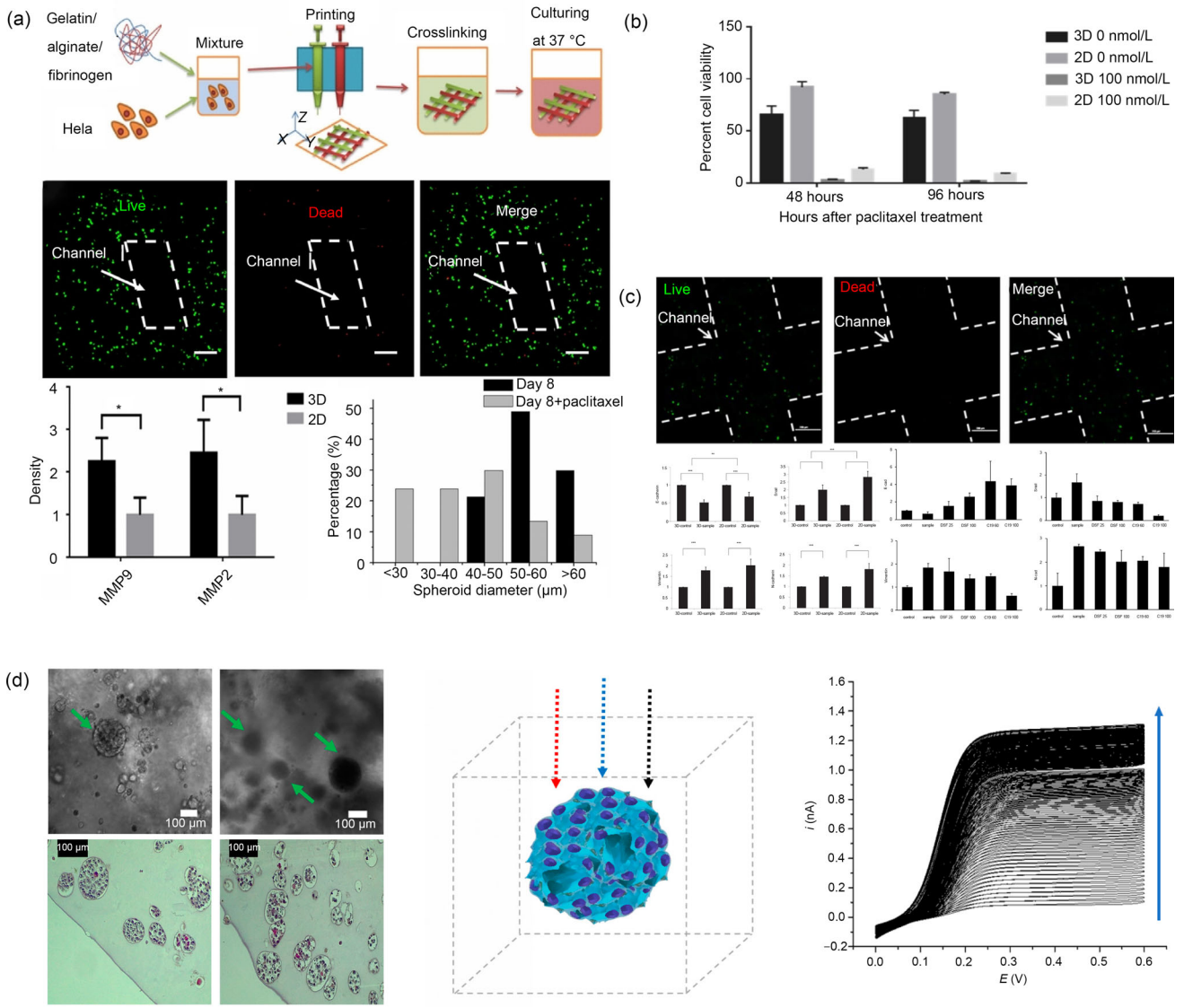


Fig. 6 A study of 3D bioprinted cervical cancer models. **a** 3D printing of Hela cells and gelatin/sodium alginate/fibrinogen hydrogels to construct an in vitro cervical cancer tumor model to study cell proliferation, MMP expression, and chemotherapy resistance (adapted and modified from Ref. [162], Copyright 2014, with permission from IOP Publishing Ltd). **b** Cell viability as determined 48 and 96 h after paclitaxel treatment (adapted and modified from Ref. [163], Copyright 2021, with permission from Elsevier Ltd). **c** 3D bioprinted in vitro model of cervical cancer used for the study of the EMT during cervical cancer metastasis (adapted and modified from Ref. [164], Copyright 2018, with permission from IOP Publishing Ltd). **d** Determination of the oxygen concentration in Hela spheres using micron spatially resolved scanning electrochemical microscopy for the construction of a drug diffusion model (adapted and modified from Ref. [165], Copyright 2023, with permission from the authors, licensed under CC BY 4.0). MMP: matrix metalloproteinase protein; EMT: epithelial-mesenchymal transition

well as that this impaired intravascular infiltration (Fig. 7d). Recently, Estermann et al. have proposed the creation of a 3D multicellular tissue model that offers a cutting-edge platform for researching how ovarian cancer cells spread and that may be crucial to the precise management of malignancies [170] (Fig. 7e). As an emerging biofabrication technology, 3D bioprinting in ovarian cancer models has been investigated less frequently. Although ovarian cancer cells have not been investigated using techniques including inkjet bioprinting, LAB, or stereolithography to date, these are promising techniques that, in combination with synthetic bioinks with improved printability properties, may permit the creation of high-throughput 3D cancerous ovarian cell models and facilitate high-throughput drug screening [171, 172].

Compared to traditional 2D cell culture models, 3D bioprinted ovarian cancer models have the advantage of better

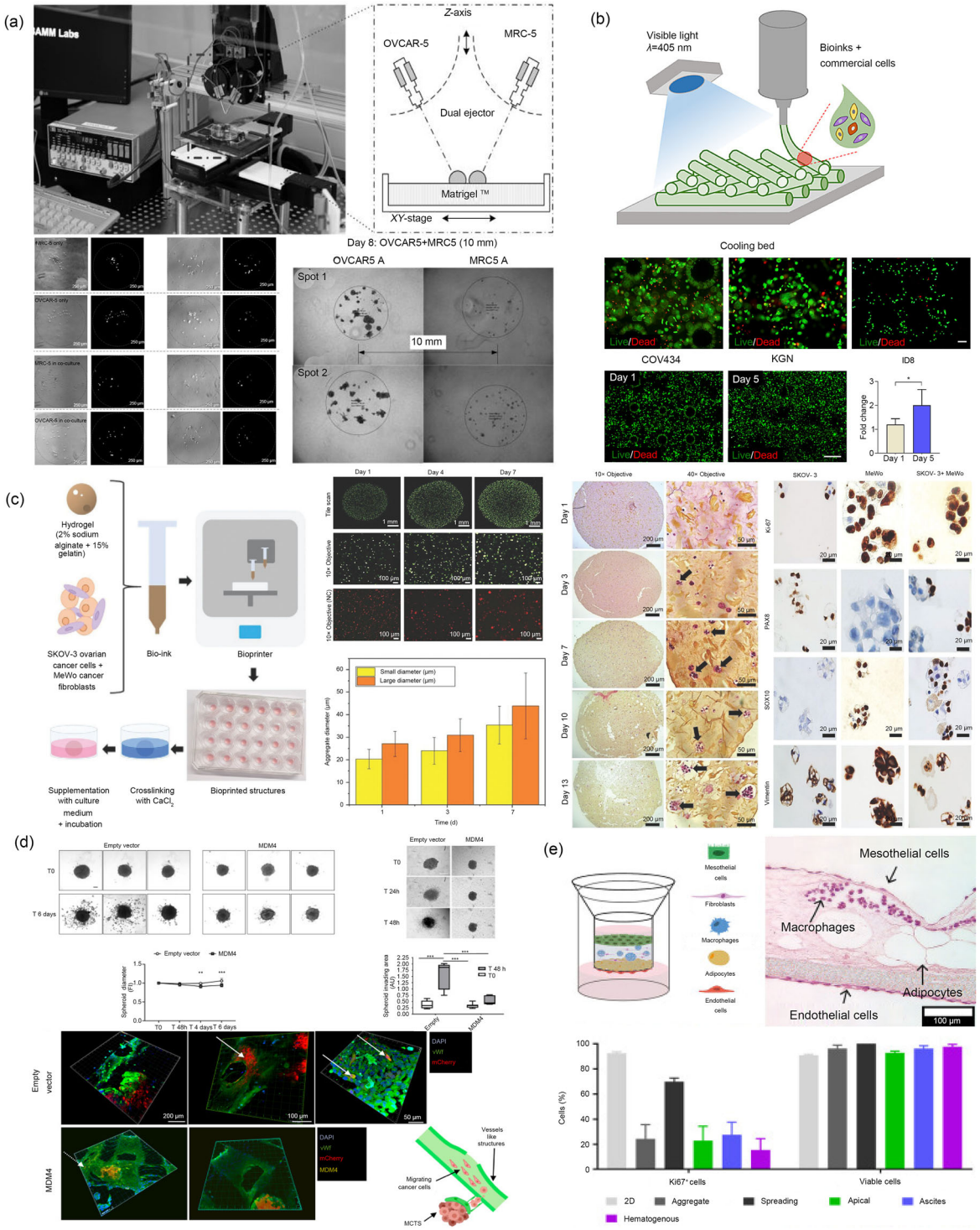


Fig. 7 A study of 3D bioprinted ovarian cancer models. **a** 3D printing of an in vitro co-culture model of ovarian cancer based on high-throughput cellular patterning, designed to study the feedback mechanism between tumor and stromal cells (adapted and modified from Ref. [166], Copyright 2011, with permission from Wiley–VCH Verlag GmbH). **b** Validation of GelMA-sodium alginate printing suitability by the shape and integrity of gel fibers printed with bioinks (adapted and modified from Ref. [167], Copyright 2021, with permission from the authors, licensed under CC BY-NC-ND 4.0). **c** 3D bioprinted ovarian cancer model to study tumor viability and proliferation as well as histological and immunological staining (adapted and modified from Ref. [168], Copyright 2023, with permission from Wiley–VCH GmbH). **d** Extruded bioprinted tumor model confirms the ability of MDM4 to reduce ovarian cancer cell migration and propagation (adapted and modified from Ref. [169], Copyright 2021, with permission from the authors, licensed under CC BY 4.0). **e** A 3D multicellular tissue model (adapted and modified from Ref. [170], Copyright 2023, with permission from the authors, licensed under CC BY 4.0). GelMA: gelatin methacryloyl; MDM4: murine double minute 4

simulating the three-dimensional morphology and microenvironment of tumors, presenting more realistic biological characteristics, and thus can better evaluate the effectiveness of different treatment strategies. However, when creating a 3D bioprinted ovarian cancer model, it is necessary to carefully select appropriate printing materials, processes, and equipment to simulate the complex biological environment of ovarian cancer cells within the body. In addition, ovarian cancer exhibits heterogeneity and individual differences, therefore requiring more detailed and personalized designs to create accurate models. To address these issues, researchers need to continuously explore and improve the technology to enhance the biological similarity and repeatability of 3D bioprinted ovarian cancer models. Further research on 3D bioprinted ovarian cancer models can provide more accurate and reliable models for the early detection of ovarian cancer, the formulation of treatment plans, and the development of new drugs. However, further exploration and improvement in technology and research are still needed in order to fully realize the potential of 3D bioprinting and bring greater benefits to patients.

Neuroblastoma

Early childhood neuroblastoma is an extracranial solid tumor with a poor prognosis. Finding patient-specific medication responses in tissue models that replicate the interaction between patient cancer cells and the tumor environment is one method for increasing cure rates. For example, Wu et al. [173] demonstrated the value of using 3D tumor models in humans for the study of anticancer drugs by using pneumatic extrusion bioprinting to fabricate a renal neuroblastoma model and evaluate the efficacy of two chemotherapeutic drugs (Fig. 8a). In another study, Nothdurfter et al. [174] developed a perfused and microvascularized tumor microenvironment model that could be directly bioprinted into a microfluidic fluidic chip, thus constructing a bioprinted microvascularized neuroblastoma-tumor-environment model, providing a novel medium-throughput biofabrication platform for future precision medicine research on cancer angiogenesis and migration (Fig. 8b). In another study, Monferrer et al. [175] used methacrylated alginate to study the relationship between the physicochemical signals of SK-N-BE (2) neuroblastoma cells and the hardness of the printable hydrogel, and used the model to extrapolate the potential of how the spatial hardness of the hydrogel could drive aspects of clinical behavior relevant to neuroblastoma patients (Fig. 8c). Similarly, López-Carrasco et al. investigated the effect of extracellular matrix stiffness on the genomic heterogeneity of neuroblastoma cells [176]. Bordoni et al. [177] prepared bioinks based on cellulose nanofibers (CNFs), alginate, and single-walled carbon nanotubes (SWCNTs) for the 3D bioprinting of conductive scaffolds in freeform reversible embedding hydrogels (FRESH) (Fig. 8d). These findings show that conductivity, with or without differentiation stimulation, enhances the division of human neuroblastoma carcinoma cells, as evidenced by the SH-SY5Y cell line. Taken in context, this study improves our understanding of the pathogenic processes behind neurodegenerative illnesses and offers a novel method for building simulated 3D brain models in vitro.

The 3D bioprinting of neuroblastoma models is a highly promising research field. Creating a 3D bioprinted neuroblastoma model requires careful selection of suitable printing materials, processes, and equipment to accurately simulate the tissue structure and cellular interactions of neuroblastoma. In addition, the heterogeneity and individual differences involved in particular neuroblastoma cases must be considered during model design to ensure that they are both representative and reliable. Although research on 3D bioprinted neuroblastoma models remains at an early stage, its prospects are promising. This technology has the potential to provide more accurate and reliable models, thereby aiding in developing a deep understanding of neuroblastomas and more effective treatment methods. However, continuous exploration and improvement in both technology and research are required to overcome current challenges and further advance this technology. In brief, 3D bioprinting of neuroblastoma models is an exciting field with tremendous potential. Through ongoing research and innovation, we hope to pave new pathways for the understanding and treatment of neuroblastoma, ultimately benefiting patients.

Other tumor models

In addition to the types listed above, 3D bioprinted tumor models have been developed to study other human tumors, including those for pancreatic cancer, lung cancer, kidney cancer, bone cancer, osteosarcoma, skin cancer, pituitary tumors, and leukemia. The most frequent malignant pancreatic tumor is pancreatic ductal adenocarcinoma (PDAC). Due to the inability of existing 2D cell culture models to mimic the three-dimensional complexity of pancreatic tissues, Hakobyan et al. [178] created arrays of 3D pancreatic cell spheroids using laser-assisted bioprinting and characterized their phenotypic evolution over time through image analysis and phenotypic characterization (Fig. 9a). Moreover, the data showed that the bioprinted spheres made of follicular and ductal cells were found to be able to mimic the early phases of PDAC development. This model could therefore offer a fresh perspective for potential PDAC therapeutic interventions. In another study, Wang et al. [179] used cryo-molded 3D bioprinting to construct a 3D tumor model of pulmonary carcinoma that could maintain activity for up to 28 days in vitro and confirmed at the molecular level that

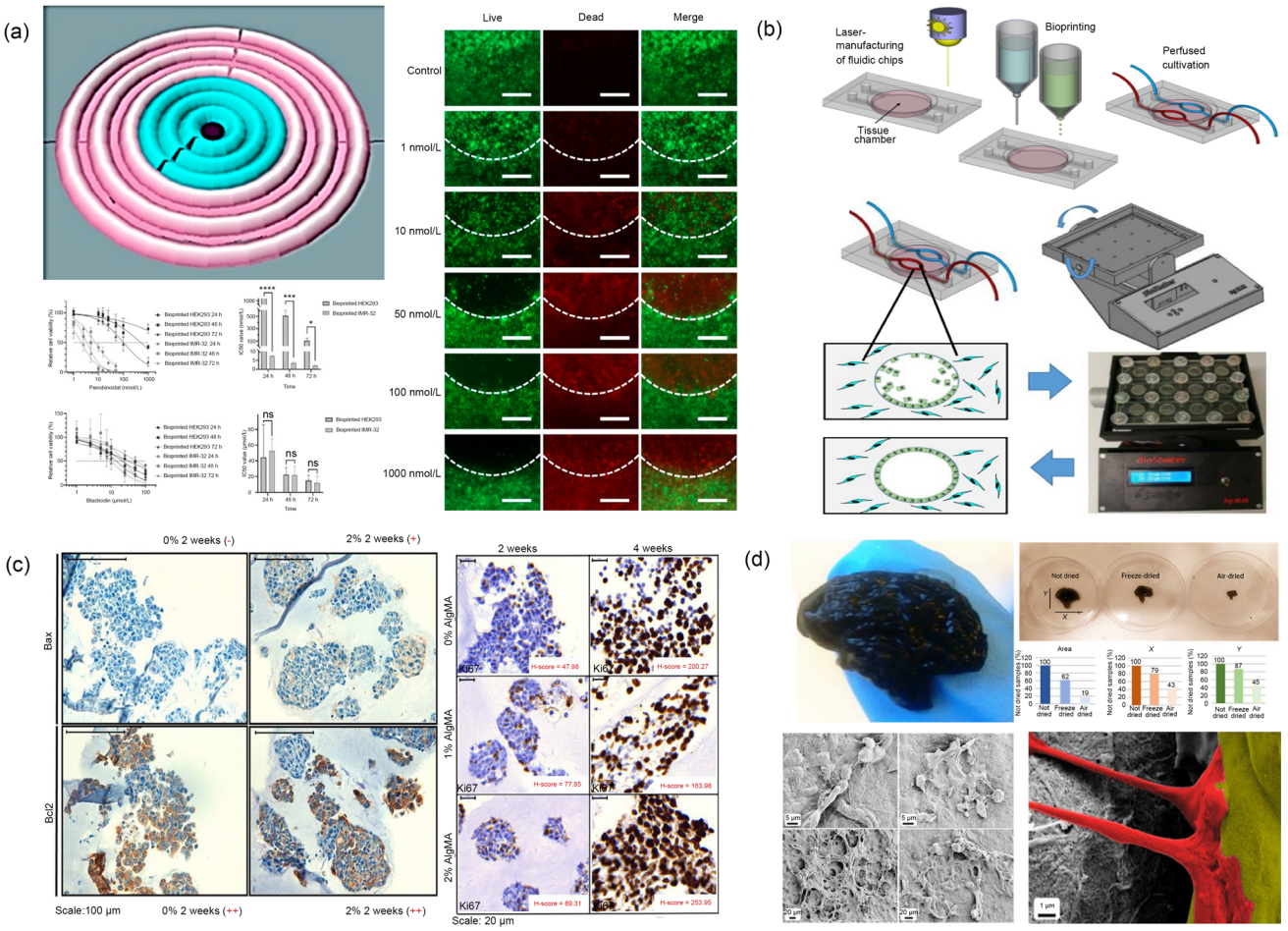


Fig. 8 A study of 3D bioprinted neuroblastoma models. **a** A renal neuroblastoma model created by pneumatic extrusion bioprinting to assess the effects of two chemotherapeutic agents (adapted and modified from Ref. [173], Copyright 2021, with permission from the authors, licensed under CC BY 4.0). **b** A tumor microenvironment model for perfusion and microvascularization (adapted and modified from Ref. [174], Copyright 2022, with permission from the authors, licensed under CC BY 4.0). **c** 3D bioprinted model to assess the effect of hydrogel hardness on neuroblastoma cell cluster dynamics and behavior (adapted and modified from Ref. [175], Copyright 2020, with permission from the authors, licensed under CC BY 4.0). **d** Freeform reversible embedding hydrogels (FRESH) 3D bioprinted conductive scaffolds based on CNF, alginate, and SWCNT (adapted and modified from Ref. [177], Copyright 2020, with permission from the authors, licensed under CC BY 4.0). CNF: cellulose nanofiber; SWCNT: single-walled carbon nanotube

lung cancer cells demonstrated enhanced invasiveness and migration (Fig. 9b). Herrada-Manchón et al. used a similar approach to bioprint a 3D model of renal cancer that survived for at least 15 days in vitro and self-assembled within hydrogels to build similar functionalized tunneling nanotube-like structures [180] (Fig. 9c). Another study showed that for alginate/gelatin hydrogels, the addition of bioglass increased the proliferation and mineralization of bioprinted SaOS-2 cells [181], but these osteoblast-like cells, when cultured in vitro, could be directly transformed into osteosarcoma-like models [182]. In addition, many bone microenvironment-based models of metastatic cancer have been reported; these include breast cancer bone metastasis models [183, 184] and prostate cancer bone metastasis models [185, 186]. In another study, Wu et al. used coaxial bioprinting to construct a 3D model of multiple myeloma in vitro that can release interleukin 6 (IL-6). The authors then used trials to explore related targeted sensitizing drugs [187] (Fig. 9d). In order to create an in vitro melanoma micro-model, Duan et al. [188] used 3D printing to create GelMA/polyethylene (glycol) diacrylate (PEGDA) scaffolds made of composites, which resembled the environmental conditions associated with human malignancy in melanoma cell (A375) growth (Fig. 9e). Based on this model, it was discovered that lignocaine's effects on melanoma cells were time- and dose-dependent and that tumor cells in the 3D culture system became increasingly insensitive toward the drug. Diao et al. [189] constructed a growth hormone pituitary adenoma model using extrusion bioprinting. Subsequent comparisons revealed that pituitary adenoma cells in the 3D environment exhibited more active

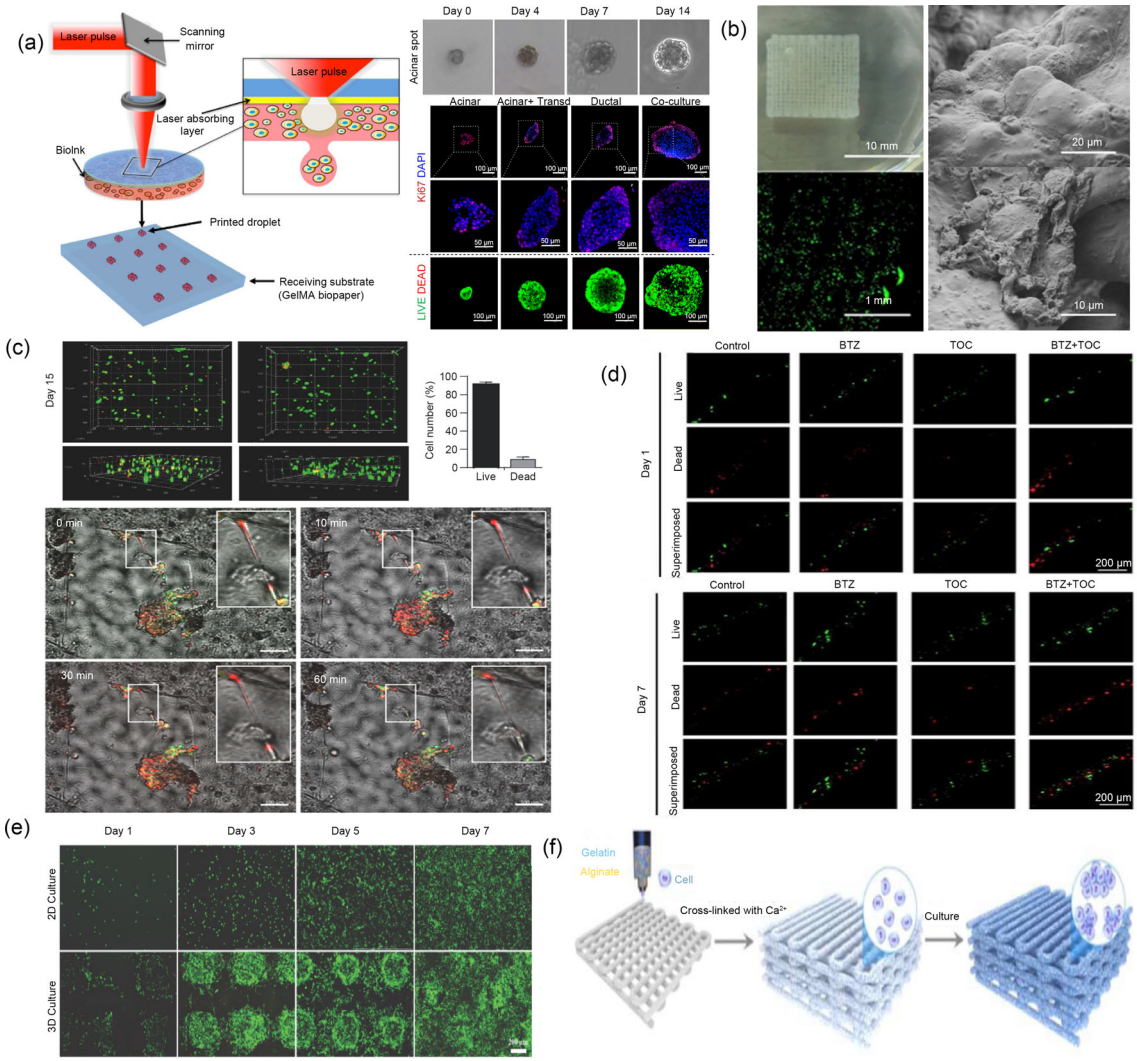


Fig. 9 3D bioprinting of multiple cellular tumor models. **a** LAB for fabricating 3D pancreatic cell sphere arrays (adapted and modified from Ref. [178], Copyright 2020, with permission from IOP Publishing Ltd). **b** Cryoprinting for constructing 3D tumor models of lung cancer to study the invasiveness and migration of lung cancer cells (adapted and modified from Ref. [179], Copyright 2018, with permission from Springer-Verlag GmbH Germany, part of Springer Nature). **c** 3D bioprinting for constructing kidney cancer models that self-assemble within hydrogels to build functionalized tunneling nanotube-like structures (adapted and modified from Ref. [180], Copyright 2021, with permission from Elsevier B.V.). **d** Coaxial bioprinting for constructing 3D models of multiple myeloma in vitro and exploring targeted sensitizing drug trials (adapted and modified from Ref. [187], Copyright 2021, with permission from Wiley–VCH GmbH). **e** In vitro construction of a melanoma micromodel used to study drug resistance (adapted and modified from Ref. [188], Copyright 2022, with permission from the authors, licensed under CC BY). **f** Extrusion bioprinting for constructing a growth hormone pituitary adenoma model to study its intrinsic characteristics (adapted and modified from Ref. [189], Copyright 2019, with permission from IOP Publishing Ltd). LAB: laser-assisted bioprinting

cell cycle progression, secretion, proliferation, invasion, and tumorigenesis. These findings may help future studies of the etiology and treatment of pituitary adenomas (Fig. 9f). In addition, by combining hydrogel with leukemia cells to create cell-containing scaffolds, Sbrana et al. [190] were able to 3D bioprint tumor model containing leukemia cells effectively, improve their in vitro viability, which could be maintained for up to 28 days, and create reproducible models of long-term 3D culture. The overall results were an effective in vitro model of chronic lymphocytic leukemia. Further RNA sequencing (RNAseq) analyses revealed changes in gene expression patterns between 2D and 3D samples, thereby demonstrating that cells behave differently in two distinct culture settings. This will make it possible to conduct more reliable investigations of the molecular and cellular interactions that take place in vivo under both benign and malignant leukemia conditions. Finally, this model may also

be applied clinically to assess how different individuals react to medications.

The development of 3D bioprinting of tumor models has been widely regarded as a significant advancement in medical research. By creating more realistic and reliable tumor models, researchers can better understand the biological characteristics, progressions, and treatment responses of tumors. This will help accelerate drug screening and development, and improve the personalization and precision of various treatments. On the other hand, concerns have been raised regarding the ethical and legal issues that may raise from the 3D bioprinting of tumor models. Furthermore, the development of 3D tumor model bioprinting faces substantial technical challenges and cost issues. The current technology remains at an early stage and requires constant improvement and innovation to enhance model accuracy and reliability. Overall, 3D bioprinting of tumor models remains a promising research field and offers better tools for the study of tumors. More importantly, it also lays the foundation for the future development of personalized treatments.

Applied research using 3D bioprinted tumor models

Construction of the tumor microenvironment

The milieu in which tumor cells thrive is known as the tumor microenvironment; it is closely related to carcinogenesis, tumor development, invasion, and metastasis (Fig. 10). It typically consists of tumor cells, malignant vessels, stromal parts, and host immune cells. Constructing simulated 3D tumor microenvironments can facilitate improvements in basic tumor research and anticancer drug screening. Conventional 2D models are unable to accurately simulate the tumor microenvironment, especially regarding oxygen and nutrient availability, and are therefore strongly restricted in their capacity to act as effective models for fundamental tumor biology research or during the evaluation of anticancer drugs [194, 195]. In a computer-controlled layer-by-layer printing process, 3D bioprinting enables the precise localization of cells and biomaterials and preserves cell viability [3]. As a result, it is viewed as a viable route for developing tissue architectures that capture the complicated nature of the tumor microenvironmental compositions and geometries [196]. For instance, in less than five days of culture, multicellular spheroids were developed in hydrogel grids that were uniformly loaded with Hela cells, a cervical cancer cell line, and the tumor cells in this 3D environment were more resistant to the antitumor chemotherapeutic drug paclitaxel than in a 2D environment [162]. In addition, 3D bioprinted microarray tumor models have replicated the specificity and diversity of patient responses to radiation in clinical settings and have described the biochemical and biophysical features of glioblastomas [78]. Using 3D printing, breast cancer cells, peripheral blood mononuclear cells, and fibroblasts were created in the same hydrogel milieu to study the self-assembly and co-culture of various cell types [197]. Although no existing model tissues can exactly duplicate every aspect of the tumor microenvironment, the majority of them offer insightful information about tumor biology.

Tumor vascularization

Compared to traditional methods for studying tumor angiogenesis (including 2D culture and animal models), 3D culture-based approaches provide tumor cells with the geometry and microenvironment required for cell growth in vivo, promote cell–cell and cell–ECM interactions, and are overall closer to in vivo tissues in terms of cell proliferation, migration, invasion, cell signaling, and gene expression, which lays the foundation for studying the mechanisms of tumor angiogenesis and development in Fig. 10 [107, 198–201].

Numerous 3D models have been created recently by researchers to explore malignant angiogenesis. Wang et al. [202] developed a 3D hydrogel co-culture model containing glioma cells and endothelial cells. The use of a porogenic agent caused endothelial cells to form vascular-like structures in the 3D hydrogel. The findings demonstrated that the 3D model dramatically boosted glioma cell proliferation while considerably reducing the expression of endothelial cell adhesion proteins. In another study, Meng et al. [203] constructed a 3D model containing tumor cells, human umbilical vein endothelial cells (HUVECs), and fibroblasts using gelatin-methacrylic acid bioinks. They then studied tumor vascularization via laser-induced loading of vascular endothelial growth factor (VEGF)/EGF capsules, which facilitated the slow release of vascular growth factors to form a chemical concentration gradient. Understanding endothelial cell vascularization in the constructed 3D tumor angiogenesis model requires better utilization of the biological functions of tumor cells in the co-culture system. This is because tumor cells can participate in tumor angiogenesis by means other than direct transdifferentiation into endothelial cells [204]. Furthermore, by secreting vascular growth factors on their own, tumor cells can attract and persuade peripheral endothelial cells to take part in tumor neovascularization [205]. Hence, the key to understanding tumor angiogenesis is to build a model that optimizes the fundamental biological characteristics of tumor cells. Chen's [206] model of a perfusable vascular network was created using a 3D bioprinting platform. In the research, mouse fibroblasts and HUVECs were co-cultured, and both single and multicellular sprouts were shown to move from the created vascular network into the matrix gel. Sousa et al.

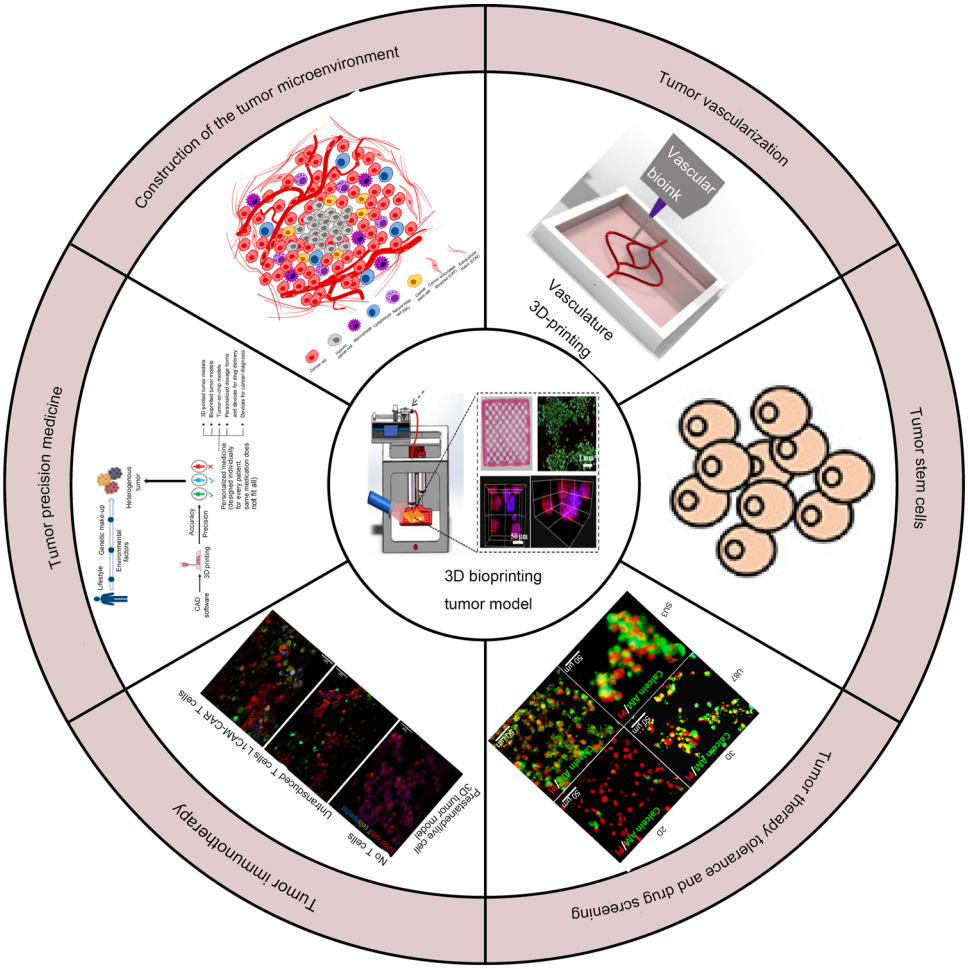


Fig. 10 Schematic of an application study of 3D bioprinted tumors. Shown are: construction of the tumor microenvironment (adapted and modified from Ref. [191], Copyright 2021, with permission from the author, licensed under CC BY 4.0); tumor vascularization (adapted and modified from Ref. [110], Copyright 2021, with permission from the authors, licensed under CC BY-NC); tumor stem cells (adapted and modified from Ref. [102], Copyright 2022, with permission from the American Chemical Society); tumor therapy tolerance and drug screening (adapted and modified from Ref. [100], Copyright 2016, with permission from IOP Publishing Ltd); tumor immunotherapy (adapted and modified from Ref. [192], Copyright 2021, with permission from the authors, licensed under CC BY); tumor precision medicine (adapted and modified from Ref. [193], Copyright 2021, with permission from the authors, under exclusive licence to American Association of Pharmaceutical Scientists); and a 3D bioprinted tumor model (adapted and modified from Ref. [134], Copyright 2022, with permission from IOP Publishing Ltd)

[207] simulated vascular basement membranes by combining 3D printing with layered assembly techniques to embed biologically active 3D multilayered microchannels in light-cured hydrogels and planted endothelial cells in them to construct tissue vascularization networks. However, these attempts have mainly focused on the use of 3D printing technology to create geometries that resemble vascular systems. In contrast, 3D bioprinting of tumor cells, especially the relevance and function of 3D bioprinted tumor cells in relation to tumor angiogenesis, has not received much attention. However, some studies have made important findings. For example, Wang et al. [99] constructed gelatin/sodium alginate/fibrinogen hydrogel scaffolds loaded with glioma cells U118 using 3D bioprinting technology, and found that the content of VEGF in the cultured glioma cells increased in the 3D bioprinted tumor model, which suggested that the tumor model created by 3D bioprinting might deserve to be investigated for the vascularization of tumors. The 3D bioprinted tumor model could better mimic the in vivo tumor microenvironment than the traditional 2D culture. In further studies, Wang et al. constructed a 3D bioprinted tumor model of glioma stem cells and found that the microenvironment provided by this model not only promoted the growth and proliferation of stem cells, but also enhanced the ability of glioma stem cells to secrete VEGF, the expression of

genes related to tumor angiogenesis, and in vitro vascularization [98]. In addition, current research indicates that 3D bioprinted glioma cells may be able to transdifferentiate into endothelial cells [208].

Tumor stem cells

The capacity to renew themselves and create diverse tumor cells is possessed by tumor stem cells, which are crucial for the survival, growth, metastasis, and recurrence of cancers (Fig. 10) [209]. When researching the biological activity of tumor stem cells, having an accurate 3D model of tumor stem cells is crucial. Investigations have demonstrated that 3D bioprinted glioma stem cells showed more stable proliferation than typical suspension cultured glioma stem cells, presumably because 3D bioprinted cells have more numerous mitochondria and rough endoplasmic reticulum in their stem cells as well as a significant number of long microvilli on their cell surface. In addition, in vitro 3D bioprinted glioma stem cells have been found to have higher cell stemness, higher expression of tumor angiogenesis-related genes, and greater angiogenic potential than those developed under suspension culture conditions [98]. Using a 3D printing platform, Herreros-Pomares et al. [210] created a non-small cell carcinoma model of lung cancer and discovered that the proliferation profile of tumor stem cells was enhanced on rigid scaffolds compared to culture on hydrogel scaffolds or tumor spheroids. However, tumor stem cells grew better in hydrogel scaffold or tumorsphere culture. Further gene expression analysis showed that the majority of the stemness and invasion promoters evaluated were more strongly expressed by tumor stem cells in 3D hydrogel scaffolds compared to control cells in 2D culture, according to gene expression analyses. Taken together, these findings demonstrate that, relative to in vivo 2D culture models, 3D printed hydrogel scaffolds may more accurately replicate the complexity of tumors and may more accurately control the biological activities of tumor stem cells. Wang et al. constructed a glioma model by 3D bioprinting using gelatin/sodium alginate/fibrinogen as biomaterials to enrich glioma stem cell-like cells. Compared with the traditional 2D culture model, the proportion of stem cell-like cells, the expression of stem cell biomarkers, and the expression of epithelial-mesenchymal transition-related genes in glioma cells cultured in 3D bioprinted hydrogel scaffolds were all significantly increased. Moreover, glioma cells produced on 3D bioprinted scaffolds made of hydrogel exhibited increased tumorigenicity and stronger treatment resistance in vitro. The hypoxic environment and the activation of EMT together promoted the enrichment of glioma stem cell-like cells. Finally, it was shown that the hydrogel microenvironment constructed using 3D bioprinting provides a promising new platform for glioma stem cell enrichment studies [99].

Tumor therapy tolerance and drug screening

Surgical excision along with radiation, chemotherapy, and additional complete therapies is the primary form of treatment for the majority of cancers. Nevertheless, some malignant tumors, such as glioblastoma, are not ideally treated with post-surgical radiotherapy, and the recurrence of malignant tumors is mostly due to the resistance of tumor cells to chemotherapeutic treatments. Since the 2D culture model of traditional methods for studying tumors has many defects, the creation of an optimal in vitro model is required to investigate the drug resistance and invasiveness of tumor cells.

Compared to traditional 2D cell culture techniques, 3D tumor models are better able to realistically emulate the tumor microenvironment, which can help to further elucidate the basic mechanisms of tumorigenesis and development, better study the behavior of tumor cells, more efficiently screen drugs, and develop more effective clinical treatments (Fig. 10). Basic research on 3D bioprinted tumor models is expected to be a bridge to actual clinical diagnosis and treatment. In the future, we may create customized tumor models for patients using 3D bioprinting technology, evaluate the effects of drug therapy in vitro, offer details on the best medication kind and dose, and create customized tumor therapies for patients. By reproducibly producing 3D cell-hydrogel structures, bioprinting technology has been able to address these criteria and produce intricate, high-throughput disease models. These models incorporate extracellular stressors and component regulation, pharmacological therapy, and studies of illness development, all of which might be helpful in better comprehending and eventually treating disease. A high-throughput bioprinted spherical system for disease modeling has been developed by Nano3D Biosciences. Its commercial equipment uses magnetic 3D bioprinting to create spheres for up to 384-well plates. Publications based on its 3D bioprinting system technology include, among other things, cancer disease models and toxicity screening. Another private firm, Organovo, is a publicly traded company in the pharmaceutical industry which produces a wide variety of tissue-engineered, bioprinted high-throughput models for drug screening. Moreover, it creates cancer disease and screening models that use a variety of cell types and associated ECM components to bioprint tumor models and form microcapillaries. These are then subjected to chemotherapy testing and high-throughput drug screening.

Tumor immunotherapy

One of the characteristics of cancer and a frequent occurrence in the tumor microenvironment is tumor immune escape [211]. Therefore, targeted therapy focusing on immune cells has become the most promising antitumor therapy

(Fig. 10) [212]. Compared with traditional cell culture technology, the 3D bioprinting platform technology can achieve the model construction of the multicellular complex tumor immune microenvironment, so its use for in vitro immune-targeted therapy for tumor research and development is highly expected.

The most promising treatment option for autoimmune disorders, cancer, and infections is now T-cell immunotherapy. T-cell therapies cannot, however, be widely used due to ineffective growth, functional flaws of isolated cells, and high cost of these treatments. Given these limitations, the development of an affordable, easily expandable, and accessible method for maintaining a population of T cells so that immune cells maintain good cancer-targeting function remains an important priority. In one study, Delalat et al. [213] used 3D-printed highly-organized micrometer lattice structures functionalized by plasma polymerization to bind monoclonal antibodies that cause cell proliferation to facilitate the expansion of therapeutic human T cell subsets, including regulatory, effector, and cytotoxic T cells, while maintaining the correct phenotype. The cell expansion platform is easy to use, accelerates cell recovery and expansion, and promises to be an ideal way to move T-cell therapies from the laboratory to the clinic. Chimeric antigen receptor (CAR) T cells are the current hotspot for tumor immunotherapy, but CAR-T therapy also faces the validity of 2D cell therapy in vitro, while animal and clinical trials are often unsatisfactory, and the validity of CAR-T therapy in 3D solid tumors is only more convincing. For example, a 3D neuroblastoma tumor model was created via bioprinting by Grunewald et al. [192] for the preclinical validation of CAR-T cell effector function targeting L1 cell adhesion molecule (L1CAM). According to these findings, the 3D model exhibited greater activation of L1CAM-specific CAR-T cells by neuroblastoma cells than the 2D co-culture did. Bioprinted 3D neuroblastoma models are a superior in vitro analytical tool for preclinical CAR-T cell characterization and may be even better at selecting CAR-T cells capable of exerting their effects in vivo than in 2D culture. They are suitable for detecting and quantifying CAR-T cells infiltrating in tumors, and can speed up preclinical testing, reduce costs, and minimize animal use.

Kim et al. [214] developed a bladder cancer microarray including tumor cells, vascular endothelial cells, and immune cells to mimic the tumor microenvironment using 3D bioprinting and microfluidics. They then assessed the immune response of this tumor model to different concentrations of Bacillus Calmette-Guerin (BCG) vaccine by THP-1 monocyte migration and determined the concentrations of various growth factors and cytokines. Briefly, the use of 3D bioprinted bladder cancer for BCG immunotherapy applications is expected to be an effective tool for analyzing drug responses, opening up new directions for the development of precision medicine for tumor immunotherapy as well as for the utilization of patient-derived cancer cells for tailored therapeutic applications.

Tumor precision medicine

Precision medicine in oncology is a therapeutic approach based on genetic information that is tightly linked to the tumor disease's pathogenesis (Fig. 10). In general, it is a tool that clinicians can use to determine the most appropriate treatment of a patient's tumor. For instance, there may be specific mutations directly associated with tumorigenesis that should inform treatment. However, not all mutations are therapeutically relevant, but they can provide information on disease characterization since they are major drivers of pathology. In this context, the use of in vitro simulated 3D tumor culture models allows tumor tissue to be extracted from patients for culture and extended to in vitro 3D tumor models for study, while still maintaining parental genotype characteristics in vivo [172, 215]. Moreover, a variety of patient-specific tumor disease models may be produced using 3D bioprinting and human-derived tumor tissue or cells. These models can be used independently or in conjunction with clinical trials through precision medicine initiatives. Precision medicine not only helps patients in the short term, but also collects large amounts of data for long-term studies of disease progression and responses to drug therapy. Thus, precision medicine, which is defined as individualized diagnosis and treatment using strategies that target patient- or disease-specific genetic, proteomic, and phenotypic traits [216], is critical for the success of patient-directed diagnosis and treatment. The behavior, progression, and response to pharmacological therapy of patient cell populations have all been better understood using 3D cell culture models than using alternatives. For example, these models can be used to predict how primary cultured cells and patients will respond to treatment since they use fewer cells to replicate the in vivo milieu. In addition, patient cells can be used to make customized models that are better suited to a patient's particular tumor than commercial cell lines, mostly because each patient has a unique set of one or more mutations. These mutations offer insight into genetic variants, cell type mixtures, and patient-specific variants. This allows investigators and patients alike to have additional personalized knowledge of the state of their specific illness.

At present, the adoption of 3D bioprinted tumor models by precision medicine protocols remains in its early stages [217]. In vitro 3D cell cultures involve the isolation of tissue directly from the patient, followed by further single-cell isolation and ECM reconstruction. Moreover, to obtain whole lineage cell types and ECM components from patient-diseased tissue or biopsies, cells can be isolated and expanded

in 2D culture. In addition, patient cell expansion is necessary for high-throughput 3D bioprinting precision medicine applications since this enables the simultaneous fabrication of numerous replicable 3D culture systems [193]. However, it is difficult to expand patient cells from tissues, particularly when dealing with large cell numbers, the tumor microenvironment, whole cell lineages, and stromal components. Culture expansion using human induced pluripotent stem cells (hiPSCs) before differentiation to produce millions of cells that differentiate into the desired diseased cell type may be a useful alternative. Although current methods have limitations, since expansion takes time and may produce tumor models that lose important parental characteristics, it remains the best option. Precision medicine is an emerging field of great interest to clinicians, patients, and researchers. In the future, many clinical oncology patients may receive precision medicine therapies thanks to the application of 3D bioprinting in tumor disease prediction models and high-throughput drug screening [22, 218].

Challenges and perspectives

Early bioprinted tumor models were relatively simple, and typically involved the arrangement and assembly of tumor cells or other relevant cell types using bioprinting technology to form a basic tumor structure. However, these models lacked the complex reconstruction of the tumor microenvironment. In contrast, current 3D bioprinted tumors offer several advantages in terms of complexity, biological similarity, controllability, and suitability for application in clinical settings. They can more accurately simulate the tumor microenvironment by adjusting printing parameters and cell assembly, thereby achieving consistent and comparable tumor models. To date, bioprinted tumors have been widely used in areas such as drug screening, personalized medicine, and surgical simulation, where they play a crucial role in advancing tumor research and treatment. Therefore, further research of bioprinted tumor models and their potential clinical applications are imperative.

Precision therapy helps physicians make more informed medical decisions while providing customized treatments for patients and improving the service level of personalized care. In the future, 3D bioprinting for precision therapy can be implemented by first obtaining tumor cells from a patient's body to build an in vitro tumor model for screening out sensitive chemotherapeutic drugs. Next, the same technique can be used for printing normal tissues in the residual cavity of the patient's resected tumor after obtaining estimates of the patient's normal cell expansion combined with the identification of sensitive chemotherapeutic drugs and their incorporation into a bioink designed to promote tissue repair and regeneration and to prevent tumor recurrence. Given the complexity involved in designing precisely tailored tumor models and products, their production and delivery remain challenging. Therefore, in-depth knowledge and detailed research are required for the future development of unique state-of-the-art models that will ultimately lead to precision therapies.

The development of 3D bioprinted replicas of tumors may significantly alter how healthcare professionals approach cancer prevention, diagnosis, and therapy. Future 3D bioprinting technology, which may be combined with gene editing, artificial intelligence, and biochip technologies, can establish more accurate tumor model prediction models and achieve high-throughput tumor drug screening. This can in turn improve screening efficiency, reduce the cost of tumor drug development, and further promote the development of precision treatments for tumors. Combined with in vitro organ culture and tissue engineering technologies, 3D bioprinted cancer models can accurately simulate the environment of real human organs, allowing us to better evaluate the safety and effectiveness of tumor therapy drugs. In conclusion, in the future, 3D bioprinting technology can be combined with a variety of new technologies to continuously advance the development of tumor models and provide more accurate, rapid, and safe solutions for precision tumor therapies.

Acknowledgements This article was partially supported by the National Natural Science Foundation of China (No. 82473256), the Jiangxi Provincial Natural Science Foundation, China (No. 20242BAB25521), Ganpo Promising Talents Supporting Plan—Talent Development Project of Leading Academic and Technological Researchers in Key Disciplines (No. 20243BCE51060), the Anhui Province Higher Education Scientific Research Project, China (No. 2024AH050818), the Anhui Provincial Natural Science Foundation, China (No. 2208085MH251), the Fundamental Research Funds for the Anhui Medical University, China (No. 2021xkj131), the Research Fund of Anhui Institute of Translational Medicine, China (No. 2023zhyx-C19), the Health Research Program of Anhui, China (No. AHWJ2023A30007), the Anhui Provincial Department of Education, Provincial Quality Engineering Project for Higher Education (Nos. 2022jyxm761 and 2023jyxm1106), and the Basic and Clinical Cooperative Research and Promotion Program of the Anhui Medical University, China (No. 2022xkjT024).

Author contributions Conception and design: HWC and XLD; administrative support: XLD; provision of study materials: PG and HXL; collection and assembly of data: YQ, HTT, ZYH, and SC; data analysis and interpretation: HXL and YQ; manuscript writing: all authors; final approval of the manuscript: all authors.

Declarations

Conflict of interest 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.

References

1. O'Connor C, Brady E, Zheng Y et al (2022) Engineering the multiscale complexity of vascular networks. Nat Rev Mater 7(9):702–716. https://doi.org/10.1038/s41578-022-00447-8
2. Derby B (2012) Printing and prototyping of tissues and scaffolds. Science 338(6109):921–926. https://doi.org/10.1126/science.1226340
3. Murphy SV, Atala A (2014) 3D bioprinting of tissues and organs. Nat Biotechnol 32(8):773–785. https://doi.org/10.1038/nbt.2958
4. Fonseca AC, Melchels FPW, Ferreira MJS et al (2020) Emulating human tissues and organs: a bioprinting perspective toward personalized medicine. Chem Rev 120(19):11128–11174. https://doi.org/10.1021/acs.chemrev.0c00342
5. Datta P, Ayan B, Ozbolat IT (2017) Bioprinting for vascular and vascularized tissue biofabrication. Acta Biomater 51:1–20. https://doi.org/10.1016/j.actbio.2017.01.035
6. Wu W, DeConinck A, Lewis JA (2011) Omnidirectional printing of 3D microvascular networks. Adv Mater 23(24):H178–H183. https://doi.org/10.1002/adma.201004625
7. Huh D, Leslie DC, Matthews BD et al (2012) A human disease model of drug toxicity-induced pulmonary edema in a lung-on-a-chip microdevice. Sci Transl Med 4(159):159ra47. https://doi.org/10.1126/scitranslmed.3004249
8. Capulli AK, Tian K, Mehandru N et al (2014) Approaching the in vitro clinical trial: engineering organs on chips. Lab Chip 14(17):3181–3186. https://doi.org/10.1039/c4lc00276h
9. Matsusaki M, Sakaue K, Kadowaki K et al (2012) Three-dimensional human tissue chips fabricated by rapid and automatic inkjet cell printing. Adv Healthc Mater 2(4):534–539. https://doi.org/10.1002/adhm.201200299
10. Yi HG (2021) Introduction to bioprinting of in vitro cancer models. Essays Biochem 65(3):603–610. https://doi.org/10.1042/EBC20200104
11. Daly AC, Prendergast ME, Hughes AJ et al (2021) Bioprinting for the biologist. Cell 184(1):18–32. https://doi.org/10.1016/j.cell.2020.12.002
12. Billiet T, Vandenhaute M, Schelfhout J et al (2012) A review of trends and limitations in hydrogel-rapid prototyping for tissue engineering. Biomaterials 33(26):6020–6041. https://doi.org/10.1016/j.biomaterials.2012.04.050
13. Wüst S, Müller R, Hofmann S (2011) Controlled positioning of cells in biomaterials—approaches towards 3D tissue printing. J Funct Biomater 2(3):119–154. https://doi.org/10.3390/jfb2030119
14. Shanks N, Greek R, Greek J (2009) Are animal models predictive for humans? Philos Ethics Humanit Med 4(1):2. https://doi.org/10.1186/1747-5341-4-2
15. Unadkat HV, Hulsman M, Cornelissen K et al (2011) An algorithm-based topographical biomaterials library to instruct cell fate. Proc Natl Acad Sci USA 108(40):16565–16570. https://doi.org/10.1073/pnas.1109861108
16. Wang PJ, Sun YZ, Shi XQ et al (2021) 3D printing of tissue engineering scaffolds: a focus on vascular regeneration. Bio-Des Manuf 4(2):344–378. https://doi.org/10.1007/s42242-020-00109-0
17. Skardal A, Atala A (2015) Biomaterials for integration with 3-D bioprinting. Ann Biomed Eng 43(3):730–746. https://doi.org/10.1007/s10439-014-1207-1
18. Xu T, Zhao WX, Zhu JM et al (2013) Complex heterogeneous tissue constructs containing multiple cell types prepared by inkjet printing technology. Biomaterials 34(1):130–139. https://doi.org/10.1016/j.biomaterials.2012.09.035
19. Ma L, Yu SJ, Xu XD et al (2023) Application of artificial intelligence in 3D printing physical organ models. Mater Today Bio 23:100792. https://doi.org/10.1016/j.mtbio.2023.100792
20. Albritton JL, Miller JS (2017) 3D bioprinting: improving in vitro models of metastasis with heterogeneous tumor microenvironments. Dis Model Mech 10(1):3–14. https://doi.org/10.1242/dmm.025049
21. Vendramin R, Litchfield K, Swanton C (2021) Cancer evolution: Darwin and beyond. EMBO J 40(18):e108389. https://doi.org/10.15252/embj.2021108389
22. Jung M, Ghamrawi S, Du EY et al (2022) Advances in 3D bioprinting for cancer biology and precision medicine: from matrix design to application. Adv Healthc Mater 11(24):e2200690. https://doi.org/10.1002/adhm.202200690
23. Ouyang L (2022) Pushing the rheological and mechanical boundaries of extrusion-based 3D bioprinting. Trend Biotechnol 40(7):891–902. https://doi.org/10.1016/j.tibtech.2022.01.001
24. Li XD, Liu BX, Pei B et al (2020) Inkjet bioprinting of biomaterials. Chem Rev 120(19):10793–10833. https://doi.org/10.1021/acs.chemrev.0c00008
25. Goodarzi Hosseinabadi H, Dogan E, Miri AK et al (2022) Digital light processing bioprinting advances for microtissue models. ACS Biomater Sci Eng 8(4):1381–1395. https://doi.org/10.1021/acsbiomaterials.1c01509
26. Enrico A, Voulgaris D, Ostmans R et al (2022) 3D microvascularized tissue models by laser-based cavitation molding of collagen. Adv Mater 34(11):e2109823. https://doi.org/10.1002/adma.202109823
27. Brunel LG, Hull SM, Heilshorn SC (2022) Engineered assistive materials for 3D bioprinting: support baths and sacrificial inks. Biofabrication 14(3):032001. https://doi.org/10.1088/1758-5090/ac6bbe
28. Wang HN, Yu HQ, Zhou X et al (2022) An overview of extracellular matrix-based bioinks for 3D bioprinting. Front Bioeng Biotechnol 10:905438. https://doi.org/10.3389/fbioe.2022.905438
29. Zhou K, Sun YD, Yang JQ et al (2022) Hydrogels for 3D embedded bioprinting: a focused review on bioinks and support baths. J Mater Chem B 10(12):1897–1907. https://doi.org/10.1039/d1tb02554f
30. Shrestha S, Lekkala VKR, Acharya P et al (2021) Recent advances in microarray 3D bioprinting for high-throughput spheroid and tissue culture and analysis. Essay Biochem 65(3):481–489. https://doi.org/10.1042/ebc20200150
31. Touya N, Devun M, Handschin C et al (2022) In vitro and in vivo characterization of a novel tricalcium silicate-based ink for bone regeneration using laser-assisted bioprinting. Biofabrication 14(2):24104. https://doi.org/10.1088/1758-5090/ac584b
32. Mondschein RJ, Kanitkar A, Williams CB et al (2017) Polymer structure-property requirements for stereolithographic 3D printing of soft tissue engineering scaffolds. Biomaterials 140:170–188. https://doi.org/10.1016/j.biomaterials.2017.06.005
33. Sharma R, Restan Perez M, da Silva VA et al (2023) 3D bioprinting complex models of cancer. Biomater Sci 11(10):3414–3430. https://doi.org/10.1039/d2bm02060b
34. Li WL, Wang M, Ma HL et al (2023) Stereolithography apparatus and digital light processing-based 3D bioprinting for tissue fabrication. iScience 26(2):106039. https://doi.org/10.1016/j.isci.2023.106039
35. Gudapati H, Dey M, Ozbolat I (2016) A comprehensive review on droplet-based bioprinting: past, present and future. Biomaterials 102:20–42. https://doi.org/10.1016/j.biomaterials.2016.06.012
36. Liu JC, Shahriar M, Xu HQ et al (2022) Cell-laden bioink circulation-assisted inkjet-based bioprinting to mitigate cell sedimentation and aggregation. Biofabrication 14(4):45020. https://doi.org/10.1088/1758-5090/ac8fb7

37. Habeshian S, Merz ML, Sangouard G et al (2022) Synthesis and direct assay of large macrocycle diversities by combinatorial late-stage modification at picomole scale. Nat Commun 13(1):3823. https://doi.org/10.1038/s41467-022-31428-8
38. Dornhof J, Zieger V, Kieninger J et al (2022) Bioprinting-based automated deposition of single cancer cell spheroids into oxygen sensor microelectrode wells. Lab Chip 22(22):4369–4381. https://doi.org/10.1039/d2lc00705c
39. Chen H, Du L, Li J et al (2022) Modeling cancer metastasis using acoustically bio-printed patient-derived 3D tumor microtissues. J Mater Chem B 10(11):1843–1852. https://doi.org/10.1039/d1tb02789a
40. Huang DT, Gibeley SB, Xu C et al (2020) Engineering liver microtissues for disease modeling and regenerative medicine. Adv Funct Mater 30(44):1909553. https://doi.org/10.1002/adfm.201909553
41. Datta P, Barui A, Wu Y et al (2018) Essential steps in bioprinting: from pre- to post-bioprinting. Biotechnol Adv 36(5):1481–1504. https://doi.org/10.1016/j.biotechadv.2018.06.003
42. Askari M, Naniz MA, Kouhi M et al (2021) Recent progress in extrusion 3D bioprinting of hydrogel biomaterials for tissue regeneration: a comprehensive review with focus on advanced fabrication techniques. Biomater Sci 9(3):535–573. https://doi.org/10.1039/d0bm00973c
43. Ballyns JJ, Gleghorn JP, Niebrzydowski V et al (2008) Image-guided tissue engineering of anatomically shaped implants via MRI and micro-CT using injection molding. Tissue Eng Part A 14(7):1195–1202. https://doi.org/10.1089/ten.tea.2007.0186
44. Sun LJ, Yang HY, Wang YN et al (2020) Application of a 3D bioprinted hepatocellular carcinoma cell model in antitumor drug research. Front Oncol 10:878. https://doi.org/10.3389/fonc.2020.00878
45. Sbirkov Y, Molander D, Milet C et al (2021) A colorectal cancer 3D bioprinting workflow as a platform for disease modeling and chemotherapeutic screening. Front Bioeng Biotechnol 9:755563. https://doi.org/10.3389/fbioe.2021.755563
46. Derakhshanfar S, Mbeleck R, Xu KG et al (2018) 3D bioprinting for biomedical devices and tissue engineering: a review of recent trends and advances. Bioact Mater 3(2):144–156. https://doi.org/10.1016/j.bioactmat.2017.11.008
47. Bishop ES, Mostafa S, Pakvasa M et al (2017) 3-D bioprinting technologies in tissue engineering and regenerative medicine: current and future trends. Genes Dis 4(4):185–195. https://doi.org/10.1016/j.gendis.2017.10.002
48. Nakielski P, Rinoldi C, Pruchniewski M et al (2022) Laser-assisted fabrication of injectable nanofibrous cell carriers. Small 18(2):e2104971. https://doi.org/10.1002/smll.202104971
49. Kanaki Z, Chandrinou C, Orfanou IM et al (2022) Laser-induced forward transfer printing on microneedles for transdermal delivery of gemcitabine. Int J Bioprint 8(2):554. https://doi.org/10.18063/ijb.v8i2.554
50. Douillet C, Nicodeme M, Hermant L et al (2022) From local to global matrix organization by fibroblasts: a 4D laser-assisted bioprinting approach. Biofabrication 14(2):15. https://doi.org/10.1088/1758-5090/ac40ed
51. Zheng Y, Chen JM, Craven M et al (2012) In vitro microvessels for the study of angiogenesis and thrombosis. Proc Natl Acad Sci USA 109(24):9342–9347. https://doi.org/10.1073/pnas.1201240109
52. Chirivì M, Bearzi C, Rosa P et al (2022) Biomimetic keratin-coated gold nanoparticles for photo-thermal therapy in a 3D bioprinted glioblastoma tumor model. Int J Mol Sci 23(17):9528. https://doi.org/10.3390/ijms23179528
53. Hakobyan D, Médina C, Dusserre N et al (2020) Laser-assisted 3D bioprinting of exocrine pancreas spheroid models for cancer initiation study. Biofabrication 12(3):035001. https://doi.org/10.1088/1758-5090/ab7cb8
54. Ali M, Pages E, Ducom A et al (2014) Controlling laser-induced jet formation for bioprinting mesenchymal stem cells with high viability and high resolution. Biofabrication 6(4):045001. https://doi.org/10.1088/1758-5082/6/4/045001
55. Guillemot F, Souquet A, Catros S et al (2010) High-throughput laser printing of cells and biomaterials for tissue engineering. Acta Biomater 6(7):2494–2500. https://doi.org/10.1016/j.actbio.2009.09.029
56. Guillotin B, Souquet A, Catros S et al (2010) Laser assisted bioprinting of engineered tissue with high cell density and microscale organization. Biomaterials 31(28):7250–7256. https://doi.org/10.1016/j.biomaterials.2010.05.055
57. Zhang ZY, Chai WX, Xiong RT et al (2017) Printing-induced cell injury evaluation during laser printing of 3T3 mouse fibroblasts. Biofabrication 9(2):025038. https://doi.org/10.1088/1758-5090/aa6ed9
58. Xiong RT, Zhang ZY, Chai WX et al (2015) Freeform drop-on-demand laser printing of 3D alginate and cellular constructs. Biofabrication 7(4):045011. https://doi.org/10.1088/1758-5090/7/4/045011
59. Mardikar SH, Niranjan K (2000) Observations on the shear damage to different animal cells in a concentric cylinder viscometer. Biotechnol Bioeng 68(6):697–704. https://doi.org/10.1002/(sici)1097-0290(20000620)68:6%3c697::aid-bit14%3e3.0.co;2-6
60. Peele BN, Wallin TJ, Zhao HC et al (2015) 3D printing antagonistic systems of artificial muscle using projection stereolithography. Bioinspir Biomim 10(5):055003. https://doi.org/10.1088/1748-3190/10/5/055003
61. Wang ZJ, Abdulla R, Parker B et al (2015) A simple and high-resolution stereolithography-based 3D bioprinting system using visible light crosslinkable bioinks. Biofabrication 7(4):045009. https://doi.org/10.1088/1758-5090/7/4/045009
62. Unagolla JM, Jayasuriya AC (2020) Hydrogel-based 3D bioprinting: a comprehensive review on cell-laden hydrogels, bioink formulations, and future perspectives. Appl Mater Today 18:100479. https://doi.org/10.1016/j.apmt.2019.100479
63. Jiao A, Trosper NE, Yang HS et al (2014) Thermoresponsive nanofabricated substratum for the engineering of three-dimensional tissues with layer-by-layer architectural control. ACS Nano 8(5):4430–4439. https://doi.org/10.1021/nn4063962
64. Ma XY, Yu C, Wang PR et al (2018) Rapid 3D bioprinting of decellularized extracellular matrix with regionally varied mechanical properties and biomimetic microarchitecture. Biomaterials 185:310–321. https://doi.org/10.1016/j.biomaterials.2018.09.026
65. Tang M, Tiwari SK, Agrawal K et al (2021) Rapid 3D bioprinting of glioblastoma model mimicking native biophysical heterogeneity. Small 17(15):e2006050. https://doi.org/10.1002/smll.202006050
66. Li JP, Chen MJ, Fan XQ et al (2016) Recent advances in bioprinting techniques: approaches, applications and future prospects. J Transl Med 14(1):271. https://doi.org/10.1186/s12967-016-1028-0
67. He Y, Gu ZM, Xie MJ et al (2020) Why choose 3D bioprinting? Part II: methods and bioprinters. Bio-Des Manuf 3(1):1–4. https://doi.org/10.1007/s42242-020-00064-w
68. Gentilin E, D'Angelo E, Agostini M et al (2022) Decellularized normal and cancer tissues as tools for cancer research. Cancer Gene Ther 29(7):879–888. https://doi.org/10.1038/s41417-021-00398-2
69. Ramesh S, Harrysson OLA, Rao PK et al (2021) Extrusion bioprinting: recent progress, challenges, and future opportunities. Bioprinting 21:e00116. https://doi.org/10.1016/j.bprint.2020.e00116

70. Augustine R, Kalva SN, Ahmad R et al (2021) 3D bioprinted cancer models: revolutionizing personalized cancer therapy. Transl Oncol 14(4):101015. https://doi.org/10.1016/j.tranon.2021.101015
71. Lowe SB, Tan VTG, Soeriyadi AH et al (2014) Synthesis and high-throughput processing of polymeric hydrogels for 3D cell culture. Bioconjug Chem 25(9):1581–1601. https://doi.org/10.1021/bc500310v
72. Hospodiuk M, Dey M, Sosnoski D et al (2017) The bioink: a comprehensive review on bioprintable materials. Biotechnol Adv 35(2):217–239. https://doi.org/10.1016/j.biotechadv.2016.12.006
73. Mobaraki M, Ghaffari M, Yazdanpanah A et al (2020) Bioinks and bioprinting: a focused review. Bioprinting 18:e00080. https://doi.org/10.1016/j.bprint.2020.e00080
74. Benwood C, Chrenek J, Kirsch RL et al (2021) Natural biomaterials and their use as bioinks for printing tissues. Bioengineering 8(2):27. https://doi.org/10.3390/bioengineering8020027
75. Hedegaard CL, Redondo-Gómez C, Tan BY et al (2020) Peptide-protein coassembling matrices as a biomimetic 3D model of ovarian cancer. Sci Adv 6(40):eabb3298. https://doi.org/10.1126/sciadv.abb3298
76. Gebeyehu A, Surapaneni SK, Huang J et al (2021) Polysaccharide hydrogel based 3D printed tumor models for chemotherapeutic drug screening. Sci Rep 11(1):372. https://doi.org/10.1038/s41598-020-79325-8
77. Kim BS, Cho WW, Gao G et al (2021) Construction of tissue-level cancer-vascular model with high-precision position control via in situ 3D cell printing. Small Methods 5(7):e2100072. https://doi.org/10.1002/smtd.202100072
78. Yi HG, Jeong YH, Kim Y et al (2019) A bioprinted human-glioblastoma-on-a-chip for the identification of patient-specific responses to chemoradiotherapy. Nat Biomed Eng 3(7):509–519. https://doi.org/10.1038/s41551-019-0363-x
79. Uhl FE, Zhang FM, Pouliot RA et al (2020) Functional role of glycosaminoglycans in decellularized lung extracellular matrix. Acta Biomater 102:231–246. https://doi.org/10.1016/j.actbio.2019.11.029
80. Aisenbrey EA, Murphy WL (2020) Synthetic alternatives to Matrigel. Nat Rev Mater 5(7):539–551. https://doi.org/10.1038/s41578-020-0199-8
81. Mancha Sánchez E, Gómez-Blanco JC, López Nieto E et al (2020) Hydrogels for bioprinting: a systematic review of hydrogels synthesis, bioprinting parameters, and bioprinted structures behavior. Front Bioeng Biotechnol 8:776. https://doi.org/10.3389/fbioe.2020.00776
82. Liu F, Wang XH (2020) Synthetic polymers for organ 3D printing. Polymers 12(8):1765. https://doi.org/10.3390/polym12081765
83. Singh SP, Schwartz MP, Tokuda EY et al (2015) A synthetic modular approach for modeling the role of the 3D microenvironment in tumor progression. Sci Rep 5:17814. https://doi.org/10.1038/srep17814
84. Roudsari LC, Jeffs SE, West JL (2018) Lung adenocarcinoma cell responses in a 3D in vitro tumor angiogenesis model correlate with metastatic capacity. ACS Biomater Sci Eng 4(2):368–377. https://doi.org/10.1021/acsbiomaterials.7b00011
85. Gill BJ, Gibbons DL, Roudsari LC et al (2012) A synthetic matrix with independently tunable biochemistry and mechanical properties to study epithelial morphogenesis and EMT in a lung adenocarcinoma model. Cancer Res 72(22):6013–6023. https://doi.org/10.1158/0008-5472.CAN-12-0895
86. Shi XL, Cheng YX, Wang J et al (2020) 3D printed intelligent scaffold prevents recurrence and distal metastasis of breast cancer. Theranostics 10(23):10652–10664. https://doi.org/10.7150/thno.47933
87. Gungor-Ozkerim PS, Inci I, Zhang YS et al (2018) Bioinks for 3D bioprinting: an overview. Biomater Sci 6(5):915–946. https://doi.org/10.1039/c7bm00765e
88. Lee HW, Lee JI, Lee SJ et al (2015) Patient-derived xenografts from non-small cell lung cancer brain metastases are valuable translational platforms for the development of personalized targeted therapy. Clin Cancer Res 21(5):1172–1182. https://doi.org/10.1158/1078-0432.CCR-14-1589
89. Benien P, Swami A (2014) 3D tumor models: history, advances and future perspectives. Future Oncol 10(7):1311–1327. https://doi.org/10.2217/fon.13.274
90. Ozbolat IT, Peng WJ, Ozbolat V (2016) Application areas of 3D bioprinting. Drug Discov Today 21(8):1257–1271. https://doi.org/10.1016/j.drudis.2016.04.006
91. Germain N, Dhayer M, Dekiouk S et al (2022) Current advances in 3D bioprinting for cancer modeling and personalized medicine. Int J Mol Sci 23(7):3432. https://doi.org/10.3390/ijms23073432
92. Ma L, Wu YT, Li YT et al (2020) Current advances on 3D-bioprinted liver tissue models. Adv Healthc Mater 9(24):e2001517. https://doi.org/10.1002/adhm.202001517
93. Thakor J, Ahadian S, Niakan A et al (2020) Engineered hydrogels for brain tumor culture and therapy. Bio-Des Manuf 3(3):203–226. https://doi.org/10.1007/s42242-020-00084-6
94. Venkataramani V, Schneider M, Giordano FA et al (2022) Disconnecting multicellular networks in brain tumours. Nat Rev Cancer 22(8):481–491. https://doi.org/10.1038/s41568-022-00475-0
95. Varn FS, Johnson KC, Martinek J et al (2022) Glioma progression is shaped by genetic evolution and microenvironment interactions. Cell 185(12):2184–2199. https://doi.org/10.1016/j.cell.2022.04.038
96. Lin K, Gueble SE, Sundaram RK et al (2022) Mechanism-based design of agents that selectively target drug-resistant glioma. Science 377(6605):502–511. https://doi.org/10.1126/science.abn7570
97. Perez-Larraya JG, Garcia-Moure M, Labiano S et al (2022) Oncolytic DNX-2401 virus for pediatric diffuse intrinsic pontine glioma. N Engl J Med 386(26):2471–2481. https://doi.org/10.1056/NEJMoa2202028
98. Wang XZ, Li XD, Dai XL et al (2018) Bioprinting of glioma stem cells improves their endotheliogenic potential. Colloids Surf B Biointerfaces 171:629–637. https://doi.org/10.1016/j.colsurfb.2018.08.006
99. Wang XZ, Dai XL, Zhang XZ et al (2019) 3D bioprinted glioma cell-laden scaffolds enriching glioma stem cells via epithelial-mesenchymal transition. J Biomed Mater Res Part A 107(2):383–391. https://doi.org/10.1002/jbm.a.36549
100. Dai XL, Ma C, Lan Q et al (2016) 3D bioprinted glioma stem cells for brain tumor model and applications of drug susceptibility. Biofabrication 8(4):045005. https://doi.org/10.1088/1758-5090/8/4/045005
101. Dai XL, Liu LB, Ouyang J et al (2017) Coaxial 3D bioprinting of self-assembled multicellular heterogeneous tumor fibers. Sci Rep 7(1):1457. https://doi.org/10.1038/s41598-017-01581-y
102. Dai XL, Shao YX, Tian XF et al (2022) Fusion between glioma stem cells and mesenchymal stem cells promotes malignant progression in 3D-bioprinted models. ACS Appl Mater Interfaces 14(31):35344–35356. https://doi.org/10.1021/acsami.2c06658
103. Wang XZ, Li XD, Dai XL et al (2018) Coaxial extrusion bioprinted shell-core hydrogel microfibers mimic glioma microenvironment and enhance the drug resistance of cancer cells. Colloids Surf B Biointerfaces 171:291–299. https://doi.org/10.1016/j.colsurfb.2018.07.042
104. Tang M, Xie Q, Gimple RC et al (2020) Three-dimensional bioprinted glioblastoma microenvironments model cellular dependencies and immune interactions. Cell Res 30(10):833–853. https://doi.org/10.1038/s41422-020-0338-1

105. Haring AP, Thompson EG, Tong YX et al (2019) Process- and bio-inspired hydrogels for 3D bioprinting of soft free-standing neural and glial tissues. Biofabrication 11(2):025009. https://doi.org/10.1088/1758-5090/ab02c9
106. DePalma TJ, Sivakumar H, Skardal A (2022) Strategies for developing complex multi-component in vitro tumor models: highlights in glioblastoma. Adv Drug Deliv Rev 180:114067. https://doi.org/10.1016/j.addr.2021.114067
107. Tang M, Rich JN, Chen SC (2021) Biomaterials and 3D bioprinting strategies to model glioblastoma and the blood–brain barrier. Adv Mater 33(5):e2004776. https://doi.org/10.1002/adma.202004776
108. Heinrich MA, Bansal R, Lammers T et al (2019) 3D-bioprinted mini-brain: a glioblastoma model to study cellular interactions and therapeutics. Adv Mater 31(14):e1806590. https://doi.org/10.1002/adma.201806590
109. Gomez-Roman N, Chalmers AJ (2019) Patient-specific 3D-printed glioblastomas. Nat Biomed Eng 3(7):498–499. https://doi.org/10.1038/s41551-019-0379-2
110. Neufeld L, Yeini E, Reisman N et al (2021) Microengineered perfusable 3D-bioprinted glioblastoma model for in vivo mimicry of tumor microenvironment. Sci Adv 7(34):eabi9119. https://doi.org/10.1126/sciadv.abi9119
111. Hubert CG, Rivera M, Spangler LC et al (2016) A three-dimensional organoid culture system derived from human glioblastomas recapitulates the hypoxic gradients and cancer stem cell heterogeneity of tumors found in vivo. Cancer Res 76(8):2465–2477. https://doi.org/10.1158/0008-5472.CAN-15-2402
112. Sung H, Ferlay J, Siegel RL et al (2021) Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71(3):209–249. https://doi.org/10.3322/caac.21660
113. Bobo D, Robinson KJ, Islam J et al (2016) Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date. Pharm Res 33(10):2373–2387. https://doi.org/10.1007/s11095-016-1958-5
114. Anselmo AC, Mitragotri S (2019) Nanoparticles in the clinic: an update. Bioeng Transl Med 4(3):e10143. https://doi.org/10.1002/btm2.10143
115. Pickup MW, Mouw JK, Weaver VM (2014) The extracellular matrix modulates the hallmarks of cancer. EMBO Rep 15(12):1243–1253. https://doi.org/10.15252/embr.201439246
116. Bonnans C, Chou J, Werb Z (2014) Remodelling the extracellular matrix in development and disease. Nat Rev Mol Cell Biol 15(12):786–801. https://doi.org/10.1038/nrm3904
117. Bissell MJ, Radisky D (2001) Putting tumours in context. Nat Rev Cancer 1(1):46–54. https://doi.org/10.1038/35094059
118. Zhu YH, Wu Y, Zhang H et al (2022) A national survey on how to improve traditional Chinese medicine learning internationally: perceptions from both teachers and students. Integr Med Res 11(4):100895. https://doi.org/10.1016/j.imr.2022.100895
119. Chaji S, Al-Saleh J, Gomillion CT (2020) Bioprinted three-dimensional cell-laden hydrogels to evaluate adipocyte-breast cancer cell interactions. Gels 6(1):10. https://doi.org/10.3390/gels6010010
120. Vinson BT, Phamduy TB, Shipman J et al (2017) Laser direct-write based fabrication of a spatially-defined, biomimetic construct as a potential model for breast cancer cell invasion into adipose tissue. Biofabrication 9(2):025013. https://doi.org/10.1088/1758-5090/aa6bad
121. Blanco-Fernandez B, Rey-Vinolas S, Bağcı G et al (2022) Bioprinting decellularized breast tissue for the development of three-dimensional breast cancer models. ACS Appl Mater Interfaces 14(26):29467–29482. https://doi.org/10.1021/acsami.2c00920
122. Mollica PA, Booth-Creech EN, Reid JA et al (2019) 3D bioprinted mammary organoids and tumoroids in human mammary derived ECM hydrogels. Acta Biomater 95:201–213. https://doi.org/10.1016/j.actbio.2019.06.017
123. Kingsley DM, Roberge CL, Rudkouskaya A et al (2019) Laser-based 3D bioprinting for spatial and size control of tumor spheroids and embryoid bodies. Acta Biomater 95:357–370. https://doi.org/10.1016/j.actbio.2019.02.014
124. Langer EM, Allen-Petersen BL, King SM et al (2019) Modeling tumor phenotypes in vitro with three-dimensional bioprinting. Cell Rep 26(3):608–623. https://doi.org/10.1016/j.celrep.2018.12.090
125. Duchamp M, Liu TT, van Genderen AM et al (2019) Sacrificial bioprinting of a mammary ductal carcinoma model. Biotechnol J 14(10):e1700703. https://doi.org/10.1002/biot.201700703
126. Cheng F, Cao X, Li HB et al (2019) Generation of cost-effective paper-based tissue models through matrix-assisted sacrificial 3D printing. Nano Lett 19(6):3603–3611. https://doi.org/10.1021/acs.nanolett.9b00583
127. Burks HE, Phamduy TB, Azimi MS et al (2016) Laser direct-write onto live tissues: a novel model for studying cancer cell migration. J Cellular Physiol 231(11):2333–2338. https://doi.org/10.1002/jcp.25363
128. Zhou X, Zhu W, Nowicki M et al (2016) 3D bioprinting a cell-laden bone matrix for breast cancer metastasis study. ACS Appl Mater Interfaces 8(44):30017–30026. https://doi.org/10.1021/acsami.6b10673
129. Belgodere JA, King CT, Bursavich JB et al (2018) Engineering breast cancer microenvironments and 3D bioprinting. Front Bioeng Biotechnol 6:66. https://doi.org/10.3389/fbioe.2018.00066
130. Jiang T, Munguia-Lopez JG, Gu K et al (2019) Engineering bioprintable alginate/gelatin composite hydrogels with tunable mechanical and cell adhesive properties to modulate tumor spheroid growth kinetics. Biofabrication 12(1):015024. https://doi.org/10.1088/1758-5090/ab3a5c
131. Swaminathan S, Hamid Q, Sun W et al (2019) Bioprinting of 3D breast epithelial spheroids for human cancer models. Biofabrication 11(2):025003. https://doi.org/10.1088/1758-5090/aafc49
132. Hong S, Song JM (2022) 3D bioprinted drug-resistant breast cancer spheroids for quantitative in situ evaluation of drug resistance. Acta Biomater 138:228–239. https://doi.org/10.1016/j.actbio.2021.10.031
133. Nam KH, Jeong CB, Kim H et al (2021) Quantitative photothermal characterization with bioprinted 3D complex tissue constructs for early-stage breast cancer therapy using gold nanorods. Adv Healthc Mater 10(18):e2100636. https://doi.org/10.1002/adhm.202100636
134. Chen Y, Xu LX, Li WL et al (2022) 3D bioprinted tumor model with extracellular matrix enhanced bioinks for nanoparticle evaluation. Biofabrication 14(2):025002. https://doi.org/10.1088/1758-5090/ac48e4
135. Degasperi E, Colombo M (2016) Distinctive features of hepatocellular carcinoma in non-alcoholic fatty liver disease. Lancet Gastroenterol Hepatol 1(2):156–164. https://doi.org/10.1016/S2468-1253(16)30018-8
136. Masuzaki R, Tateishi R, Yoshida H et al (2007) Assessing liver tumor stiffness by transient elastography. Hepatol Int 1(3):394–397. https://doi.org/10.1007/s12072-007-9012-7
137. Ling WW, Lu Q, Lu CL et al (2014) Effects of vascularity and differentiation of hepatocellular carcinoma on tumor and liver stiffness: in vivo and in vitro studies. Ultrasound Med Biol 40(4):739–746. https://doi.org/10.1016/j.ultrasmedbio.2013.08.011
138. Kondo F (2009) Histological features of early hepatocellular carcinomas and their developmental process: for daily practical

clinical application. Hepatol Int 3(1):283–293. https://doi.org/10.1007/s12072-008-9107-9
139. Zhang R, Ma M, Dong G et al (2017) Increased matrix stiffness promotes tumor progression of residual hepatocellular carcinoma after insufficient heat treatment. Cancer Sci 108(9):1778–1786. https://doi.org/10.1111/cas.13322
140. You Y, Zheng QD, Dong YY et al (2015) Higher matrix stiffness upregulates osteopontin expression in hepatocellular carcinoma cells mediated by integrin beta1/GSK3beta/beta-Catenin signaling pathway. PLoS ONE 10(8):e0134243. https://doi.org/10.1371/journal.pone.0134243
141. Schrader J, Gordon-Walker TT, Aucott RL et al (2011) Matrix stiffness modulates proliferation, chemotherapeutic response, and dormancy in hepatocellular carcinoma cells. Hepatology 53(4):1192–1205. https://doi.org/10.1002/hep.24108
142. Liu C, Liu Y, Xie HG et al (2015) Role of three-dimensional matrix stiffness in regulating the chemoresistance of hepatocellular carcinoma cells. Biotechnol Appl Biochem 62(4):556–562. https://doi.org/10.1002/bab.1302
143. Li Y, Zhang T, Pang Y et al (2019) 3D bioprinting of hepatoma cells and application with microfluidics for pharmacodynamic test of Metuzumab. Biofabrication 11(3):034102. https://doi.org/10.1088/1758-5090/ab256c
144. Hwang HH, You ST, Ma XY et al (2021) High throughput direct 3D bioprinting in multiwell plates. Biofabrication 13(2):025007. https://doi.org/10.1088/1758-5090/ab89ca
145. Ying GL, Jiang N, Maharjan S et al (2018) Aqueous two-phase emulsion bioink-enabled 3D bioprinting of porous hydrogels. Adv Mater 30(50):e1805460. https://doi.org/10.1002/adma.201805460
146. Polez RT, Morits M, Jonkergouw C et al (2022) Biological activity of multicomponent bio-hydrogels loaded with tragacanth gum. Int J Biol Macromol 215:691–704. https://doi.org/10.1016/j.ijbiomac.2022.06.153
147. Xie F, Sun L, Pang Y et al (2021) Three-dimensional bioprinting of primary human hepatocellular carcinoma for personalized medicine. Biomaterials 265:120416. https://doi.org/10.1016/j.biomaterials.2020.120416
148. Mao SS, He JY, Zhao Y et al (2020) Bioprinting of patient-derived in vitro intrahepatic cholangiocarcinoma tumor model: establishment, evaluation and anti-cancer drug testing. Biofabrication 12(4):045014. https://doi.org/10.1088/1758-5090/aba0c3
149. Force USPST, Davidson KW, Barry MJ et al (2021) Screening for colorectal cancer: US preventive services task force recommendation statement. JAMA 325(19):1965–1977. https://doi.org/10.1001/jama.2021.6238
150. Pelka K, Hofree M, Chen JH et al (2021) Spatially organized multicellular immune hubs in human colorectal cancer. Cell 184(18):4734–4752. https://doi.org/10.1016/j.cell.2021.08.003
151. Kotsiliti E (2022) Origin of CAFs in colorectal cancer. Nat Rev Gastroenterol Hepatol 19(2):79. https://doi.org/10.1038/s41575-021-00573-8
152. Becker WR, Nevins SA, Chen DC et al (2022) Single-cell analyses define a continuum of cell state and composition changes in the malignant transformation of polyps to colorectal cancer. Nat Genet 54(7):985–995. https://doi.org/10.1038/s41588-022-01088-x
153. Becker LM, LeBleu VS (2018) Endoglin targeting in colorectal tumor microenvironment. Clin Cancer Res 24(24):6110–6111. https://doi.org/10.1158/1078-0432.CCR-18-2023
154. Rohlenova K, Veys K, Miranda-Santos I et al (2018) Endothelial cell metabolism in health and disease. Trends Cell Biol 28(3):224–236. https://doi.org/10.1016/j.tcb.2017.10.010
155. Bhat AA, Nisar S, Singh M et al (2022) Cytokine- and chemokine-induced inflammatory colorectal tumor microenvironment: emerging avenue for targeted therapy. Cancer Commun 42(8):689–715. https://doi.org/10.1002/cac2.12295
156. Chen HX, Cheng YX, Wang XC et al (2020) 3D printed in vitro tumor tissue model of colorectal cancer. Theranostics 10(26):12127–12143. https://doi.org/10.7150/thno.52450
157. Han H, Park Y, Choi YM et al (2022) A bioprinted tubular intestine model using a colon-specific extracellular matrix bioink. Adv Healthc Mater 11(2):e2101768. https://doi.org/10.1002/adhm.202101768
158. Cadamuro F, Marongiu L, Marino M et al (2023) 3D bioprinted colorectal cancer models based on hyaluronic acid and signalling glycans. Carbohydr Polym 302:120395. https://doi.org/10.1016/j.carbpol.2022.120395
159. Wang PP, Sun LJ, Li CC et al (2023) Study on drug screening multicellular model for colorectal cancer constructed by three-dimensional bioprinting technology. Int J Bioprint 9(3):694. https://doi.org/10.18063/ijb.694
160. Burkholder-Wenger AC, Golzar H, Wu Y et al (2022) Development of a hybrid nanoink for 3D bioprinting of heterogeneous tumor models. ACS Biomater Sci Eng 8(2):777–785. https://doi.org/10.1021/acsbiomaterials.1c01265
161. Zhang YM, Wang ZX, Hu QF et al (2022) 3D bioprinted GelMA-nanoclay hydrogels induce colorectal cancer stem cells through activating Wnt/beta-catenin signaling. Small 18(18):e2200364. https://doi.org/10.1002/smll.202200364
162. Zhao Y, Yao R, Ouyang LL et al (2014) Three-dimensional printing of Hela cells for cervical tumor model in vitro. Biofabrication 6(3):035001. https://doi.org/10.1088/1758-5082/6/3/035001
163. Gospodinova A, Nankov V, Tomov S et al (2021) Extrusion bioprinting of hydroxyethylcellulose-based bioink for cervical tumor model. Carbohydr Polym 260:117793. https://doi.org/10.1016/j.carbpol.2021.117793
164. Pang Y, Mao SS, Yao R et al (2018) TGF-beta induced epithelial-mesenchymal transition in an advanced cervical tumor model by 3D printing. Biofabrication 10(4):044102. https://doi.org/10.1088/1758-5090/aadbde
165. Becconi M, De Zio S, Falciani F et al (2023) Nano-electrochemical characterization of a 3D bioprinted cervical tumor model. Cancers 15(4):1327. https://doi.org/10.3390/cancers15041327
166. Xu F, Celli J, Rizvi I et al (2011) A three-dimensional in vitro ovarian cancer coculture model using a high-throughput cell patterning platform. Biotechnol J 6(2):204–212. https://doi.org/10.1002/biot.201000340
167. Wu T, Gao YY, Su J et al (2022) Three-dimensional bioprinting of artificial ovaries by an extrusion-based method using gelatin-methacryloyl bioink. Climacteric 25(2):170–178. https://doi.org/10.1080/13697137.2021.1921726
168. Baka Z, Godier C, Lamy L et al (2023) A coculture based, 3D bioprinted ovarian tumor model combining cancer cells and cancer associated fibroblasts. Macromol Biosci 23(3):e2200434. https://doi.org/10.1002/mabi.202200434
169. Lucà R, Assenza MR, Maiullari F et al (2021) Inhibition of the mTOR pathway and reprogramming of protein synthesis by MDM4 reduce ovarian cancer metastatic properties. Cell Death Dis 12(6):558. https://doi.org/10.1038/s41419-021-03828-z
170. Estermann M, Coelho R, Jacob F et al (2023) A 3D multi-cellular tissue model of the human omentum to study the formation of ovarian cancer metastasis. Biomaterials 294:121996. https://doi.org/10.1016/j.biomaterials.2023.121996
171. Yee C, Dickson KA, Muntasir MN et al (2022) Three-dimensional modelling of ovarian cancer: from cell lines to organoids for discovery and personalized medicine. Front Bioeng Biotechnol 10:836984. https://doi.org/10.3389/fbioe.2022.836984

172. Mazzocchi A, Soker S, Skardal A (2019) 3D bioprinting for high-throughput screening: Drug screening, disease modeling, and precision medicine applications. Appl Phys Rev 6(1):011302. https://doi.org/10.1063/1.5056188
173. Wu DW, Berg J, Arlt B et al (2021) Bioprinted cancer model of neuroblastoma in a renal microenvironment as an efficiently applicable drug testing platform. Int J Mol Sci 23(1):122. https://doi.org/10.3390/ijms23010122
174. Nothdurfter D, Ploner C, Coraça-Huber DC et al (2022) 3D bioprinted, vascularized neuroblastoma tumor environment in fluidic chip devices for precision medicine drug testing. Biofabrication 14(3):035002. https://doi.org/10.1088/1758-5090/ac5fb7
175. Monferrer E, Martin-Vano S, Carretero A et al (2020) A three-dimensional bioprinted model to evaluate the effect of stiffness on neuroblastoma cell cluster dynamics and behavior. Sci Rep 10(1):6370. https://doi.org/10.1038/s41598-020-62986-w
176. López-Carrasco A, Martin-Vano S, Burgos-Panadero R et al (2020) Impact of extracellular matrix stiffness on genomic heterogeneity in MYCN-amplified neuroblastoma cell line. J Exp Clin Cancer Res 39(1):226. https://doi.org/10.1186/s13046-020-01729-1
177. Bordoni M, Karabulut E, Kuzmenko V et al (2020) 3D printed conductive nanocellulose scaffolds for the differentiation of human neuroblastoma cells. Cells 9(3):682. https://doi.org/10.3390/cells9030682
178. Hakobyan D, Medina C, Dusserre N et al (2020) Laser-assisted 3D bioprinting of exocrine pancreas spheroid models for cancer initiation study. Biofabrication 12(3):035001. https://doi.org/10.1088/1758-5090/ab7cb8
179. Wang X, Zhang XZ, Dai XL et al (2018) Tumor-like lung cancer model based on 3D bioprinting. 3 Biotech 8(12):501. https://doi.org/10.1007/s13205-018-1519-1
180. Herrada-Manchón H, Celada L, Rodriguez-Gonzalez D et al (2021) Three-dimensional bioprinted cancer models: a powerful platform for investigating tunneling nanotube-like cell structures in complex microenvironments. Mater Sci Eng C Mater Biol Appl 128:112357. https://doi.org/10.1016/j.msec.2021.112357
181. Wang XH, Tolba E, Schroder HC et al (2014) Effect of bioglass on growth and biomineralization of SaOS-2 cells in hydrogel after 3D cell bioprinting. PLoS ONE 9(11):e112497. https://doi.org/10.1371/journal.pone.0112497
182. Fischetti T, Di Pompo G, Baldini N et al (2021) 3D printing and bioprinting to model bone cancer: the role of materials and nanoscale cues in directing cell behavior. Cancers 13(16):4065. https://doi.org/10.3390/cancers13164065
183. Zhu W, Castro NJ, Cui HT et al (2016) A 3D printed nano bone matrix for characterization of breast cancer cell and osteoblast interactions. Nanotechnology 27(31):315103. https://doi.org/10.1088/0957-4484/27/31/315103
184. Vanderburgh JP, Guelcher SA, Sterling JA (2018) 3D bone models to study the complex physical and cellular interactions between tumor and the bone microenvironment. J Cell Biochem 119(7):5053–5059. https://doi.org/10.1002/jcb.26774
185. Qiao H, Tang TT (2018) Engineering 3D approaches to model the dynamic microenvironments of cancer bone metastasis. Bone Res 6:3. https://doi.org/10.1038/s41413-018-0008-9
186. Jasuja H, Kar S, Katti DR et al (2021) Perfusion bioreactor enabled fluid-derived shear stress conditions for novel bone metastatic prostate cancer testbed. Biofabrication 13(3):035004. https://doi.org/10.1088/1758-5090/abd9d6
187. Wu D, Wang ZY, Li J et al (2021) A 3D-bioprinted multiple myeloma model. Adv Healthc Mater 11(7):e2100884. https://doi.org/10.1002/adhm.202100884
188. Duan JH, Cao YY, Shen ZZ et al (2022) 3D bioprinted GelMA/PEGDA hybrid scaffold for establishing an in vitro model of melanoma. J Microbiol Biotechnol 32(4):531–540. https://doi.org/10.4014/jmb.2111.11003
189. Diao JF, Zhang CB, Zhang DN et al (2019) Role and mechanisms of a three-dimensional bioprinted microtissue model in promoting proliferation and invasion of growth-hormone-secreting pituitary adenoma cells. Biofabrication 11(2):025006. https://doi.org/10.1088/1758-5090/aaf7ea
190. Sbrana FV, Pinos R, Barbaglio F et al (2021) 3D bioprinting allows the establishment of long-term 3D culture model for chronic lymphocytic leukemia cells. Front Immunol 12:639572. https://doi.org/10.3389/fimmu.2021.639572
191. Ziółkowska-Suchanek I (2021) Mimicking tumor hypoxia in non-small cell lung cancer employing three-dimensional in vitro models. Cells 10(1):141. https://doi.org/10.3390/cells10010141
192. Grunewald L, Lam T, Andersch L et al (2021) A reproducible bioprinted 3D tumor model serves as a preselection tool for CAR T cell therapy optimization. Front Immunol 12:689697. https://doi.org/10.3389/fimmu.2021.689697
193. Bhuskute H, Shende P, Prabhakar B (2021) 3D printed personalized medicine for cancer: applications for betterment of diagnosis, prognosis and treatment. AAPS PharmSciTech 23(1):8. https://doi.org/10.1208/s12249-021-02153-0
194. Colombo E, Cattaneo MG (2021) Multicellular 3D models to study tumour-stroma interactions. Int J Mol Sci 22(4):1633. https://doi.org/10.3390/ijms22041633
195. Bleijs M, van de Wetering M, Clevers H et al (2019) Xenograft and organoid model systems in cancer research. EMBO J 38(15):101654. https://doi.org/10.15252/embj.2019101654
196. Datta P, Dey M, Ataie Z et al (2020) 3D bioprinting for reconstituting the cancer microenvironment. npj Precis Oncol 4:18. https://doi.org/10.1038/s41698-020-0121-2
197. Bojin F, Robu A, Bejenariu MI et al (2021) 3D bioprinting of model tissues that mimic the tumor microenvironment. Micromachines 12(5):535. https://doi.org/10.3390/mi12050535
198. Verbridge SS, Chandler EM, Fischbach C (2010) Tissue-engineered three-dimensional tumor models to study tumor angiogenesis. Tissue Eng Part A 16(7):2147–2152. https://doi.org/10.1089/ten.TEA.2009.0668
199. Li S, Yang KF, Chen XY et al (2021) Simultaneous 2D and 3D cell culture array for multicellular geometry, drug discovery and tumor microenvironment reconstruction. Biofabrication 13(4):045013. https://doi.org/10.1088/1758-5090/ac1ea8
200. Bray LJ, Werner C (2018) Evaluation of three-dimensional in vitro models to study tumor angiogenesis. ACS Biomater Sci Eng 4(2):337–346. https://doi.org/10.1021/acsbiomaterials.7b00139
201. Chwalek K, Bray LJ, Werner C (2014) Tissue-engineered 3D tumor angiogenesis models: potential technologies for anti-cancer drug discovery. Adv Drug Deliv Rev 79–80:30–39. https://doi.org/10.1016/j.addr.2014.05.006
202. Wang C, Li JF, Sinha S et al (2019) Mimicking brain tumor-vasculature microanatomical architecture via co-culture of brain tumor and endothelial cells in 3D hydrogels. Biomaterials 202:35–44. https://doi.org/10.1016/j.biomaterials.2019.02.024
203. Meng FB, Meyer CM, Joung D et al (2019) 3D bioprinted in vitro metastatic models via reconstruction of tumor microenvironments. Adv Mater 31(10):e1806899. https://doi.org/10.1002/adma.201806899
204. Lu IN, Dobersalske C, Rauschenbach L et al (2021) Tumor-associated hematopoietic stem and progenitor cells positively linked to glioblastoma progression. Nat Commun 12(1):3895. https://doi.org/10.1038/s41467-021-23995-z
205. Tatla AS, Justin AW, Watts C et al (2021) A vascularized tumoroid model for human glioblastoma angiogenesis. Sci Rep 11(1):19550. https://doi.org/10.1038/s41598-021-98911-y

206. Miller JS, Stevens KR, Yang MT et al (2012) Rapid casting of patterned vascular networks for perfusable engineered three-dimensional tissues. Nat Mater 11(9):768–774. https://doi.org/10.1038/nmat3357
207. Sousa CFV, Saraiva CA, Correia TR et al (2021) Bioinstructive layer-by-layer-coated customizable 3D printed perfusable microchannels embedded in photocrosslinkable hydrogels for vascular tissue engineering. Biomolecules 11(6):863. https://doi.org/10.3390/biom11060863
208. Wang XZ, Li XD, Ding JJ et al (2021) 3D bioprinted glioma microenvironment for glioma vascularization. J Biomed Mater Res A 109(6):915–925. https://doi.org/10.1002/jbm.a.37082
209. Ruiz-Garcia H, Alvarado-Estrada K, Schiapparelli P et al (2020) Engineering three-dimensional tumor models to study glioma cancer stem cells and tumor microenvironment. Front Cell Neurosci 14:558381. https://doi.org/10.3389/fncel.2020.558381
210. Herreros-Pomares A, Zhou X, Calabuig-Farinas S et al (2021) 3D printing novel in vitro cancer cell culture model systems for lung cancer stem cell study. Mater Sci Eng C Mater Biol Appl 122:111914. https://doi.org/10.1016/j.msec.2021.111914
211. Boumahdi S, de Sauvage FJ (2020) The great escape: tumour cell plasticity in resistance to targeted therapy. Nat Rev Drug Discov 19(1):39–56. https://doi.org/10.1038/s41573-019-0044-1
212. Demaria O, Cornen S, Daëron M et al (2019) Harnessing innate immunity in cancer therapy. Nature 574(7776):45–56. https://doi.org/10.1038/s41586-019-1593-5
213. Delalat B, Harding F, Gundsambuu B et al (2017) 3D printed lattices as an activation and expansion platform for T cell therapy. Biomaterials 140:58–68. https://doi.org/10.1016/j.biomaterials.2017.05.009
214. Kim JH, Lee S, Kang SJ et al (2021) Establishment of three-dimensional bioprinted bladder cancer-on-a-chip with a microfluidic system using bacillus calmette-guerin. Int J Mol Sci 22(16):8887. https://doi.org/10.3390/ijms22168887
215. Augustine R, Kalva SN, Ahmad R et al (2021) 3D bioprinted cancer models: revolutionizing personalized cancer therapy. Transl Oncol 14(4):101015. https://doi.org/10.1016/j.tranon.2021.101015
216. Jameson JL, Longo DL (2015) Precision medicine—personalized, problematic, and promising. N Engl J Med 372(23):2229–2234. https://doi.org/10.1056/NEJMsb1503104
217. Nieto D, Jiménez G, Moroni L et al (2022) Biofabrication approaches and regulatory framework of metastatic tumor-on-a-chip models for precision oncology. Med Res Rev 42(5):1978–2001. https://doi.org/10.1002/med.21914
218. Wang J, Feng XY, Li ZC et al (2022) Patient-derived organoids as a model for tumor research. Prog Mol Biol Transl Sci 189(1):259–326. https://doi.org/10.1016/bs.pmbts.2022.03.004