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Bioprinting of *in vitro* models for personalized therapeutic delivery

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Abstract

Personalized therapeutic delivery aims to match the type, dose, timing, and localisation of treatment to each patient's unique biological profile, requiring platforms that can model individual responses and precisely control how therapeutics are released. Achieving this precision is challenging because conventional 2D cultures and animal models fail to reproduce the 3D architecture and microenvironmental cues that shape drug, gene, and growth-factor dynamics in human tissues. Bioprinted *in vitro* models address these limitations by enabling the spatially defined assembly of cells, hydrogels, and bioactive components into physiologically relevant constructs. This review examines how bioprinting is advancing personalized therapeutic delivery, focusing on how bioink chemistry, construct architecture, and matrix mechanics influence transport behavior, release kinetics, and overall therapeutic performance. We highlight bioprinted liver, cardiac, and tumor models as predictive testbeds for evaluating patient-specific responses, and discuss advanced delivery strategies, including *in situ* bioprinting and 4D adaptive systems. Together, these developments position bioprinted *in vitro* platforms as integrated tools for designing, testing, and optimizing personalized therapeutic interventions within the broader framework of personalized medicine.

Keywords: 3D printing; *In vitro* models; Bioprinting; Personalized therapy

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1. Introduction

Personalized therapeutic delivery seeks to design and control the spatial and temporal release of therapeutic agents in a manner tailored to each patient's unique molecular, cellular, and microenvironmental characteristics, forming a central pillar of

personalized medicine.[1,2] Achieving this level of precision requires platforms that not only deliver drugs locally and in a controlled manner, but also allow their effects to be evaluated in systems that approximate human tissue structure and function.[3-6] However, conventional models struggle to meet these demands. 2D monolayer cultures lack the spatial organization, extracellular gradients, and mechanical context that regulate cell behavior *in vivo*, leading to altered phenotypes and limited predictive value.[7] Animal models, while more complex, are costly, time-intensive, and often show incomplete concordance with human-specific pathways, contributing to discrepancies in drug response and poor translational success.[8] Together, these limitations hinder accurate prediction of therapeutic efficacy and reduce the capacity to personalize treatment strategies.

Bioprinted *in vitro* models address many of these constraints by enabling the fabrication of controlled 3D environments that better reflect native tissue organization and function. Through the precise spatial patterning of cells, hydrogels, and biochemical cues, bioprinting can recreate physiological architecture, extracellular matrix (ECM) composition, and microenvironmental signaling with significantly improved fidelity compared with conventional *in vitro* systems.[9-12] Compared to cell-free 3D printing, which typically fabricates acellular scaffolds that are later seeded with cells, bioprinting provides direct control over cellular composition, spatial patterning, and cell–matrix interactions from the outset. This reduces common limitations of post-seeding, including non-uniform cell distribution, poor penetration into thick scaffolds, and batch-to-batch variability in microenvironment formation. It also enables engineered heterogeneity that is difficult to achieve with cell-free printing, including gradients in stiffness, ligand density, oxygenation, and soluble-factor presentation, as well as spatially defined interfaces between parenchymal, stromal, endothelial, and immune compartments.[13-15] These constructs can be engineered with patient-derived cells, biomolecules, and data-informed design parameters, enabling disease-specific microenvironments and dynamic biological processes to be modeled in a patient-relevant manner.[16,17] Such bioprinted *in vitro* platforms support mechanistic studies, prediction of therapeutic efficacy, and planning of treatment strategies on an individual basis.

Beyond replicating tissue structure, bioprinting directly supports personalized therapeutic delivery through controlled spatial and temporal release of drugs, genes, and growth factors (GFs). Architected hydrogels, compartmentalized scaffolds, and stimuli-responsive materials permit dosing profiles tailored to patient-specific needs, enabling localized, sustained, or cue-triggered exposure. Emerging modalities, including *in situ* bioprinting and 4D shape-morphing systems, extend these capabilities by allowing constructs to conform to complex anatomy and adapt to evolving physiological conditions.[18-20]

Existing reviews of 3D bioprinting tend to emphasize printing technologies and bioink formulations,[9,10,21,22] regenerative tissue fabrication and *in vivo* implantation,[13] or bioprinted platforms for drug discovery and screening.[14,15] These topics are usually treated separately, without explicitly connecting *in vitro* disease models to the design of personalized delivery strategies. In this review, we instead focus on bioprinted *in vitro* systems as integrated testbeds for personalized therapy. We bring together bioprinted disease models, small-molecule drug depots, gene delivery scaffolds, and growth-factor-based interventions within a single framework, and analyze how architectural design, material selection, and spatiotemporal control of release jointly influence model fidelity and therapeutic readouts. In addition, we discuss how emerging adaptive modalities, including *in situ* and 4D bioprinting and acoustics-enabled approaches,[18,23,24] can be harnessed not only for regenerative implantation but also to create responsive *in vitro* platforms specifically designed for patient-tailored drug, gene, and growth-factor delivery.

2. Bioprinting

Bioprinting is an additive manufacturing approach that deposits living cells, biomaterials, and bioactive factors in a spatially controlled manner to fabricate 3D tissues and model systems with defined architecture and function. It extends conventional 3D printing using bioinks composed of hydrogels, polymers, and cell suspensions, enabling constructs that capture key aspects of native ECM, cellular organization, and microenvironmental signalling.[3-5,25-29] A wide range of bioprinting technologies has been developed, including inkjet, extrusion-based, laser-assisted, and stereolithography (SLA) systems, each offering distinct trade-offs in resolution, throughput, material compatibility, and cell handling.[25,30-34] These advances, combined with tissue-specific bioink engineering and high-resolution printing strategies, are increasingly being directed toward *in vitro* platforms that support disease modeling, drug screening, and localized therapeutic delivery.[25,35,36]

2.1. Classification of 3D bioprinting techniques

In this review, we classify the bioprinting technologies into four main groups by their building principles, including inkjet bioprinting, extrusion-based bioprinting, laser-assisted bioprinting (LAB), and SLA bioprinting (Figure 1).

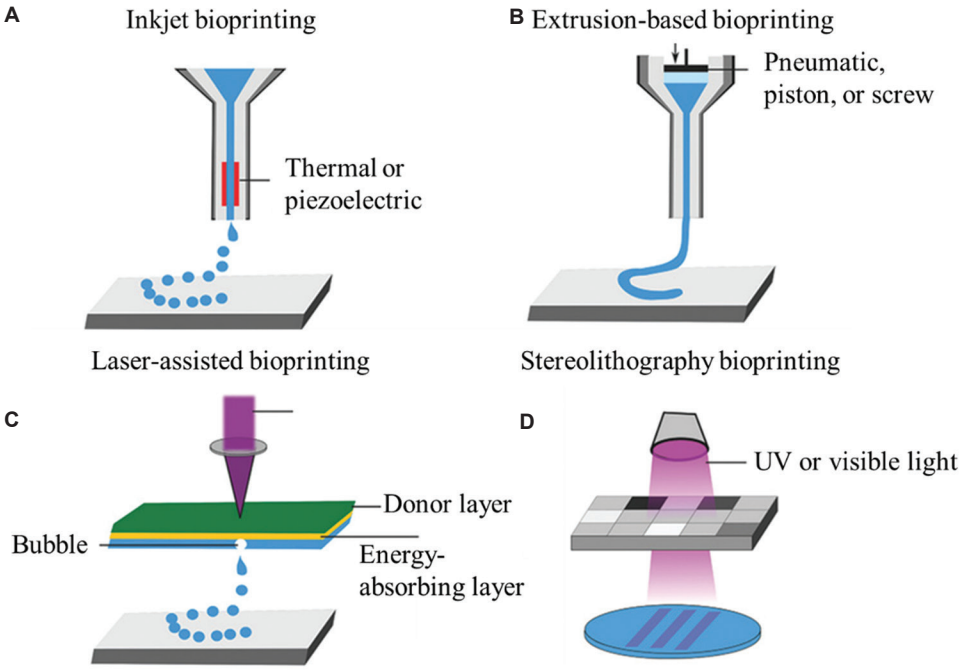

Figure 1. Schematic representation of the four main bioprinting methods. (A) Inkjet bioprinting: Utilizes piezoelectric or thermal actuators to eject precise, small droplets of bioinks containing hydrogels and cells. (B) Extrusion-based bioprinting: Deposits filaments of viscous bioinks continuously through a nozzle, driven by pneumatic or mechanical (piston or screw-based) force. This technique excels in fabricating constructs with high cell densities and structural integrity. (C) Laser-assisted bioprinting: Uses a focused laser pulse to vaporize a thin donor layer (typically metallic or energy-absorbing material), generating high-pressure bubbles that propel droplets of bioink onto the substrate. (D) Stereolithography bioprinting: Employs ultraviolet or visible light to selectively polymerize photoreactive bioinks layer-by-layer, creating a 3D construct. Adapted from Foyt *et al.*[37]

Inkjet bioprinters dispense tiny droplets of bioink (10–50 μm diameter; 1–100 pL) in controlled volumes that form part of the final construct.[38-41] In general, inkjet printers can offer high cell viability.[31] On the other hand, inkjet bioprinters have disadvantages, including the lack of precision regarding droplet size and placement, frequent nozzle clogging, unstable dispensing trajectory, non-uniform droplet size, and premature gelation.[31] High cell or ECM densities increase the risks of clogging and inconsistent droplet formation, limiting printable formulations. The bioink needs to be in a liquid form with low viscosity to allow droplet formation, which narrows the material range.[30,31]

LAB is based on the laser-induced forward transfer technique used to pattern metal particles, but has been applied to print cells and liquid materials with cell-level resolution for tissue engineering.[25,32-34] LAB can precisely pattern bioink droplets within 5.6 ± 2.5 μm of the intended pattern, improving its control over cell density and 3D patterning.[25,35] It can be applied to fabricate cell-based biosensors and print microscale tissue models and organs-on-chips to study cellular interactions and test drugs.[25-29] Disadvantages of LAB include low flow rate, high cost, metallic residues in the printed construct, and limited printing size due to its low flow rate, all of which greatly limit its application for bioprinting tissues or organs.[25,30]

Extrusion-based bioprinters consist of pneumatic or mechanical (screw-driven or piston) bioink dispensing systems and three-axis robotic stages that provide controlled relative motion between printhead and substrate along x, y, and z axes.[30,31,42] Overall, the extrusion-based bioprinting technique has the ability to dispense materials with a wide range of fluid properties and viscosities.[43] Extrusion-based bioprinter can provide improved structural integrity.[44-46] It also provides high deposition and printing speed, which can facilitate scalability over short timeframes.[47] A major limitation of current extrusion bioprinting is reduced post-print cell viability. Post-printing cell viability is in the range of 40–86%, which is lower than that of inkjet-based printers (generally over 80%).

SLA bioprinting is a high-resolution, light-based additive manufacturing technique that produces 3D biological structures by selectively photocuring layers of cell-laden, photocrosslinkable bioinks using ultraviolet (UV) or visible light.[48,49] SLA bioprinters can typically achieve feature resolutions in the 10s of micrometers, with some advanced systems reaching 1–2 μm in the x–y plane. Z-axis layer thickness is usually between 1

and 50 μm, depending on the resin, optics, and printer configuration.[48,50] SLA offers key advantages, including micro- to nanoscale geometric fidelity, the capability to replicate complex tissue architectures, and a high-quality surface finish. Furthermore, its transparent printed structures facilitate imaging compared with other 3D printing techniques, making it particularly advantageous for medical device fabrication.[51,52] However, the need for specialized photocrosslinkable bioinks constrains it, as dense or opaque formulations reduce light penetration and UV exposure or photoinitiator by-products may cause cytotoxic effects.[11,53]

2.2. Hydrogels for 3D bioprinting

During the bioprinting process, the biomaterial solution or mixture of multiple biomaterials, usually encapsulating the desired cell types, used for constructing tissue structures, is termed bioink.[21] Choosing an appropriate bioink is critical: It must be biocompatible to maintain cell viability, have suitable rheology for high-resolution deposition, and provide sufficient post-print mechanical stability to preserve construct shape.[22,54] Hydrogels are the predominant bioinks. These water-swollen polymer networks have high water content, enabling nutrient and waste transport and creating an ECM-like microenvironment that supports cell adhesion, proliferation, migration, and differentiation.[55-59] Their gelation permits homogeneous cell seeding or encapsulation, and biochemical or physical cues can be incorporated to direct cell behavior.[60]

There are various materials used to form hydrogels for tissue engineering applications. These can be categorized as natural or synthetic hydrogels.[61] Natural hydrogels include alginate, collagen, agarose, fibrin, and gelatin, and have the advantage of resembling native ECM chemically and structurally. Due to the natural origin (e.g., bovine fibrinogen and rat tail collagen), the compositions and properties of natural hydrogels may vary from one batch to the next.[62] Synthetic hydrogels commonly used in tissue engineering include polyethylene oxide (PEO), polyvinyl alcohol (PVA), Pluronic F127, and composites thereof. Synthetic hydrogels possess reproducibility and tailorability of their chemistry and properties.[63-65]

2.2.1. Natural hydrogels

Collagen provides native ECM ligands and supports migration and differentiation, with well-established biocompatibility and enzymatic degradability.[66,67] Chemical modification and crosslinking can tune mechanics and degradation, and permit the conjugation of glycosaminoglycans or GFs.[68] Its low viscosity and slow gelation reduce shape fidelity. Therefore, collagen is commonly concentrated, reinforced, or blended to meet *in vitro* printing and handling requirements.[69]

Alginate is a linear copolymer of β-*D*-mannuronic acid and α-*L*-guluronic acid derived from brown seaweed or bacteria.[64] It is biocompatible and widely used for cell encapsulation in *in vitro* models, but native alginate lacks cell-adhesive ligands and shear-thinning, limiting cell–matrix interaction and printability at higher viscosities.[70] Typical formulations are 1–4% w/v and are often insufficiently viscous to print unaided. Practical strategies include partial pre-crosslinking with $CaCl_2$ before extrusion and post-print stabilisation in a $CaCl_2$ bath, or direct printing onto/into $CaCl_2$ to trigger immediate gelation.[66,71-73] Degradation at physiological pH can be rapid, so alginate is frequently blended or functionalized when longer culture or remodeling is required.

Gelatin is a collagen-derived, water-soluble polypeptide with excellent biocompatibility but poor mechanical stability and rapid enzymatic degradation in physiological conditions, limiting its use as a standalone bioink.[74-76] It is therefore often used as a blend component to enhance bioactivity and printability, for example, with alginate.[74,77] Methacrylated gelatin (GelMA) introduces photocurable groups, enabling rapid, spatially controlled crosslinking and tunable stiffness while maintaining adhesive motifs.[74,78] The final product has been called three different names: Gelatin methacrylate,[79] gelatin methacryloyl,[80] and gelatin methacrylamide,[81] with the same acronym GelMA.

Cellulose is a linear polysaccharide composed of β-1,4-linked *D*-glucose units that pack into highly ordered fibrils through extensive hydrogen bonding, giving it high tensile strength and low solubility in water.[82] It is the main structural component of plant cell walls and the most abundant renewable biopolymer. Cellulose-based materials are widely used as scaffolds and reinforcement phases in biopolymer hydrogels for tissue engineering.[83]

Chitosan is a linear cationic polysaccharide obtained by the deacetylation of chitin, whose primary amine groups confer pH-responsive solubility, mucoadhesion, intrinsic antibacterial activity, and the ability to form polyelectrolyte complexes with anionic polymers, proteins, and nucleic acids.[84] In hydrogel and bioink design, chitosan can be physically gelled by temperature or ionic crosslinking with multivalent anions. It is frequently chemically modified to improve solubility at physiological pH, enable photocrosslinking, and tune mechanical properties for 3D bioprinting.[85]

2.2.2. Synthetic hydrogels

PEO is the polymer of ethylene oxide monomers with a chemical formula of $(CH_2CH_2O)_n$. Based on the molecular

weight (MW), this polymer has different names, including polyethylene glycol (MW < 20 kDa) and poly(oxyethylene) (any MW).[86] On its own, PEO lacks viscosity and shape retention for 3D printing. Therefore, it is combined with other polymers to tune extrusion behavior and diffusion, or used sacrificially to create porosity and channels. In blends, it can support chondrocyte viability and ECM deposition for cartilage-relevant *in vitro* models.[87]

Pluronic F127 (Poloxamer 407) is an amphiphilic PEO–poly(propylene oxide) (PPO)–PEO block copolymer that forms micelles and undergoes thermo-reversible gelation near physiological temperature.[88-90] Above its critical micellization temperature and concentration, it self-assembles into micelles with hydrophobic PPO cores and hydrophilic PEO shells, enabling the encapsulation of hydrophobic drugs and enhancing cellular uptake.[90-93] This micellization underlies its thermogelling behavior, where viscosity increases near physiological temperature, allowing printable constructs with good shape fidelity and minimal shear stress on embedded cells.[90,92,93] F127 is widely studied in tissue engineering and drug delivery due to its ability to load diverse therapeutics, support local release, and serve as a transient 3D matrix. It has been shown to promote adhesion, angiogenesis, and collagen deposition at defect sites, facilitating tissue regeneration.[90] In bioprinting, its tunable rheology allows extrusion over a broad concentration and temperature range with high post-print viability.[88,94,95]

PVA is a water-soluble, Food and Drug Administration-approved polymer valued for mechanical robustness and biocompatibility.[57] It typically requires freeze–thaw or UV/chemical crosslinking, which is not cell-friendly for encapsulation, and its low protein and cell adhesion limit its use as a standalone bioink.[96] For *in vitro* models, PVA is best used as a structural or carrier component, or blended and surface-modified to introduce bioactivity; mineral or fibrous reinforcements can improve load-bearing performance where needed.[57,97] These anti-fouling properties are useful for barrier layers and drug-delivery films, reducing infection and adhesions.[98]

2.3. Cells for bioprinting

Across the *in vitro* bioprinting literature, cell sourcing is typically reported using three high-level, non-overlapping classes: Established cell lines, primary cells, and stem cell-based systems.[99] This framing is widely used in bioprinting reviews because it maps cleanly onto the main trade-off that governs *in vitro* interpretability: Standardization and scalability versus physiological fidelity and donor specificity.

Established cell lines remain the dominant option for method development and many screening-oriented bioprinted models because they expand reliably, tolerate printing-associated stresses, and support reproducible cross-study benchmarking of bioinks, printing parameters, and assay workflows.[9,10,30] Cell lines are frequently used in tumor and disease microenvironment reconstructions, where throughput and geometric control are prioritized, but reviewers generally expect explicit caveats when these models are positioned as predictors of patient-specific response.[100-102] Representative examples include bioprinted cervical cancer constructs using HeLa cells[103] and cervical dysplasia models incorporating SiHa cells alongside skin-relevant compartments.[104]

Primary cells, isolated directly from tissues, are preferred when differentiated function and physiological relevance are central to the *in vitro* endpoint. This is particularly evident in liver modeling, where primary human liver cells and human tissue-derived constructs are used to stabilize metabolic function for drug discovery and hepatotoxicity assessment.[105] For example, primary hepatocyte-based systems are commonly supported by microenvironment design and co-culture strategies to preserve clinically relevant enzyme activity.[106] For *in vitro* bioprinting studies, these factors make source reporting (species, donor context, isolation, and passage) a major determinant of how confidently results can be compared across studies.[7]

Stem cell-based systems are treated as a distinct class in most reviews because their differentiation and maturation trajectories, rather than simple expansion, become the dominant experimental variables. Adult stem or stromal cells, especially mesenchymal stem or stromal cells, are among the most common bioprinted human cell types because they expand robustly and support bone, cartilage, and wound-healing related applications.[13,107,108] Pluripotent stem cells (PSCs) and induced PSC-derived lineages extend this direction toward donor-matched, multi-lineage human modeling, but reviews emphasize that differentiation efficiency and maturation state must be controlled to avoid confounding bioink or printing effects.[99,109]

2.4. Bioink design rules: Rheology, gelation, and stability

Bioprinting performance is governed by a modality-specific coupling between material properties and process parameters, so material requirements should be framed by the underlying deposition physics. For inkjet bioprinting, droplet generation imposes tight bounds on viscosity and surface tension, while cell or particle loading is limited by nozzle clogging and satellite droplets, making actuation waveform and nozzle wetting critical controls.[110] In extrusion-based bioprinting,

printability depends primarily on rheology and post-deposition stabilisation, including shear-thinning to limit pressure, yield stress and elastic recovery for filament shape retention, and gelation or crosslinking kinetics matched to layer stacking. Environmental factors can become first-order variables for hydrated systems.[111] In SLA bioprinting, the key constraints shift to photochemistry and optics, including resin viscosity and recoating behavior, photoinitiator efficiency and cytocompatibility, light attenuation, oxygen inhibition, and the exposure–cure depth relationship that controls fidelity and overcuring in complex geometries. Exposure settings such as curing depth, cumulative overcuring, print thickness, and print orientation greatly impact dimensional accuracy in ocular-relevant structures.[112] For LAB, stable transfer depends on thin-film formation and laser–bioink coupling, where viscosity and viscoelasticity interact with laser fluence and donor-layer design to determine jet stability and cell stress.[113]

3. Bioprinting *in vitro* models for personalized therapeutic delivery

Bioprinting provides a versatile platform for creating patient-specific *in vitro* models that bridge experimental research and clinical application.[13] By integrating precise spatial control of cells, biomaterials, and bioactive factors, it enables the fabrication of tissues that mimic native structure and function, supporting both disease modeling and therapeutic testing under physiologically relevant conditions.[114] These models facilitate high-fidelity drug screening and the development of targeted interventions while reducing reliance on animal testing. Beyond modeling, bioprinting offers opportunities for personalized delivery of drugs, genes, and GFs, allowing controlled spatial and temporal release tailored to individual patient needs.[115] Emerging modalities—including 4D bioprinting, *in situ* fabrication, and acoustic levitation systems—are further expanding the precision and adaptability of this technology, moving the field toward responsive, patient-tailored platforms that unify modeling, diagnosis, and treatment within a single bioprinted framework.[23,24] A comparative overview of representative bioprinted in vitro models and delivery strategies discussed in this section, including bioink composition, printing modality, model type, and reported therapeutic outcomes, is summarised in Table 1.

3.1. Disease modeling and drug screening

Bioprinted *in vitro* models offer a powerful alternative to conventional 2D cultures and animal studies for investigating disease mechanisms and evaluating therapeutics. By organising multiple cell types within biomimetic scaffolds that replicate the ECM, vascularisation, and mechanical cues of native tissues, these models capture pathophysiological processes with higher fidelity. Such systems can reproduce tumor microenvironments, fibrotic niches, or organ-specific architectures, enabling more predictive assessments of drug efficacy and toxicity while reducing reliance on animal testing. The integration of patient-derived cells further supports personalized drug screening, allowing therapies to be tested directly in constructs that reflect individual genetic and cellular contexts. Combined with high-content imaging, omics readouts, and microfluidic perfusion, bioprinted models provide a dynamic and controllable platform for mechanistic studies, biomarker discovery, and preclinical drug evaluation in a physiologically relevant setting.

Three-dimensional bioprinting allows for the fabrication of tissue-specific scaffolds that mimic native environments and facilitate drug testing, disease progression studies, and personalized treatment strategies. While material compatibility can pose challenges, bioprinting enables precise deposition of biomimetic scaffolds, integrating cells into controlled architectures to simulate physiological conditions. Unlike traditional 2D culture systems, 3D-printed tissue models offer improved fluidic properties and mechanical accuracy, closely replicating native tissue behavior and drug interactions.[7]

Among different organs, the liver is central to xenobiotic metabolism and detoxification, making hepatotoxicity research a priority in preclinical drug screening.[116] However, species differences limit the predictive power of animal models, and patient-to-patient variability in liver disease progression further complicates therapeutic assessment.[8] To overcome these challenges, extrusion-based bioprinting has been applied to fabricate hepatic constructs with improved physiological relevance. Kang *et al.*[117] created a five-layered hepatic scaffold using alginate hydrogel and hepatocyte-like cells, demonstrating albumin secretion and asialoglycoprotein receptor expression *in vitro*, with continued proliferation and albumin production after implantation *in vivo* (Figure 2A). Kizawa *et al.*[105] developed a scaffold-free 3D-bioprinted human liver tissue where hepatocyte spheroids self-assembled into organized microtissues. The construct maintained drug, glucose, and lipid metabolism as well as bile acid secretion for over 7 weeks, with sustained expression and activity of cytochrome P450 3A4 (CYP3A4) and other hepatic enzymes. The tissue also preserved insulin-regulated glucose production and formed sinusoid- and bile-duct-like structures, demonstrating self-organisation and long-term metabolic stability absent in conventional 2D or short-lived spheroid models. Furthermore, tissues printed from Zucker-fatty-rat hepatocytes replicated non-alcoholic fatty liver disease pathology, confirming the system's suitability for disease modeling and preclinical hepatotoxicity screening. This scaffold-free approach exemplifies how bioprinting can

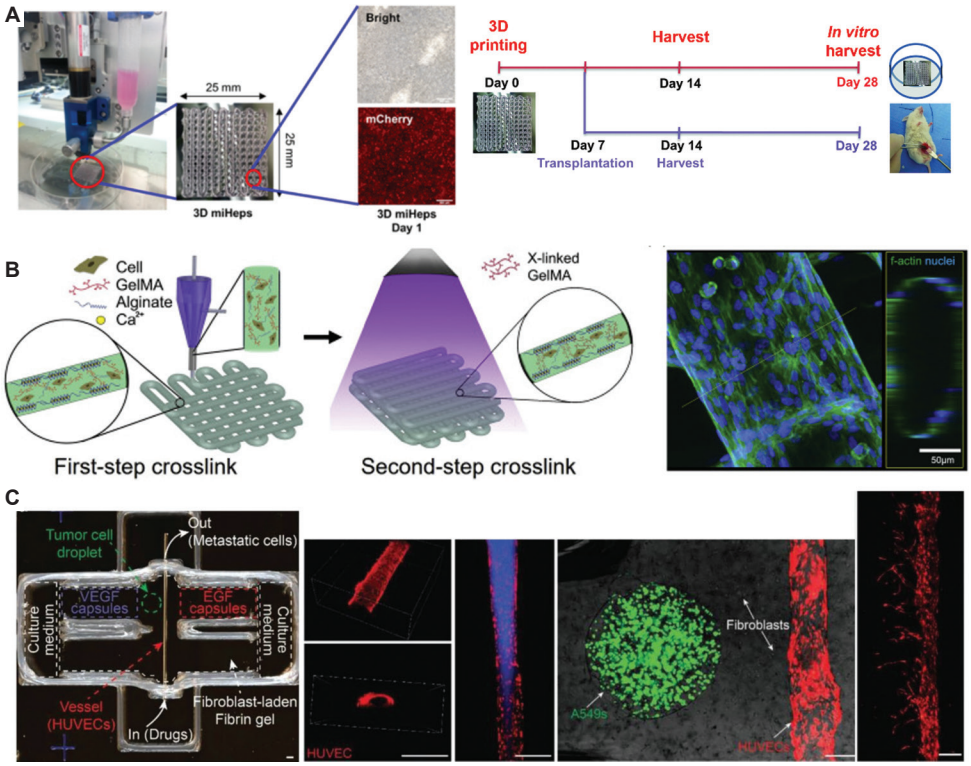

Figure 2. Bioprinted *in vitro* disease models and drug screening platforms. (A) Extrusion-based bioprinting of cell-laden constructs of hepatocyte-like tissues that can be cultured *in vitro* or transplanted *in vivo* and analyzed over time for function and treatment response. Reprinted with permission from Kang *et al.*[117] Copyright © 2018 Mary Ann Liebert. (B) Two-step crosslinked, cell-laden lattices that provide mechanically stable 3D microenvironments for evaluating drug effects. Reprinted with permission from Zhang *et al.*[118] Copyright © 2016 Elsevier. (C) 3D-printed *in vitro* tumor models mimicking metastatic dissemination by the integration of tumor cells, vascular conduits, and factor signals within a cell-laden fibrin gel to reconstruct tumor microenvironments. Reprinted with permission from Meng *et al.*[100] Copyright © 2019 Wiley-VCH

produce physiologically relevant, patient-specific hepatic models that improve the prediction of drug metabolism and toxicity.

Cardiotoxicity remains a major concern in drug development, with animal models often failing to predict human cardiac responses, leading to drug withdrawal from the market.[119] Bioprinted *in vitro* cardiac scaffolds can improve drug screening and reduce reliance on animal testing. Zhang *et al.*[118] engineered a cardiac construct by integrating extrusion and photocuring bioprinting with alginate/GelMA bioinks and endothelial cells (Figure 2B). The resulting scaffold mimicked anisotropic cardiac organisation and supported rat cardiomyocytes in a perfusion bioreactor, enabling organ-on-a-chip applications. The model responded to doxorubicin with a dose-dependent reduction in beating rate, confirming its relevance for drug screening.

Despite advancements in cancer treatments, drug development remains highly inefficient, with a 95% failure rate in clinical trials.[102] This is largely due to inadequate preclinical models that do not capture the complexity of the tumor microenvironment. Bioprinting enables precise reconstruction of tumor models incorporating cytokine gradients, nutrient transport, and dynamic stromal–cancer interactions.[101] Injectable vascularized scaffolds have been integrated to promote angiogenesis, tumor progression, and drug response, providing more predictive platforms for screening. Shi *et al.*[120] designed a 3D-printed distal scaffold composed of poly(lactic-co-glycolic acid) (PLGA), chitosan, and gelatin, loaded with 5-fluorouracil and doxorubicin. The scaffold provided controlled local drug release, absorbed blood at the resection site, and maintained a tumor-inhibiting microenvironment, thereby reducing recurrence and distal metastases. These studies show how bioprinting can model tumor biology while supporting localized, post-surgical therapy.

Drug screening evaluates candidate compounds for activity, safety, toxicity, and efficacy, forming a critical step in pharmaceutical development. Conventional *in vivo* methods remain costly, time-intensive, and often limited by interspecies differences. Bioprinted *in vitro* tissues provide a compelling alternative, offering physiologically relevant human models that reduce reliance on animal testing,

Table 1. A summary of research and manufactured applications in 3D printing technologies for drug delivery products

Bioinks	Printing methods	*In vitro* models	Results	References
Alginate hydrogel/mouse-induced hepatocyte-like cells	Extrusion-based bioprinting	Hepatic liver structure	Cell growth and albumin increase *in vitro* and *in vivo*	117
Hepatic drug/metabolic enzyme	Scaffold-free bioassembly	Liver tissue	Glucose production bile acid secretion	105
Endothelial cells+GelMA/Alginate/Rat cardiomyocyte	Extrusion and photocuring bioprinting	Heart on a chip	Cardiovascular drug screening on a chip	118
Nanocellulose–alginate bioink laden with human chondrocytes	Extrusion-based bioprinting	Primary human chondrocyte cartilage constructs	High print fidelity and viability; supports cartilage-relevant ECM formation	145
Decellularized ECM hydrogel with iPSC-derived cardiomyocytes and endothelial cells	Extrusion-based bioprinting	Patient-matched vascularized cardiac tissue constructs	Thick, perfusable patches with vascular features	146
Porcine aortic endothelial cells with plasmid DNA	Inkjet bioprinting	Gene delivery scaffold	Achieved controlled spatial transfection and expression, and localized gene delivery	132
Alginate hydrogel/$CaCO_3$+bone marrow derived MSCs	Extrusion-based bioprinting	Growth-factor releasing scaffold	Spatially direct MSC differentiation	144
Polylactide+nitrofurantoin+hydroxyapatite	Multi-material extrusion	Drug-eluting implant/disc	Tunable release profiles enhanced antibacterial efficacy	127
GelMA/ChiMA/AlgiMA scaffolds with AAV-2 or lipofectamine–DNA	Digital light processing bioprinting	Gene delivery scaffold with tunable release	Controlled viral release; matched transfection kinetics in 293T cells	138
PCL/VEGF/BMP-2	Extrusion-based bioprinting	Bone regeneration construct	Controlled growth factor delivery/improved bone repair	141

Abbreviations: AAV-2: Adeno-associated virus type 2; AlgiMA: alginate-MA; BMP-2: Bone morphogenetic protein 2; ChiMA: chitosan-MA; ECM: Extracellular matrix; iPSC: Induced pluripotent stem cell; MSC: Mesenchymal stem cell; PCL: Polycaprolactone; VEGF: Vascular endothelial growth factor; GelMA: Methacrylated gelatin.

enable repeated interventions, and lower overall costs.[14,121] In addition, bioprinting *in vitro* tissues can reduce animal use and enable repeated interventions in human-relevant models, significantly lowering costs compared to *in vivo* methods. These advantages make *in vitro*-based drug screening a promising tool in drug delivery research and development.[15,122]

In vitro drug-screening approaches can be grouped into three types: (i) 3D tissue constructs, which capture multicellular organisation and microenvironmental cues; (ii) organ-on-a-chip systems, which integrate microfluidics to simulate perfusion and barrier function; and (iii) larger-scale tissue/organ constructs, designed to replicate structural and functional complexity.[15] Each approach enhances the predictive power of preclinical testing compared with traditional 2D culture.

An emerging application of bioprinting in drug screening is the fabrication of 3D-printed tumor models and the precise monitoring of the delivered drug. To enhance the translatability of potential anticancer drugs, a variety of tumor models have been developed. These constructs include formats such as cell-laden scaffolds, multicellular spheroids, and tumor metastasis models. For example, Zhao *et al.*[123] investigated cervical tumor structures by 3D-printing HeLa cells in a hydrogel to mimic the ECM characteristics and the complex microstructure of cervical cancer. The 3D cell-laden constructs could successfully mimic the microenvironment of the tumor and better capture physiologically cell–cell and cell–ECM interactions in comparison to the 2D model. Therefore, 3D tumor cell-laden models are expected to yield more informative results. In another study, vascularized tumor models were engineered to replicate key stages of metastasis, with stromal cells and GFs inducing coordinated migration of tumor and endothelial cells.[100] This platform was then used to screen immunotoxins, demonstrating its potential for evaluating anticancer therapeutics in a dynamic, disease-relevant setting (Figure 2C).

Overall, 3D bioprinting enables the creation of complex, biomimetic drug-screening models that better reflect human physiology than 2D systems. While challenges such as standardization and accurate prediction of *in vivo* toxicity remain, these advances highlight the promise of bioprinted constructs as next-generation platforms for safer, more personalized drug development.

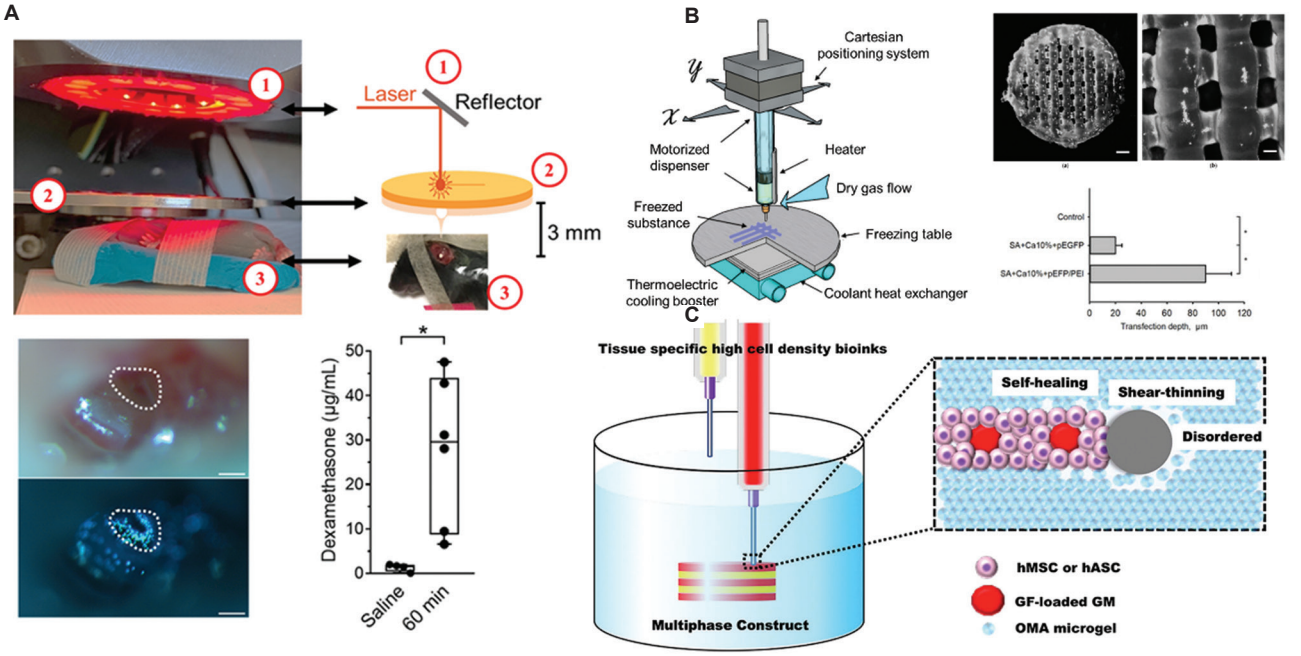

Figure 3. Bioprinting strategies for personalized delivery of drugs, genes, and growth factors. (A) Round window membrane imaging post-laser-assisted bioprinting of thermosensitive hydrogel containing dexamethasone phosphate for intracochlear drug delivery, enabling precise deposition and controlled diffusion across the round window membrane. Reprinted with permission from Jaffredo *et al.*[128] Copyright © 2023 Elsevier. (B) Cryoprinting-based extrusion of sodium alginate scaffolds encapsulating plasmid DNA (*pEGFP*), preserving gene integrity and achieving spatially confined *in vivo* transfection. Adapted from Khvorostina *et al.*[129] (C) Tissue-specific, high-cell-density bioinks integrated with growth-factor-laden gelatin microparticles (GMs), providing self-healing and shear-thinning behavior for spatiotemporal control of osteochondral tissue formation. Adapted with permission from Jeon *et al.*[130] Copyright © 2025 Elsevier
Abbreviations: hASC: Human adipose-derived stem cell; hMSC: Human mesenchymal stem cell; OMA: Oxidized and methacrylated alginate.

3.2. Delivery of drugs, genes, and GFs

Precise control of exposure in space and time is central to personalized therapy.[115] Bioprinting enables spatial and temporal control by patterning depots, barriers, channels, and gradients within defined 3D architectures. Material chemistry and crosslinking determine mesh size, degradability, and affinity, which together tune loading, stability, and sustained or pulsatile release of small molecules, biologics, nucleic acids, and GFs.[124,125] Architectures such as core–shell filaments, multilayers, perfusable networks, and granular microgels support directional transport and combination regimens, and 4D responsiveness allows dosing schedules that adapt to physiological cues. In the subsections that follow, we outline modality-specific strategies, quantitative characterization in bioprinted models, and practical issues of sterility, consistency, and regulatory acceptance.

3.2.1. 3D bioprinting in controlled drug delivery

Drug delivery is a fundamental process in therapeutic interventions, beginning with the release of a pharmaceutical compound into a biological system, followed by its absorption, distribution, metabolism, and eventual excretion (ADME).[126] Water *et al.*[127] developed a patch incorporating nitrofurantoin and hydroxyapatite within polylactide strands, forming structured drug-loaded discs. Their study demonstrated that drug release from these discs successfully inhibited *Staphylococcus aureus* growth when reaching 30%, showcasing the potential of bioprinting for localized and patient-specific treatment.

Jaffredo *et al.*[128] demonstrated LAB's potential for minimally invasive intracochlear drug administration by fabricating thermosensitive hydrogels containing dexamethasone phosphate, which were deposited onto the mouse round window membrane for controlled diffusion into the perilymphatic space (Figure 3A). Shi *et al.*[120] developed an "intelligent" 3D-printed scaffold composed of PLGA, gelatin, and chitosan, loaded with dual anti-cancer agents—doxorubicin and 5-fluorouracil. Using electro-hydrodynamic jet (E-jet) printing, the team fabricated a porous, pH-responsive structure with integrated hemostatic and wound-healing functions. The scaffold responded to the mildly acidic tumor microenvironment by accelerating drug release, while its outer gelatin–chitosan layer absorbed blood and residual tumor cells after resection. *In vitro* assays showed strong cytotoxicity toward triple-negative breast cancer cells and excellent fibroblast and endothelial cell compatibility. *In vivo*, the

scaffold significantly reduced tumor recurrence and distal metastasis, improved survival, and promoted tissue repair without systemic toxicity. Their study demonstrates how 3D bioprinting can yield multifunctional, responsive implants for postoperative, patient-specific chemotherapy and local wound regeneration.

Bioprinting enables precision, multi-drug release by controlling scaffold architecture at the microscale, creating patient-specific delivery systems that improve efficacy and limit systemic side effects. Integrating bioprinting with personalized medicine supports bespoke dosing schedules and spatial drug placement, but clinical adoption depends on better bioinks, scalable manufacturing, and clear regulatory pathways. Progress in stimuli-responsive bioinks that react to physiological cues, together with real-time imaging and computational modeling to optimize diffusion profiles, will further improve control. With sustained interdisciplinary work, bioprinted drug-delivery platforms can support tailored therapies that align with individual physiology and disease course.

3.2.2. 3D bioprinting in gene delivery

Gene modification techniques have been widely explored for the replacement, editing, splicing, and regulation of inactive or defective genes. One key approach is gene editing, which can introduce therapeutic nucleic acids into cells to correct genetic defects or enhance cellular functions. An extension of gene editing is gene silencing, which enables targeted treatment of various diseases, including viral infections, neuroblastoma, and ophthalmological disorders.[131] Various techniques exist for gene delivery into cells, including electroporation, liposome-mediated transfection, microinjection, and viral transfection. Gene therapy has demonstrated potential for both *in vivo* and *in vitro* tissue regeneration, yet its clinical translation remains challenging due to low cell viability, immune responses, viral toxicity, low transfection efficiency, and the need for additional post-treatment processing.[132-134] Given these drawbacks, innovative biofabrication techniques such as 3D bioprinting present a promising alternative for safe and efficient gene delivery.

Three-dimensional bioprinting positions GFs, stem cells, and nucleic acids within architected scaffolds to create controlled microenvironments for gene therapy.[135] Spatial patterning of depots and gradients, combined with material-controlled mesh size, degradability, and affinity, enables precise spatial and temporal release for localized and sequential dosing with adjuvants that boost transfection and expression. Printed matrices also support the differentiation of autologous cells into multiple lineages for personalized interventions.[136] Genetically modified cells can serve as bioactive inks, with print parameters governing localisation, dose, and delivery order while preserving viability.[137] Compared with conventional methods, bioprinted constructs limit systemic exposure and toxicity by matching release to target sites and cell residence times, improving overall efficiency.[136]

Drop-on-demand methods enable precise placement of vectors and cells. For example, Xu *et al.*[132] used inkjet bioprinting to deposit plasmid vectors encoding a fluorescent reporter alongside porcine aortic endothelial cells, achieving successful transfection *in vitro* and *in vivo*, and demonstrating controlled gene expression for regenerative applications. Xiang *et al.*[138] used digital light processing to print GelMA, chitosan-MA (ChiMA), and alginate-MA (AlgiMA) scaffolds encapsulating adeno-associated virus type 2 (AAV-2) or lipofectamine–DNA. They showed that release kinetics could be dialled by electrostatics: AAV released slowly from negatively charged AlgiMA (~4.6% by day 14), moderately from GelMA (~45.5% by day 14), and rapidly from positively charged ChiMA (~70.9% by day 14). They further linked these tunable releases to adjustable transfection kinetics in 293T cells, demonstrating scaffold-mediated, light-printed control of gene delivery. Khvorostina *et al.*[129] cryoprinted sodium-alginate ("gene-activated") scaffolds with plasmid DNA (*pEGFP*). The process preserved plasmid integrity, supported *in vitro* HEK293 transfection, and produced detectable *EGFP* expression *in vivo* after implantation, with figures reporting transfection depth and increased numbers of *EGFP*-positive cells versus controls—evidence that extrusion-printed, vector-laden hydrogels can act as local gene depots (Figure 3B).

Combining bioprinting with gene delivery creates tightly controlled, patient-specific treatments that aim to maximize efficacy while limiting adverse effects. Key needs include bioinks that preserve vector activity and cell health, scalable and sterile workflows, and rigorous characterization of dose, kinetics, and off-target effects to support regulatory acceptance. Integrating nanotechnology, responsive biomaterials, and bioprinted architecture will underpin next-generation regenerative gene therapies tailored to individual patients.

3.2.3. 3D bioprinting in GF therapy

GFs play a crucial role in tissue engineering, facilitating cell–cell communication within the surrounding microenvironment.[139] These signaling molecules bind to specific receptors on cell membranes, influencing cell fate, proliferation, and differentiation. The duration, concentration, and spatial distribution of GFs regulate

cellular responses, making precise control over their release essential for effective tissue regeneration.[139,140] Despite their regenerative potential, GF therapy faces several challenges. GFs are large molecules, limiting their penetration into tissues. They possess a short half-life, reducing their effectiveness over time. In addition, systemic delivery at high concentrations can lead to toxicity, causing unintended side effects. These limitations underscore the need for targeted and sustained delivery methods, particularly in bone regeneration, where inefficient delivery can lead to heterotopic ossification.[139,141]

Jeon *et al.*[130] demonstrated a 3D bioprinting strategy for GF delivery using tissue-specific, high-cell-density bioinks incorporated with GF–laden gelatin microparticles (GMs) (Figure 3C). The bioinks, composed of individual stem cells or cell aggregates, were printed into a photocrosslinkable, shear-thinning, and self-healing oxidized methacrylated alginate microgel-supporting bath, which maintained high structural fidelity and enabled cellular condensation. Sustained and spatially controlled release of GFs such as transforming GF-beta 1 and bone morphogenetic protein 2 from the GMs promoted localized differentiation of stem cells into cartilage and bone, respectively, leading to the formation of multiphase osteochondral constructs. The system provided precise spatial control of biochemical cues without external supplementation, enabling engineered tissues with defined architecture and function. This approach highlights how bioprinting can integrate GF delivery directly within high cell-density bioinks to achieve spatiotemporal control of cell differentiation for regenerative tissue fabrication.

Three-dimensional bioprinting provides an effective platform for encapsulating GFs within scaffolds, ensuring uniform distribution and controlled release. Studies have demonstrated that biodegradable polymeric scaffolds serve as efficient carriers for GF delivery. For example, PLGA and polyester–urethane scaffolds have been shown to support angiogenesis by enabling sustained release of vascular endothelial GF (VEGF) and fibroblast GF-2.[142,143] Alginate-based bioinks have also emerged as a promising material for controlled release of human vascular endothelial cell GF. The MW of alginate influences its degradation rate, thereby allowing precise modulation of GF release. In addition, the choice of crosslinking strategy affects printability, protein delivery, and mechanical properties, making alginate a versatile carrier for endothelial GF delivery.[144]

The integration of 3D bioprinting with GF therapy provides a controlled, localized, and sustained delivery system, overcoming the limitations of traditional delivery methods. By precisely tuning scaffold composition and degradation rates, bioprinting enables spatially and temporally controlled GF release, improving regenerative outcomes. As research advances, further optimization of bioinks, crosslinking methods, and scaffold architectures will be critical for enhancing the therapeutic potential of GFs in tissue engineering.

3.3. Emerging bioprinting modalities for personalized therapeutic delivery

3.3.1. In situ bioprinting

In situ bioprinting represents a major evolution in additive manufacturing for healthcare, enabling the direct deposition of bioinks, drugs, or living cells at the site of injury or treatment.[18] Unlike conventional *ex situ* fabrication, where constructs are printed separately and later implanted, *in situ* approaches eliminate transfer steps and allow real-time adaptation to patient anatomy. This technique can tailor geometries and compositions according to intraoperative imaging or sensor feedback, creating structures that match individual defect contours and physiological environments.[19,147] Such capability makes *in situ* printing especially promising for personalized drug delivery, as it enables precise placement of therapeutic materials with spatial control, reducing systemic exposure while enhancing local efficacy. For example, extrusion- and light-based systems have been used to print antibiotic- or chemotherapeutic-laden hydrogels directly into tissue defects, achieving localized and sustained drug release with minimal surgical disruption. The combination of real-time printing and site-specific formulation aligns with the broader goals of personalized medicine, allowing each construct's dosage, shape, and degradation rate to be tuned to the patient's biological response.[16,24,148]

A recent breakthrough in this field is the development of omnidirectional and multi-material *in situ* 3D printing using acoustic levitation.[23,149,150] Chen *et al.*[151] developed an acoustophoretic system that uses an array of ultrasonic transducers to acoustically trap, levitate, and position droplets of material mid-air, enabling contact-free, nozzle-less deposition of bioinks and functional materials in any orientation (Figure 4). AcoustoFab can handle a wide viscosity range (1–5 × 10^6 mPa·s) and print multiple materials, from structural polymers to cell-laden hydrogels, maintaining high cell viability (>90%) for at least 10 days in culture. By printing directly onto non-planar and living substrates, the technology enables conformal, patient-specific deposition of therapeutic and structural materials without mechanical interference or contamination risk. For drug delivery, this means that drug-loaded hydrogels or multi-material composites can be printed directly on wound sites or complex tissue geometries, offering spatial and temporal control over drug release, tissue regeneration, or sensing functions.

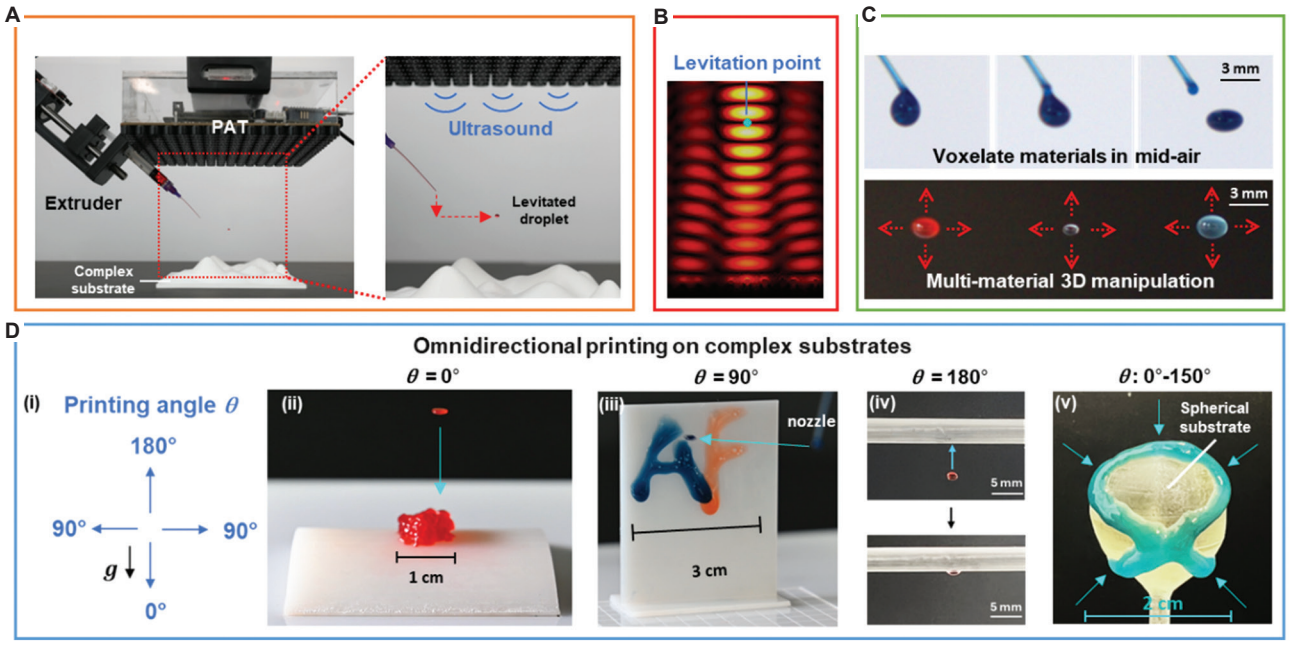

Figure 4. Acoustophoretic 3D printing enables omnidirectional, multi-material fabrication. (A) A phased array transducer levitates droplets for precise deposition on complex substrates. (B) Acoustic field visualization showing the levitation point. (C) Mid-air voxelation and multi-material manipulation. (D) Omnidirectional printing at varied angles (0–180°) on flat, vertical, inverted, and spherical surfaces, demonstrating adaptive and contactless printing. Adapted from Chen *et al.*[151]

3.3.2. 4D bioprinting

The emergence of 4D bioprinting—an evolution of 3D bioprinting that incorporates time-dependent, stimuli-responsive behaviors—offers transformative advantages for personalized medicine. Unlike static constructs, 4D-bioprinted scaffolds and tissues can adapt, self-transform, and dynamically interact with their environment, enabling precision in drug, gene, and cell delivery. Such constructs can self-fold, unfold, or deform to release therapeutic agents at specific times and locations, providing spatiotemporal control that enhances treatment efficacy while minimizing systemic side effects.[152-155]

Most 4D bioprinting systems leverage stimuli-responsive polymer networks to induce programmed, time-dependent shape change. Common triggers include temperature, humidity or hydration, and ionic or chemical cues, which act by modulating polymer swelling, reversible crosslinking, or interfacial strain to generate differential deformation between printed regions.[152,156,157] Thermoresponsive polymers are widely used because their phase transitions can be engineered near physiological temperatures. For example, crosslinked poly(N-isopropylacrylamide) (pNIPAM) hydrogels swell and shrink with temperature, and an early pNIPAM–polycaprolactone bilayer demonstrated reversible folding and unfolding in water for controlled encapsulation and release[158] (Figure 5A). However, the limited biocompatibility and biodegradability of pNIPAM restrict long-term applications. Humidity-responsive and other hydration-driven, nature-inspired designs provide an alternative: Cheng *et al.*[159] reported a biobased hygromorphic 4D-printing strategy using cellulosic bilayers to create weather-responsive facade shading. They quantified humidity- and temperature-dependent actuation, demonstrated cyclic durability including long-term outdoor exposure, and validated scalability in a building-scale prototype (Figure 5B). Ion-responsive approaches have also emerged, where ionic crosslinking with Ca^{2+} or Zn^{2+} tunes scaffold stiffness and shape. Pal *et al.*[160] developed interparticle crosslinked microgels exhibiting Hofmeister-driven ion-responsive shrinking, enabling multi-material 4D constructs with programmable deformation and enhanced cell migration and vascularisation (Figure 5C).

The implications extend beyond therapy into disease modeling, but the same time-dependent behaviors that make 4D bioprinting attractive for dynamic *in vitro* models also create a direct route to personalized therapeutic delivery.[153] By encoding stimulus responsiveness into the printed matrix, constructs can be designed to deliver payloads on demand, in a spatially localized manner, and with kinetics that adapt to the patient's microenvironment, rather than relying on a fixed, pre-determined release profile. In practice, this enables release that is coupled to

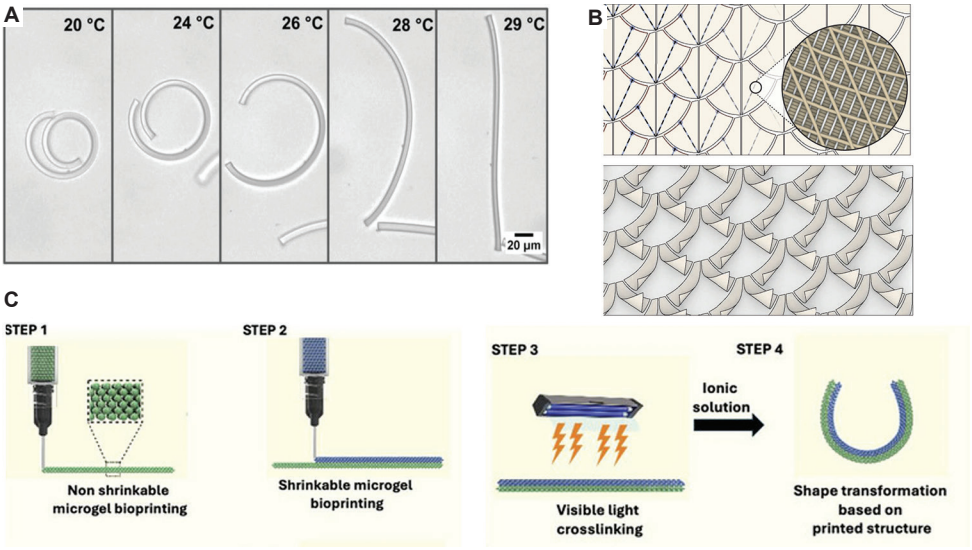

Figure 5. Stimuli-responsive and architected bioprinted structures enabling programmed shape and function. (A) Characterization of the spiral microgel at different temperatures. Reprinted with permission from Zhang *et al.*[158] Copyright © 2019 Wiley-VCH. (B) Bioinspired hygromorphic shading tile with a tessellated, scale-like layout. The inset highlights the printed fibrous microstructure that programs directional swelling, enabling humidity-driven out-of-plane curling and aperture modulation. Adapted from Cheng *et al.*[159] (C) In multi-material 4D extrusion bioprinting, a methacrylated gelatin microgel–hydrogel base is printed beneath ion-responsive microgels crosslinked with 405 nm light and transformed in ionic solution according to the pattern. Reprinted with permission from Pal *et al.*[160] Copyright © 2025 Wiley-VCH

clinically relevant cues such as changes in hydration, ionic composition, pH, temperature, inflammatory mediators, or externally applied triggers, supporting patient-specific dosing windows, feedback-aligned treatment schedules, and reduction of systemic exposure. These same principles improve disease modeling because stimuli-responsive, bioprinted constructs allow tissues to be interrogated under controlled yet evolving conditions that better reflect *in vivo* progression and treatment response. This has been applied in organ-on-a-chip platforms that integrate perfusion and biomechanical cues, and in 4D bioprinting systems capable of real-time adjustments to stimuli, resulting in more predictive models for drug testing and clinical translation[7,161,162] Innovative micro- and nanoscale strategies further enhance personalization and responsiveness. For example, multisomes—water-in-oil droplets with multiple internal compartments—have been produced via 4D printing and explored as controlled-release carriers.[163-165] By tuning osmolarity or humidity, these carriers can respond to environmental stimuli, enabling precise control over drug delivery.

3.3.3. Multi-material and multi-phase bioprinting

An additional emerging direction is multi-material and multi-phase bioprinting, which is essential for recapitulating sharp tissue boundaries and graded interfaces that are not achievable with single-bioink constructs. Recent work has advanced both the printing strategies and the target models. At the process level, Stacey *et al.*[166] demonstrated colinear extrusion as an alternative multi-material approach that enables the co-deposition of distinct materials in a spatially controlled manner while mitigating some limitations of multi-nozzle switching, supporting more continuous transitions in composition and mechanics for tissue engineering constructs. At the application level, biphasic and interfacial designs are being formalized for clinically relevant junctions, such as osteochondral repair. Yu *et al.*[167] used computational modeling to design and evaluate osteochondral interface scaffolds with comprehensive interfacial mechanical properties, highlighting how interfacial stiffness, stress transfer, and geometry should be co-designed rather than treated as two independent phases. In soft tissue, Puistola *et al.*[168] introduced a multi-material strategy to bioprint human stem cell-based corneal stroma with heterogeneous design, illustrating how spatially patterned mechanical microenvironments can be leveraged to better mimic lamellar organisation and guide cell behavior. Multi-material and biphasic constructs can allow therapeutic delivery and functional restoration to be tailored by region, for example targeting an injured interface while preserving neighboring healthy tissue. Furthermore, they provide more predictive patient-specific *in vitro* platforms by capturing the boundary conditions that govern transport, mechanics, and cell fate decisions.

4. Challenges and outlook

Bioprinting has advanced substantially as a platform for personalized therapeutic delivery. However, several

scientific, technical, and translational challenges still limit its broader impact. A central issue is bioink design. Single formulations are expected to provide print fidelity, support high cell viability, permit controlled degradation, and enable predictable release of drugs, genes, and GFs across clinically relevant time scales, which remains difficult to achieve in a single system.[9-12] Balancing shear-thinning for printability with structural stability, transport properties, and preservation of bioactivity is particularly challenging when incorporating sensitive vectors or proteins.[130] In parallel, quantitative tools for characterizing diffusion, binding, and release in complex, cell-laden constructs are still maturing, complicating the rational design and comparison of delivery strategies across studies.[107,108]

Scalability and reproducibility present additional barriers. Bioprinting outcomes are highly sensitive to temperature, humidity, ink rheology, and crosslinking kinetics. Therefore, even minor variations in formulation or process can lead to batch-to-batch differences in construct architecture, mechanics, and release profiles.[169-171] Moving from bespoke laboratory workflows to Good Manufacturing Practice-compliant manufacturing will require standardized bioink synthesis and sterilization, robust print parameter windows, and in-line quality control to monitor structure, cell distribution, and payload loading in real time.[9,13] Regulatory pathways for hybrid products that combine degradable matrices, living cells, and active therapeutics are also still evolving, and long-term *in vivo* behavior, including degradation products, immune responses, and the stability of drug and gene delivery functions, remains incompletely understood.[114,135] Addressing these issues will demand closer alignment between materials development, pharmaceutical quality guidance, and regulatory science.

Looking forward, emerging modalities offer promising routes to overcome some of these limitations. *In situ* bioprinting enables direct deposition of drug- or cell-laden materials into defects or onto tissue surfaces, allowing constructs to be customized to patient anatomy and intraoperative conditions.[19,147] Intelligent *in situ* systems that combine robotics, sensing, and multi-material printing are beginning to demonstrate geometry-aware, point-of-care delivery with reduced handling and contamination risk.[16,24,148] Acoustic levitation-based *in situ* printing, such as AcoustoFab, further introduces contact-free, omnidirectional manipulation of multiple materials over a wide viscosity range, which is particularly attractive for depositing therapeutic hydrogels on delicate or non-planar substrates.[149,151] In parallel, 4D bioprinting and stimuli-responsive hydrogels create constructs that change shape or function in response to temperature, ions, or biochemical cues, enabling on-demand or feedback-driven release profiles that better match dynamic disease states.[152,153,160] Integration with artificial intelligence-driven design, process optimization, and sustainability frameworks will potentially accelerate this trajectory by guiding material selection, print parameter tuning, and diffusion modelling.[169,172-174] If these developments in smart materials, *in situ* fabrication, automation, and regulatory alignment can be brought together, bioprinted *in vitro* and *in situ* systems are well positioned to evolve from experimental platforms into clinically relevant, adaptive tools for personalized therapeutic delivery.

5. Conclusion

Three-dimensional bioprinting offers a versatile route to *in vitro* models that combine physiologically relevant microenvironments with programmable control over the spatial and temporal delivery of drugs, genes, and GFs. By precisely organizing cells, hydrogels, and bioactive components in 3D, these platforms address key limitations of 2D cultures and animal models, improving the fidelity of disease modeling and the prediction of therapeutic response. Bioprinted liver, cardiac, and tumor constructs already demonstrate their value as testbeds for optimizing exposure profiles and exploring personalized delivery strategies, while advanced architectures such as compartmentalized scaffolds, perfusable networks, and stimuli-responsive hydrogels, together with emerging *in situ*, 4D, and acoustics-enabled bioprinting, point toward geometry-aware and dynamically regulated therapeutic delivery. Realizing this potential will require advances in bioink design, process standardization, scalability, and regulatory alignment. As these challenges are overcome, bioprinted *in vitro* platforms could become central tools for designing, testing, and refining personalized therapeutic delivery strategies.

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Ethics approval and consent to participate

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Consent for publication

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Availability of data

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