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Addressing Unmet Clinical Needs with 3D Printing Technologies

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Recent advances in 3D printing have enabled the creation of novel 3D constructs and devices with an unprecedented level of complexity, properties, and functionalities. In contrast to manufacturing techniques developed for mass production, 3D printing encompasses a broad class of fabrication technologies that can enable 1) the creation of highly customized and optimized 3D physical architectures from digital designs; 2) the synergistic integration of properties and functionalities of distinct classes of materials to create novel hybrid devices; and 3) a biocompatible fabrication approach that facilitates the creation and cointegration of biological constructs and systems. This progress report describes how these capabilities can potentially address a myriad of unmet clinical needs. First, the creation of 3D-printed prosthetics to regain lost functionalities by providing structural support for skeletal and tubular organs is highlighted. Second, novel drug delivery strategies aided by 3D-printed devices are described. Third, the advancement of medical research heralded by 3D-printed tissue/organ-on-chips systems is discussed. Fourth, the developments of 3D-printed tissue and organ regeneration are explored. Finally, the potential for seamless integration of engineered organs with active devices by leveraging the versatility of multimaterial 3D printing is envisioned.

1. Introduction

The ability to overcome the limitations of human biology using tools plays a critical role in our survival and evolution.[1] In medicine, advances in design and manufacturing have significantly improved the quality of life and prolonged the average life span. Medical devices such as prosthetics evolved from crafted rudimentary parts, recorded as early as the Egyptian era,[2] to electrically powered active prosthetics[3] today. A significant portion of the progress of such developments is driven by the increasing affordability of tools, materials, and devices that are made available through industrial production.

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Mass production is a powerful concept that has transformed modern society. Fueled by the expansion of the market size and the availability of resources due to globalization, machine-assisted mass production has enabled manufacturing of parts at a fraction of the cost of traditional manual labor. Instead of custom-producing tools and devices for individual needs, economies of scale incentivize the production of large numbers of identical copies. For instance, custom-tailored apparel is becoming increasingly rare and relatively unaffordable despite individual anatomical differences. Instead of optimizing for individual need and comfort, mass production manufacturing has compelled society to tolerate a finite set of prescribed designs determined by the overall market.

In medicine, a significant subset of clinical needs remains unaddressed due to the fundamental limitations of technologies that evolved from mass production. The human body is a complex 3D system, developed in response to fine-tuned physiological and environmental conditions. The design and manufacturing methodologies in mass production often fail to adequately address the geometric, mechanical, and material compatibilities between manufacturing technologies and the human body. For example, conventional hip replacement surgeries utilize one of the five types of U.S. Food and Drug Administration (FDA)-approved replacement devices: metal-on-polyethylene, ceramic-on-polyethylene, metal-on-metal, ceramic-on-ceramic, and ceramic-on-metal.[4] However, many instances of hypersensitivity and failures of metal hip implants have been reported. These devices are restricted by the limited geometries of replacement hip implants, which interferes with normal hip movement and affects the quality of life. Orthopedic surgeons are now looking into using 3D printing methods to create customized and cost-effective total joint replacements that are tailored to each patient's unique skeleton.[5] Indeed, the concept of mass customization is increasingly being adopted via 3D printing. Manufacturers worldwide have created ≈30,000 prosthetic limbs and more than half a million dental implants in 2011 with 3D printing.[6] However, efforts in design and development remain inadequate in areas where economies of scales are no longer applicable, regardless of the urgency of clinical needs. For example, in 2012, less than 0.05% of overall medical and dental manufacturing utilized 3D printing technologies despite of the advantages.[6]

3D printing is a process by which material is joined or solidified under computer control to create a 3D object.[7–9] The concept of 3D printing was first invented by Chuck Hull, who coined the term "stereolithography" in the early 1980s. Later, in 1989, Emanuel Sachs and Michael Cima invented binder jetting technology and introduced the term "3D printing."[7] Initially, 3D printing was primarily used as an industrial rapid prototyping tool with a limited set of materials, such as photopolymer and powder.[8] However, over the past decades, the emergence of desktop printing companies and the internet has propelled the transition from a costly industrial platform to an affordable desktop appliance.[10,11] Furthermore, recent advances in materials research have enabled the inception of novel 3D printing platforms, from a micrometer-scale fabrication with two-photon polymerization[12] to a faster and relatively seamless 3D printing with continuous liquid interface production (CLIP).[13] The development of digital technologies, such as 3D medical scanning, is facilitating the seamless transition from a digital design space to a physical device fabrication.

Critically, in a stark contrast to manufacturing techniques developed for mass production, 3D printing encompasses a broad class of fabrication technologies that could enable 1) the creation of highly customized and optimized 3D physical architectures from digital designs, 2) the synergistic integration of properties and functionalities of distinct classes of materials to create novel hybrid devices, and 3) a biocompatible fabrication approach that propels the creation and cointegration of biological constructs and electronic systems.

In this progress report, we describe recent advances on how these capabilities can potentially address a myriad of unmet clinical needs. We will first elucidate the different classes of 3D printing technologies, with specific emphasis on the subset of those technologies that can have a substantial impact in biomedicine. We then highlight the development of distinct classes of 3D printing technologies that address various unmet needs with novel devices, such as prosthetics, drug delivery, tissue-on-a-chip, tissue engineering constructs, and bioelectronics, as highlighted in **Figure 1**.

Specifically, we will first highlight the creation of 3D-printed prosthetics to restore lost functionalities by providing skeletal support. We will describe how 3D-printed prosthetics for anophthalmic cavity, spine, skull, and limb replacement is superior to costly and painful prosthetics made with conventional manufacturing technologies. Indeed, 3D printing of biocompatible materials can create patient-specific prosthetics tailored to each patient's unique anatomy and needs. For example, as shown in Figure 1A, Zhu et al. created a novel 3D-printed bone-specific biomimetic environment for evaluating breast cancer metastasis to bone tissue.[14] Similarly, we show how the creation of tubular structure with novel materials can restore supporting soft tubular tissues. Morrison et al. designed 3D-printed, patient-specific, and bioresorbable external airway splints that are able to accommodate airway growth while preventing external compression.[15]

Second, we will describe the development of novel drug delivery strategies using 3D-printed devices. Here, 3D printing enables the creation of unique architectures to allow painless delivery of therapeutic agents and tailored drug release profiles. For example, as shown in Figure 1G, hollow microneedles of different architectural designs fabricated by 3D printing can be used to deliver therapeutic agents.[16,17]

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Third, we will describe how 3D printing enhances the organ-on-a-chip platform. 3D printing technologies are instrumental for recapitulating microenvironments to better understand cellular mechanics at the cell and tissue levels. For example, as shown in Figure 1D, Zhang et al. reported a 3D-bioprinted endothelialized myocardium by directly printing endothelial cells within microfibrous hydrogel scaffolds.[18] They further embedded the organoids into a specially designed microfluidic perfusion bioreactor to complete the endothelialized-myocardium-on-a-chip platform for cardiotoxicity testing. In cancer research, a novel method of 3D printing, using HeLa cells and gelatin/alginate/fibrinogen hydrogels, has been reported to create in vitro cervical tumor models.[19]

Fourth, we highlight the recent ongoing efforts in tissue regeneration using 3D bioprinting. 3D and biocompatible fabrication capability of 3D printing can create biological constructs to potentially regenerate damaged tissues and organs. We highlight examples of promising research using 3D printing in heart valves and skin regeneration, as shown in Figure 1B. Extending its capabilities further, 3D-printed scaffolds with physical cues and path-specific biochemical gradients can guide the regeneration of damaged nerve plexuses.[20]

Finally, we envision the development of multimaterial 3D printing to accelerate the creation of bioelectronic constructs to impart active functionalities to an otherwise passive construct. The integration of medical instruments with electronics opens the possibility of sophisticated bioelectronic devices capable of processing biofeedback. The cointegration and co-printing of microelectronic devices, including actuators,[21] optoelectronics,[22,23] and sensing modalities[24,25] could enable the development of advanced active bioelectronic devices with the ability to mimic or surpass complex functionalities intrinsic to biological organs, illustrated in the example at Figure 1F. Progress has been made already with the combination of the printed electronics and biological constructs to produce bioprinted ears[26] and cardiac microphysical devices[27] as extensions of human capabilities.

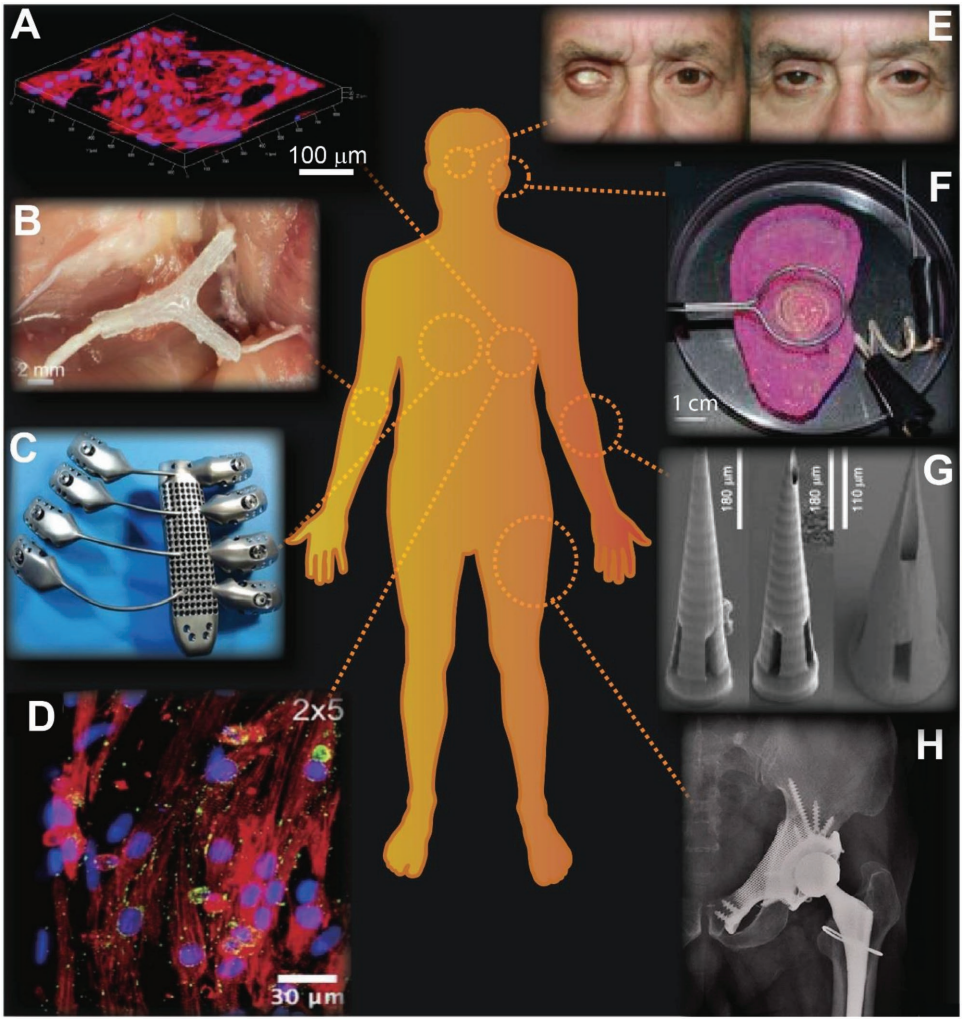

Figure 1. 3D printing technology to address numerous clinical needs. A) A 3D-printed biomimetic bone environment was developed for evaluating breast cancer bone metastasis by growing mesenchymal stem cells (MSCs) on 3D bone matrix (actin and DNA are colored red and blue, respectively). Reproduced with permission.[14] Copyright, 2016 Elsevier. B) A 3D-printed network guide for regenerating damaged nerve plexuses. Reproduced with permission.[20] Copyright 2015, Wiley-VCH. C) 3D-printed titanium prosthetics used for sternocostal reconstruction by SLS process. Reproduced with permission.[53] Copyright 2015, Oxford University Press. D) An endothelialized myocardium by 3D printing endothelial cells encompassed within microfibrous hydrogel scaffolds. Immunofluorescence staining of sarcomeric α-actinin (red) and connexin-43 (green) of cardiomyocytes seeded on bioprinted microfibrous scaffolds is shown here. Reproduced with permission.[18] Copyright 2016, Elsevier. E) A 3D-printed personalized ocular prosthesis to replicate the anophthalmic cavity. The patient with the 3D-printed mold (left) can be compared to his final prosthesis (right). Reproduced with permission.[60] Copyright 2016, BMJ Publishing Group Ltd. F) "Bionic ears" created by co-printing an alginate hydrogel matrix seeded with chondrocyte cells with conducting silicone. Reproduced with permission.[26] Copyright 2013, American Chemical Society. G) Hollow micrometer-scale microneedles of different geometries were fabricated using two photon polymerization method using organically modified ceramic. Reproduced with permission.[16] Copyright 2007, Wiley-VCH. H) A 3D-printed pelvic implant conforming to a patient's anatomy. Reproduced with permission.[85] Copyright 2015, Taylor & Francis.

2. 3D Printing Method for Addressing Clinical Needs

3D printing is a broad class of manufacturing technology[9] that uses light-based and ink-based printing.[9,28] Broadly speaking, light-based 3D printing encompasses technologies such as stereolithography (SLA) of photocurable resin[29,30] or selective laser sintering (SLS)[31] of polymeric powders.[9] In contrast, ink-based 3D printing consists of droplet-based printing method,[7,32,33] direct ink writing,[34] and filament-based printing method.[9] In this section, we will highlight several key technologies that can be employed to address unmet clinical needs. For further details and discussions of 3D printing technologies, the reader is referred to several excellent reviews[9,35,36] that provide in-depth discussions.

SLA is a solid free-form fabrication (SFF) method[36] where laser or ultraviolet (UV) light[30,37] selectively photopolymerizes liquid resin (**Figure 2**A). When a layer has been photopolymerized, new liquid resin is introduced to incorporate the next layer. The same process is repeated until the 3D object is completed. Other variants of light-based 3D printing technologies include digital projection lithography (DLP),[9,37,38] CLIP,[13] and two-photon polymerization-based printing (2PP).[9,39]

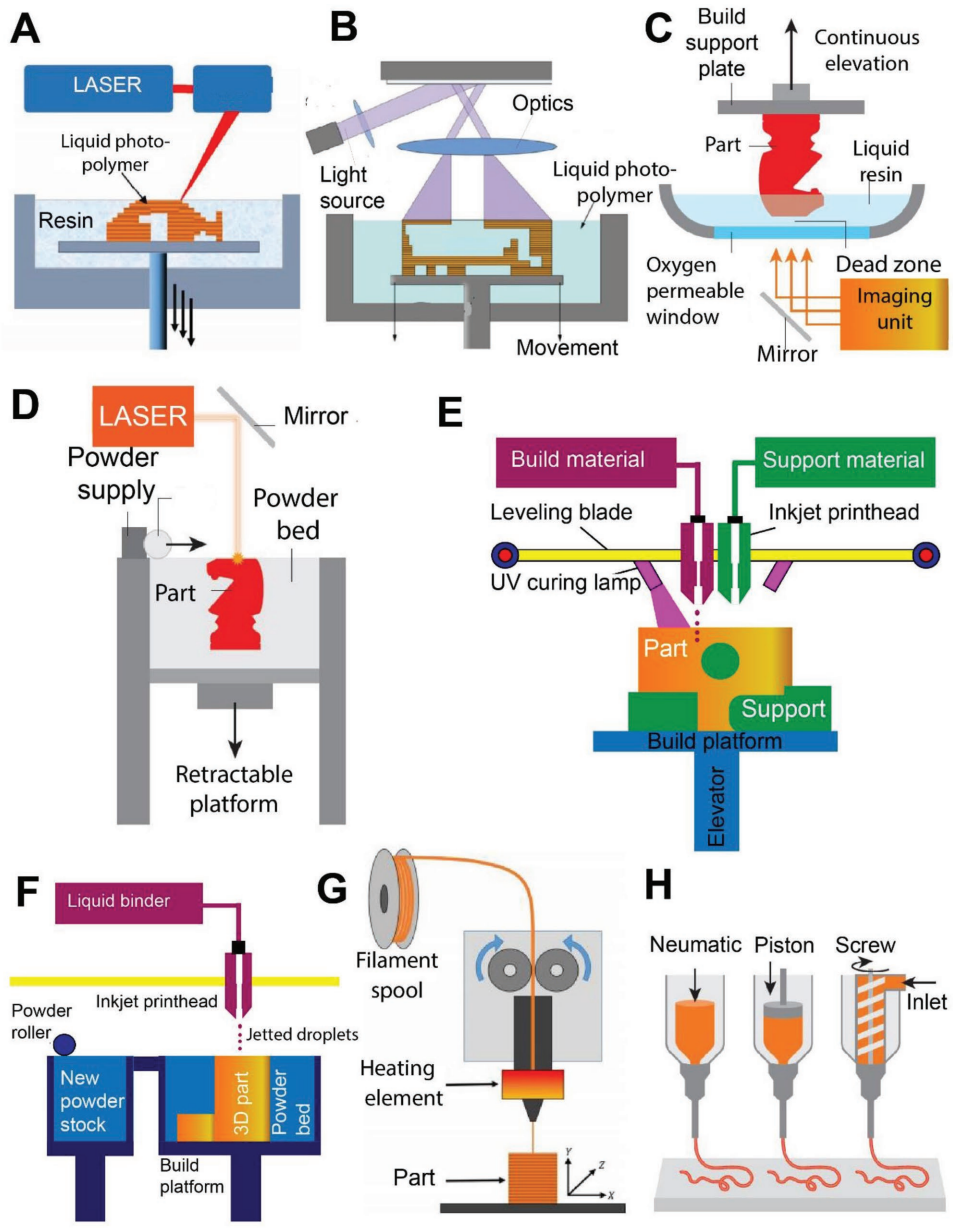

Figure 2. Schematic diagram of light- and ink-based 3D printing class of technologies. A) Schematic of a light-based, top-down stereolithographic (SLA) apparatus part production process. Laser beam is cast over a vat of photopolymerized resin for free-form fabrication. Reproduced with permission.[226] Copyright 2016, Elsevier. B) Digital projection lithography (DLP) 3D printing, where a 2D cross-section of light strikes the air–liquid surface of a vat of photopolymerizable resin. The build stage sinks into the vat. Reproduced with permission.[35] Copyright 2018, Wiley-VCH. C) 3D free-form structure fabricated from the photopolymerization resin vat through a continuous liquid interface production (CLIP) technology. Reproduced with permission.[9] Copyright 2016, Nature Publishing Group. D) 3D printer setup diagram for selective laser sintering (SLS). Reproduced with permission.[9] Copyright 2016, Nature Publishing Group. E) Schematic of direct inkjet printing. Both build and support material are jetted over a platform through printhead. The schematic shows jetting of photopolymerized droplets while UV light source cures. F) Schematic of inkjet on powder bed. Binder (adhesive) is jetted on the powder bed. G) Schematic of fused deposition modeling (FDM) where filaments are extruded through heated nozzle in layer-by-layer building approach. Reproduced with permission.[226] Copyright 2016, Elsevier. H) Schematic of direct ink writing (DIW) printing method. Viscoelastic ink is being extruded from a syringe. Reproduced with permission.[9] Copyright 2016, Nature Publishing Group.

In DLP, a spatial light modulating (SLM) element, such as a liquid-crystal display (LCD) or digital micromirror device (DMD),[37] is used in lieu of a laser to project a digital pattern onto liquid-resin reservoir[35] (Figure 2B). Both DLP and CLIP can print an entire layer at once, whereas SLA depends on the point source of the laser.[9] CLIP leverages a similar principal as DLP, with the addition of uncured resin (so-called "dead zone") between the object and oxygen-permeable window by controlling the oxygen flux. This enables a highly efficient and continuous printing process. A 3D structure can be drawn out of resin at rates of hundreds of millimeters per hour, surpassing the speed of similar light-based 3D printing technologies

(Figure 2C).[13] In biomedicine, processes such as DLP has been widely used in the fabrication of prosthesis, including clinical applications for mandibular reconstruction,[40] stents,[41] and microneedles.[42]

However, most demonstrations with DLP have been limited to a single material fabrication. Recently, Miri et al. presented a novel method for multimaterial DLP fabrication of heterogeneous hydrogel constructs.[43] They constructed a novel microfluidic device with four on/off pneumatic valves, used for fast switching between hydrogel bioinks. Integrating this device with a DLP 3D printing setup, they fabricated heterogeneous gelatin methacryloyl (GelMA) and poly(ethylene glycol) diacrylate (PEGDA) constructs.[43] The enhanced fabrication speed of this multimaterial DLP-based bioprinting platform can potentially allow the fabrications of larger cell-laden constructs by improving cell viability.[43]

On the other hand, 2PP uses ultrashort laser pulse to achieve polymerization with two-photon absorption at the focal point of the laser. The confinement of the photopolymerization to a voxel size enables a significant enhancement of print resolution on the order of 100 nm,[9] several orders higher than SLA or DLP method.[44,45] Additionally, the maximum size of 2PP is in the order of 1 cm^3, whereas other light-based processes such as CLIP can create parts with overall dimension exceeding 100 cm^3.[9] In medicine, 2PP has been widely applied in fields such as microfluidics,[46] biomedical implants and microdevices,[47–49] and microneedles.[16]

SLS, another class of light-based technology, selectively sinters powders using high power laser (Figure 2D).[31,50] SLS can be used to create structures using different polymers and metals at a minimum print resolution of 100 μm.[9] In this process, sequential layers of powder are spread over the bed. The nonsintered powder functions as structural support for the 3D-printed part during the printing process. SLS can be used to create internal tubular support (e.g., airway splint[51]) and other 3D polymeric structures as well as 3D metal structures, useful for structural prosthesis, such as calcaneal prothesis[52] or supporting structures for sternocostal reconstruction.[53]

In ink-based 3D printing, material is extruded through a nozzle either as droplets or filament. Hot-melt printing,[32] direct inkjet printing,[33] and inkjet on a powder bed[7,54] are examples of droplet-based 3D printing that use low viscosity fluids (2–10^2 mPa s) as print material.[55] Specifically, for hot-melt printing, wax-based inks are heated to form droplets and dispersed through a nozzle. After dispersion, droplets cool down and solidify. Direct inkjet printing can be used with photopolymers to create 3D structure by using UV-light-cured photopolymer droplets (Figure 2E). Alternatively, inkjet on powder bed technology can jet binder/adhesive onto the powder bed to create a 3D structure (Figure 2F). The primary difference between this method and SLS is that a laser source is not required for binding. Droplet-based 3D printing has numerous clinical applications from designing drugs[56] to biomedical research. These methods have largely been used to fabricate highly porous drugs,[57,58] nanofilm medicine for precise dosage,[59] and ocular prosthesis.[60]

On the other hand, direct ink writing (DIW)[34] and fused deposition modeling (FDM) are extruded through nozzle as filaments. In general, these filamentary extrusion-based printing techniques have a wider selection of ink options,[34,61] which can be considered an advantage over light-based 3D printing technologies where the material choices are limited to custom formulated photopolymers.

Moreover, FDM is a process where thermoplastic filaments are driven with a motorized heated nozzle (Figure 2G). The heated nozzle melts the thermoplastic polymer and constructs a 3D structure layer-by-layer, which then solidifies at room temperature. FDM is compatible with numerous thermoplastic polymers, such as polypropylene, polylactic acid, polycarbonate,[62] and various classes of flexible thermoplastic polyurethane. Further, FDM can be expanded to achieve multimaterial printing to create composite structure with multiple material requirements. FDM has been used extensively for a variety of biomedical applications, such as drug delivery architectures,[63–66] biosensors,[67] and prosthesis,[68,69] due to its use of biocompatible polymers.[63–69]

In comparison to FDM, DIW is compatible with a wider range of materials. For instance, viscoelastic material such as concentrated polymers, colloidal suspensions, and fugitive organic[70–72] can be synthesized and used as ink to create structures with high aspect ratio or spanning features by optimizing ink composition and printing parameters (Figure 2H).[34] Conveniently, DIW is widely compatible with a range of materials, with viscosities ranging from 10^2 to 10^6 mPa s. For example, Lewis and co-workers demonstrated the DIW of hydrogel composite inks that can be used to create programmable, shape-morphing structures.[73] Importantly, DIW is highly compatible with biological materials due to its ability of creating 3D architecture without extreme temperature or harsh chemical processing. For instance, DIW can use cell-laden hydrogels[70] to create biological constructs such as ears,[26] valve conduits,[74] all of which will be highlighted in the later sections.

Further, the DIW method has recently been improved by incorporating pneumatically pressure-controlled multilateral extrusion through a single nozzle which is controlled by valves loaded with different bioink reservoirs.[75] The programed control of valve opening and regulated pressure of each channel ensures faster fabrication than multinozzle direct writing. For demonstration, Liu et al. leveraged this new technique and used Festo valves and printhead to bioprint 3D constructs such as blood-vessel-like structures containing dual, triple, and quadruple materials. Organ-like constructs including brain, heart, liver, kidney, lung, stomach, bladder, prostrate, intestines, and pancreas are now possible to create with multiple bioink through this method.[75]

In summary, the choice of 3D printing technology is highly dependent on the desired features and requirements, such as feature resolution, fabrication speed, build volume, and material compatibility.[9] **Table 1** enumerates the different features of 3D printing techniques and highlights the key advantages and disadvantages of different printing methods. **Table 2** summarizes the clinical applications of different 3D printing technologies as well as the developed 3D-printed materials for the specific clinical applications.

3. 3D-Printed Prosthetics for Restoring Skeletal Support and Functionality

The term "prosthesis," as defined by Cambridge Dictionary, is "an artificial body part, such as an arm, foot, or tooth that

Table 1. Overview of the different classes of 3D printing technologies.

Printing method	Approximateresolution and speed	Multimaterial printing capability	Advantage	Limitation	Bioprinting example
Stereolithography (SLA)	Resolution: 50–200 μm[9] Speed: 10^6 mm^3 h^{-1}[229]	No	▪ Higher resolution than, e.g., FDM[35] ▪ Fabrication speed[183] ▪ Relatively smoother surface finishing[183]	▪ Limitation on resin choice	[230]
Selective laser sintering (SLS)	Resolution: ≈ 20–100 μm[229,231] Speed: 10^6 mm^3 h^{-1}[229,232]	No	▪ Powder works as support base ▪ Support metal printing	▪ Not bioprinting compatible[35] ▪ High temperature due to high power laser	
Two-photon polymerization (2PP)	Resolution: 100 nm[9] Speed: ≈ 80 nm s^{-1}–2 cm s^{-1}[35]	No	▪ Higher resolution than other light-based print method[35]	▪ Slow process ▪ High cost ▪ Limitation over build volume[9]	
Digital projection lithography (DLP)	Resolution: Pixel size dependent (e.g., 1 μm)[35] Speed: 25–1000 mm min^{-1}[35]	No	▪ Faster than SLA ▪ 2D projection ensures higher throughput[35]	▪ Requirement of large volume photopolymer	[43]
Continuous liquid interface production (CLIP)	Resolution: 10–100 μm[13] Speed: 500 mm h^{-1}[13]	No	▪ Oxygen permeable membrane makes it faster than SLA and DLP[13,35] ▪ Low cost[13] ▪ Smooth surface	▪ Limited on single material printing	
Direct ink writing (DIW)	Resolution: 10–250 μm[9] Speed: 10^5 mm^3 h^{-1}[229]	Yes	▪ Wide variety of material choice ▪ Multiple material printing	▪ Print resolution dependent on the properties of the inks[35,229]	[18,26,177,233]
Fused deposition modeling (FDM)	Resolution: 100 μm[229] Speed: 10^5 mm^3 h^{-1}	Yes	▪ Widely available thermoplastic material[35] ▪ Relatively inexpensive setup[183] ▪ Multiple material printing	▪ Relatively lower resolution ▪ Requires supporting structure ▪ Interlayer fusion can be affected by circular cross-section of filament[35]	
Direct inkjet printing	Resolution: 50–200 μm[9,229] Speed: 5×10^5 m^3 h^{-1}[229]	Yes	▪ Multiple material can be jetted	▪ Requires low viscous ink (<0.25 Pa s)[229]	[234]
Inkjet on powder bed	Resolution: 50–400 μm[235] Speed: ≈ 25 mm h^{-1}[236]	No	▪ Capability to tailor highly porous structure ▪ Low cost process	▪ Lower mechanical properties due to high porosity	

replaces a missing part." The earliest prostheses date back to ancient Egypt.[2] Later, the Greek historian, Herodotus (484 BC), recorded the usage of wooden lower limb prosthesis by a soldier.[2] After that period, bronze plates with wooden core and leather straps were used for lower limb prostheses. The modern prosthesis is precipitated by the technological innovations driven by the two World Wars.[2] In 1915, the first powered pneumatic hand was invented in Germany.[76] Later, after the formation of the Committee on Prosthetics Research and Development (CPRD) by the National Research Council in 1945, advancements in powered limb prosthesis progressed rapidly. Over the last several decades, cybernetic approaches for orthopedic prosthesis became increasingly popular.[77] However, the locomotion and functionality of the prosthesis are still limited. In this section, we highlight how advancements in 3D printing can potentially address these unmet challenges.

The ability to create highly customized, free-form 3D architecture enables the creation of prostheses that are lightweight[52,78] and highly customizable.[79–81] Patients with conventional prosthetic devices often suffer from pain and discomfort due to the weight and stiffness of the material.[81] Here, 3D printing is used to create optimized prosthetics to reduce weight and discomfort by incorporating soft materials.[82] It is anticipated that prosthetic hands fabricated using 3D printing will weigh less than the regular human hand.[78,81] Undoubtedly, these developments can improve the quality of life by reducing the joint pain and fatigue that many patients with prostheses may experience.

Another unmet clinical need in prosthesis research is a highly functional upper limb prostheses for children. Patients with upper limb amputations require a prosthesis with grasping capabilities[83] to perform basic activities of daily living. In one example, children with upper-limb differences have benefitted from "cyborg beast,"[69] a 3D-printed prosthetic hand (**Figure 3**A). Zuniga et al.[69] used desktop 3D printer (FDM) to build these low-cost prosthetics designed for 11 children between the ages of 3 and 16 years and subsequently demonstrated the feasibility of a prosthetic system that can accommodate natural growth of the children. The rapid growth rate in children makes 3D-printed prosthetic hands a much cheaper and more adaptable option.[78] Research to increase the functionality of upper limb prostheses is aimed toward high energy efficiency, lightweight, and easy customization.[81] Saharan and Tadesse[79] printed 3D-customized robotic hands with a twisted and coiled polymer (TCP) muscle-based locking system to improve energy efficiency. In another example, Slade et al. developed anthropomorphic myoelectric prosthetic hands for transradial amputees.[81]

For lower limb prosthesis, one of the challenges in fabrication is to ensure exact fitting to residual limbs. Comotti et al.[68]

Table 2. Overview of the clinical applications with 3D printing technologies.

3D printing method	Clinical application	Example of clinical application	3D-printed material
Stereolithography (SLA)	Cancer research	▪ Nanocomposite bone matrix[14]	▪ Hydrogel resins (40% w/w poly(ethylene glycol) (PEG, M_n 300), 60% w/w poly(ethylene glycol) diacrylate (PEGDA, M_n 700), and photoinitiator 0.5% w/w of PEGDA[14]
Selective laser sintering (SLS)	Prothesis implant	▪ Pelvic implant[85]	▪ Medical grade Ti6Al4V[85]
		▪ Tracheobronchial splint[15]	▪ 96% CAPA 6501 PCL (Polysciences Inc.) and 4% hydroxyapatite (Plasma Biotal Ltd.)[15]
Digital projection lithography (DLP)		▪ Vascular stent[41]	▪ mPDC polymer[41]
	Cancer research	▪ Biomimetic microstructures for cancer cell migration[164]	▪ PEGDA (M_n = 700, Sigma)[164]
		▪ Tumor angiogenesis model[43]	▪ GelMA laden with scattered breast cancer cells (MCF7)[43]
	Drug delivery	▪ Microneedle[17]	▪ Poly(propylene fumarate) (PPF)[17]
	Tissue engineering	▪ Musculoskeletal systems[43]	▪ NIH/3T3 fibroblasts and C2C12 skeletal muscle cells[43]
Two-photon polymerization (2PP)	Drug delivery	▪ Microneedle[237]	▪ Ormocer[49]; acrylate-based polymer, e-shell 300[237]
	Tissue engineering	▪ Scaffolds for tissue engineering[238,239]	▪ PEGDA[238] ▪ Poly(ε-caprolactone-*co*-trimethylenecarbonate)-*b*-poly(ethylene glycol)-*b*-poly(ε-caprolactone-*co*-trimethylenecarbonate) with 4,4′-bis(diethylamino)benzophenone[239]
	Prosthesis	▪ Middle-ear bone replacement[240]	▪ Ormocer[240]
Direct ink writing (DIW)	Tissue engineering	▪ Liver tissue[177]	▪ Collagen bioink consisting of three different cell types—hepatocytes (HCs), human umbilical vein endothelial cells, and human lung fibroblasts on a polycaprolactone (PCL) scaffold[177]
		▪ Skin tissue[174]	▪ Polyelectrolyte gelatin–chitosan (PGC) hydrogels[174]
		▪ Adipose tissue construct[172]	▪ Decellularized adipose tissue (DAT) matrix bioink with encapsulated human adipose tissue–derived mesenchymal stem cells (hASCs)[172]
		▪ Human-scale tissue construct (mandible bone reconstruction)[176]	▪ Human amniotic fluid–derived stem cell (hAFSCs)–laden composite hydrogels, supporting polycaprolactone (PCL) polymer and a sacrificial Pluronic F-127 hydrogel[176]
		▪ Osteochondral tissue regeneration[233]	▪ PCL and alginate solution as frame on which osteoblasts and chondrocytes cell-laden hydrogel dispensed[233]
		▪ Nerve regeneration pathways to regrow nerve[20]	▪ Silicone rubber ink[20]
		▪ Endothelialized myocardium[18]	▪ Mixture of alginate (Sigma-Aldrich), gelatin methacryloyl (GelMA), and photoinitiator Irgacure 2959[18]
	Bioelectronics	▪ Bionic ear to enhance hearing ability[26]	▪ Chondrocyte-seeded alginate hydrogel matrix with silver nanoparticle (AgNP)[26]
		▪ Cardiac microphysiological device[27]	▪ Thermoplastic polyurethane (TPU), PDMS, silver particle–filled polyamide (Ag:PA) ink, polylactic acid (PLA), acrylonitrile butadiene styrene (ABS), and cardiomyocytes[27]
	Cancer research	▪ Cervical tumor model (in vitro) for cancer research[19]	▪ Fibrogen/HeLa mixture with gelatin and sodium alginate solution[19]
	Drug research	▪ Human HepG2/C3A spheroid is bioprinted to assess drug toxicity in liver[153]	▪ GelMA hydrogel[153]
	Scaffold fabrication	▪ Aortic valve scaffold[74]	▪ PEGDA hydrogels supplemented with alginate[74]
		▪ Microporous scaffolds for bioprosthetic ovary[178]	▪ Gelatin (porcine, type A; Sigma-Aldrich)[178]
	Valve	▪ Heart valve conduits[170]	▪ Hydrogels based on methacrylated hyaluronic acid (Me-HA) and methacrylated gelatin (Me-Gel) encapsulating human aortic valvular interstitial cells (HAVICs)[170]
Fused deposition modeling (FDM)	Prosthesis	▪ Upper and lower limb prosthesis[68,69]	▪ Polylactide plastic[68,69] ▪ ABS[69]

Table 2. Continued.

3D printing method	Clinical application	Example of clinical application	3D-printed material
	Drug delivery	▪ Tablet[63–65]	▪ Polyvinyl alcohol (PVA) loaded with drug (fluorescein, paracetamol)[63–65]
		▪ Biodegradable microneedle[66]	▪ Polylactic acid[66]
		▪ Mouthguard for drug delivery[137]	▪ Poly(L-lactic acid) (PLLA) and PVA filaments loaded with clobetasol propionate (CBS) and vanillic acid (VA).[137]
Direct inkjet printing	Prosthesis implant	▪ Prosthetic socket for residual limb[80]	▪ VeroWhitePlus rigid opaque printing material[80]
		▪ Ocular prosthesis[60]	▪ Biocompatible MED 610 resin[60]
		▪ Aortic trileaflet valve mold[169]	▪ Silicone, polyurethane, acrylate, autologous tissue[169]
Inkjet on powder bed	Drug delivery	▪ Tablets[241,242]	▪ Colloidal silicon dioxide (SiO_2), mannitol, polyvinylpyrrolidone (PVP) K30, and lactose with paracetamol and alizarin[241,242]
		▪ Orodispersible tablets[241,243]	▪ Microcrystalline cellulose (MCC), glycerine, Tween 80, povidone, sucralose with levetiracetam[241,243]
Electron beam melting (EBM)	Prosthesis implant	▪ Fenestrated triangular implant[84]	▪ Ti6Al4V ELI powder[84]
		▪ Prosthesis for sternocostal reconstruction[53]	▪ Surgical grade titanium alloy[53]
Combined FDM and DIW	Drug research	▪ Reactionware	▪ Polypropylene (PP)[141]

developed a customizable lower limb socket using 3D printing technology to address this issue. After using 3D scanning to model the patient-specific limb socket, researchers 3D printed a personalized lower limb designed to maximize comfort during movement. Webber and Davis[80] reported the use of a photocurable inkjet printing method for printing a prosthetic limb socket with a unique cooling feature so as to prevent overheating and excessive sweating as well as concomitant skin macerations.[80]

In addition, 3D-printed fenestrated triangular titanium implant[84] with porous surfaces and bioactive agents can potentially improve bony fixation and biomechanical stability, in comparison to solid triangular titanium plasma spray (TPS)–coated implant. This improvement could ultimately provide more desirable outcomes for patients with sacroiliac (SI) joint dysfunction. Furthermore, electron beam melting 3D printer enables the creation of titanium lightweight lower limb hollow calcaneal prosthesis[52] with anchor points (Figure 3B). This allows for the firm attachment of the prosthesis to the Achilles tendon, plantar fascia, spring ligament, and soft tissues on the medial and lateral sides. 3D printing can also devise a patient-specific hip implant that is needed as a part of clinical treatment after pelvic tumor resection. Wong et al.[85] prefabricated patient-specific implants to evaluate the biomechanical properties and design to match the bone defect (Figure 3C). Remarkably, the patient could walk with satisfactory hip function 11 months postoperation. Nevertheless, further studies with a larger patient population are needed to evaluate the clinical efficacy of this promising technology.

Traditional fabrication of ocular prosthesis is typically accomplished by first obtaining a mold of the anophthalmic cavity using dental impression material.[60] This method results in increased pressure and distortion of the anophthalmic socket, and hence, a poor connection between the socket and the impression mold. To address this challenge, an ocular prosthesis was recently reported to be constructed by polyjet 3D printing to fit the anophthalmic cavity (Figure 3D).[60] Ruiters et al. successfully fitted a 68 year old male patient who previously suffered from a blind right eye with a new 3D-printed anophthalmic cavity. In addition, the free-form fabrication capability of stereolithography has been used to achieve precise mandibular reconstruction (Figure 3E).[40] Azuma et al.[40] reported 16 clinical cases of mandibular reconstruction addressed by 3D-printed models, which comparatively achieved more satisfactory and better esthetic outcomes than patients treated with conventional reconstruction methods.

Sternal reconstruction using 3D printing is not only aimed at preserving respiratory mechanics but also to achieve a cosmetic effect.[53] Aranda et al. recently fabricated a novel 3D-printed titanium rib cage using a 3D laser sintering printing method (Figure 3F).[53] Surgical implantation of this 3D-printed sternum into the chest of a patient preserved thoracic function with a superior cosmetic result. Subsequently, surgeons in Wales recently rebuilt a patient's chest with 3D-printed ribs based on computed tomography (CT) scan images.[86]

The ability of 3D-printed patient-specific prosthetics to address a multitude of unmet needs is rapidly being translated into the clinic. Recently, BioArchitects, a company in the United States, announced 510(k) clearances by the FDA for a 3D-printed personalized titanium cranial/craniofacial plate implant. The lightweight and biocompatible characteristics of the implant are effective in restoring bone defects of the skull and face (Figure 3G). With the advancement of modern medicine toward individualized treatment, customized prosthetics will become not just more accessible and affordable but will also achieve superior functional and aesthetic outcomes in comparison to current treatment options.[87–89] Such noteworthy developments have also been discussed in the following review articles.[90–103]

4. 3D-Printed Prosthetics for Restoring Supporting Soft Tubular Tissues

Internal soft tubular tissues require mechanical support by a splint[15] or a stent[41] in the events of occlusion.[104] However,

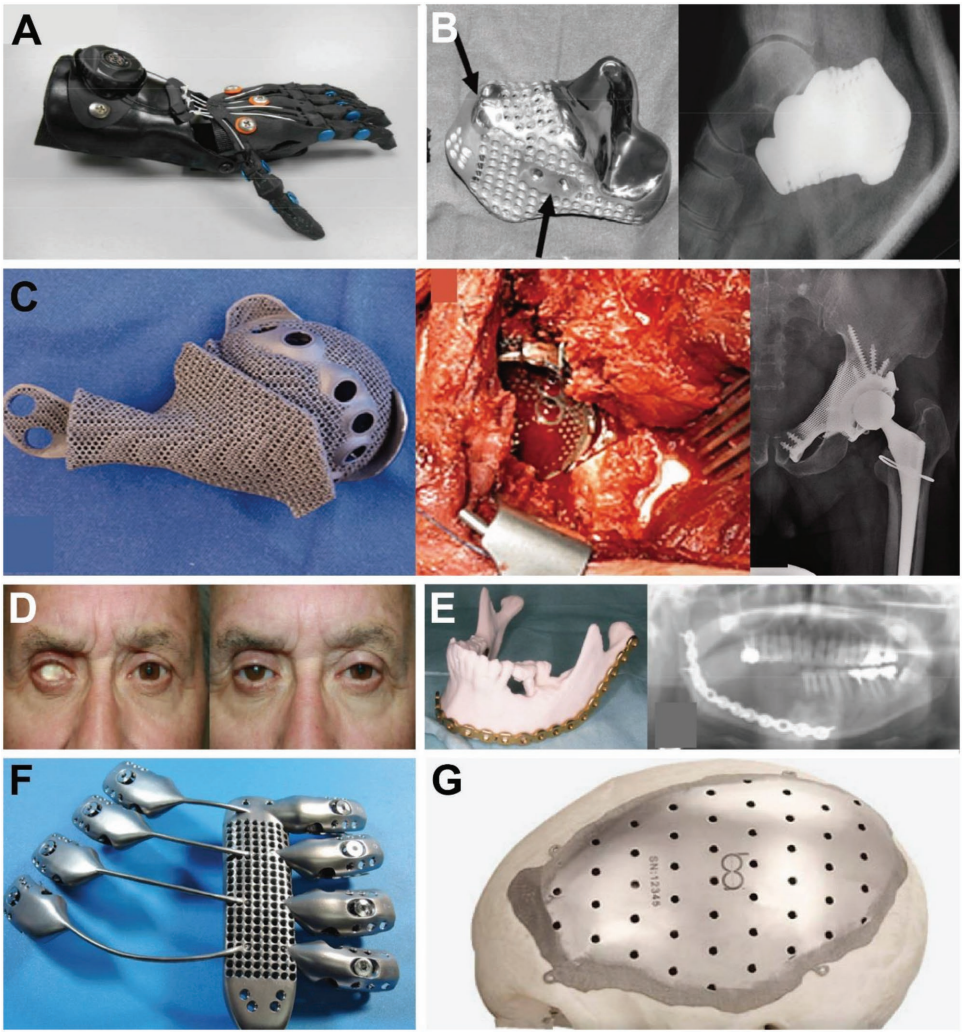

Figure 3. 3D-printed prosthetics for restoring skeletal support and functionality. A) A 3D-printed prosthetic hand designed for children with upper-limb differences. Reproduced with permission.[69] Copyright 2015, Springer Nature. B) 3D-printed titanium calcaneal prosthesis was fabricated with a hollow cavity to reduce the overall weight (left). Anchor points (arrows) were used to attach ligaments to the prosthesis. Postoperative lateral radiograph visualizes the fit of calcaneal prosthesis (right). Reproduced with permission.[52] Copyright 2015, Elsevier. C) Pelvic implant designed to fit patient anatomy (left). The implant was fitted precisely to the bone defect after tumor resection (middle). Anteroposterior radiograph of the pelvis after 10 months of the surgery shows consistently good implant alignment. Reproduced with permission.[85] Copyright 2015, Taylor & Francis. D) A 3D-printed ocular prosthesis was designed to fit a patient's anophthalmic cavity. The 3D-printed mold (left) is compared with his final prosthesis (right). Reproduced with permission.[60] Copyright 2016, BMJ Publishing Group Ltd. E) 3D printing aided mandibular reconstruction provides a precise, fast, and inexpensive method for surgical reconstruction. Reproduced with permission.[227] Copyright 2009, Elsevier. The left shows the 3D medical rapid prototyping model with the prebent reconstruction plate. The right panel is a pantomograph of a patient following reconstructive surgery with prebent plates based on medical rapid prototyping (MRP) models. Reproduced with permission.[40] Copyright 2014, BioMed Central Ltd. F) 3D-printed titanium prosthetics used for sternocostal reconstruction. Reproduced with permission.[53] Copyright 2015, Oxford University Press. G) A 3D-printed custom titanium cranial/craniofacial plate implant by BioArchitects. Reproduced with permission.[228] Copyright 2016, BioArchitects.

conventional support systems have several limitations, including material flexibility, biocompatibility, and complex resizing in long-term implantation.[15] In this section, we highlight how 3D-printed patient-specific biocompatible soft tubular tissue prosthesis can overcome these prevailing challenges.

Dynamic airway collapse in newborns causes fatal respiratory complications that may lead to recurrent airway obstruction, cardiopulmonary syndromes, and death.[51,105] The canonical treatment using fixed-size airway stents restricts airway growth and further hinders natural recovery after the critical period. FDA restricted the usage of conventional airway stents on children, citing significant side effects such as secondary airway stenosis.[15] In this aspect, 3D bioprinting can solve many of these challenges by imparting flexible and n properties that are critical for long-term implantation in children.[51,106] For example, Morrison et al.[15] have 3D-printed patient-specific archetype airway splints to treat tracheobronchomalacia (TBM) (**Figure 4**A). Specifically, using SLS technology, a biocompatible and bioresorbable airway splint with polycaprolactone (PCL)[107,108] was 3D printed.[15] The structural integrity of the splint allows for it to remain in vivo for two to three years before absorption. The digital fabrication capability of 3D printing allows for the creation of

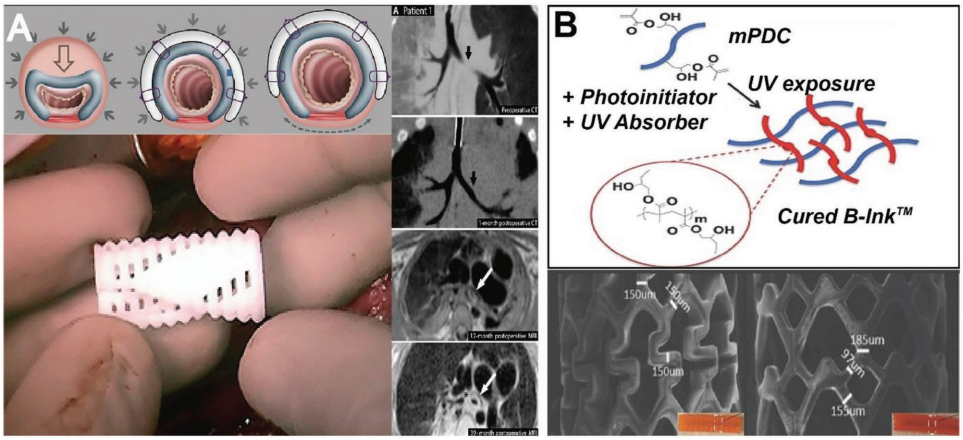

Figure 4. 3D-printed prosthetics for restoring supporting soft tubular tissues. A) A personalized 3D-printed external airway splint designed to accommodate airway growth. The structural integrity prevented external compression of the airway over long period of time before bioresorption. Reproduced with permission.[15] Copyright 2015, American Association for the Advancement of Science. B) A customizable and bioresorbable 3D-printed vascular stent (top) to be produced on demand after an arterial blockage. Two types of stent are illustrated with different structures, base design (bottom left) and arrowhead design (bottom right). Reproduced with permission.[41] Copyright 2015, Wiley-VCH.

personalized splints informed by each patient's unique anatomy. Notably, the structure is designed to expand in concordance with the patient's airway growth. The authors observed an immediate airway expansion after externally suturing the splints. Three infants with severe TBM were subsequently implanted with these external airway stents, which successfully demonstrated the desired degradation after 38 months of observation.

Moreover, atherosclerotic diseases,[109] resulting from obstruction of blood flow, are often treated with vascular stenting following balloon angioplasty.[110] However, the major disadvantages to the use of permanent stents should not be neglected.[111] Permanent stents, made from a metal framework, cause mechanical damage during deployment and predispose vascular tissues to intimal hyperplasia and thrombosis.[41] Therefore, it is necessary to develop bioresorbable stents (BRSs) with delayed absorption to accommodate the vessel healing process. Van Lith et al.[41] reported a personalized bioresorbable vascular stent by DLP technique (Figure 4B). Bioresorbable biomaterial ink was formulated by mixing methacrylated poly(1,12 dodecameth-ylene citrate) (mPDC) with a solvent to reduce viscosity as well as to mix UV absorbing agent in order to the curing depth. After stent deployment through tapered tube in vitro, antioxidant BRS was deployed inside the explanted porcine artery to assess the reinforcement of blood vessels.[41] Moreover, upon removing the compressive load, the artery instantaneously recoiled to its original diameter, confirming that the elastomeric properties of the BRS were retained with better personalized fitting, mechanical properties, and biocompatibility.

5. 3D-Printed Drug Delivery System

The development of drug delivery has significantly improved disease treatment and management strategies.[59,112–114] Drugs are typically delivered through liquid,[115] capsule/tablet,[116] dosage, paste, gel, spray, or programmable drug implant forms.[117] However, achieving a personalized, controlled, and precise drug delivery remains challenging with current drug delivery strategies. The reader is referred to several literature sources which provide in-depth discussions on drug delivery systems.[63,118–129] In this section, we highlight how the advances of 3D printing can potentially overcome these long-standing challenges.

5.1. 3D Printing for Oral Drug Delivery

3D printing technologies provide fabricated tablets with release properties that are difficult to achieve by conventional tablet-pressing technologies.[130] This can be achieved by fabricating complex geometries, barriers, porosity, and mixtures. Further, biocompatible materials can be 3D printed and retained in the body for a long period of time, allowing for drug reservoir implants and long-term retention devices.[131] In 2015, the FDA approved the first 3D-printed drug formulation, levetiracetam, by Spritam, a tablet of high porosity that can dissolve as quickly as in 11 s to assist the delivery of drug for a specific patient who experience difficulties in swallowing.[57,58] The porosity of the drugs can be tailored using inkjetting techniques. In addition, the free-form fabrication capability of FDM can be used to create geometrically tailored architecture to achieve a prolonged selective drug release[132] and a customized dosage. Goyanes et al.[64] demonstrated the versatility of FDM to optimize the release profile by changing the surface area-to-volume ratio. Specifically, different shapes of tablets have been fabricated with drug-loaded filaments (4% paracetamol) using the hot-melt extrusion method. The authors found that the drug release profiles vary with the different volume ratios of tablets.[65] Tablet configurations of drug delivery devices can also be altered by 3D printing. Goyanes et al. recently developed capsule-shaped solid devices with two different drug-loaded internal structures: a multilayer device and a DuoCaplet which contains a caplet encapsulated within a larger caplet (**Figure 5**A).[63] The multilayer structure (Figure 5A, left) allows the simultaneous and independent drug release of the multiple drugs (caffeine

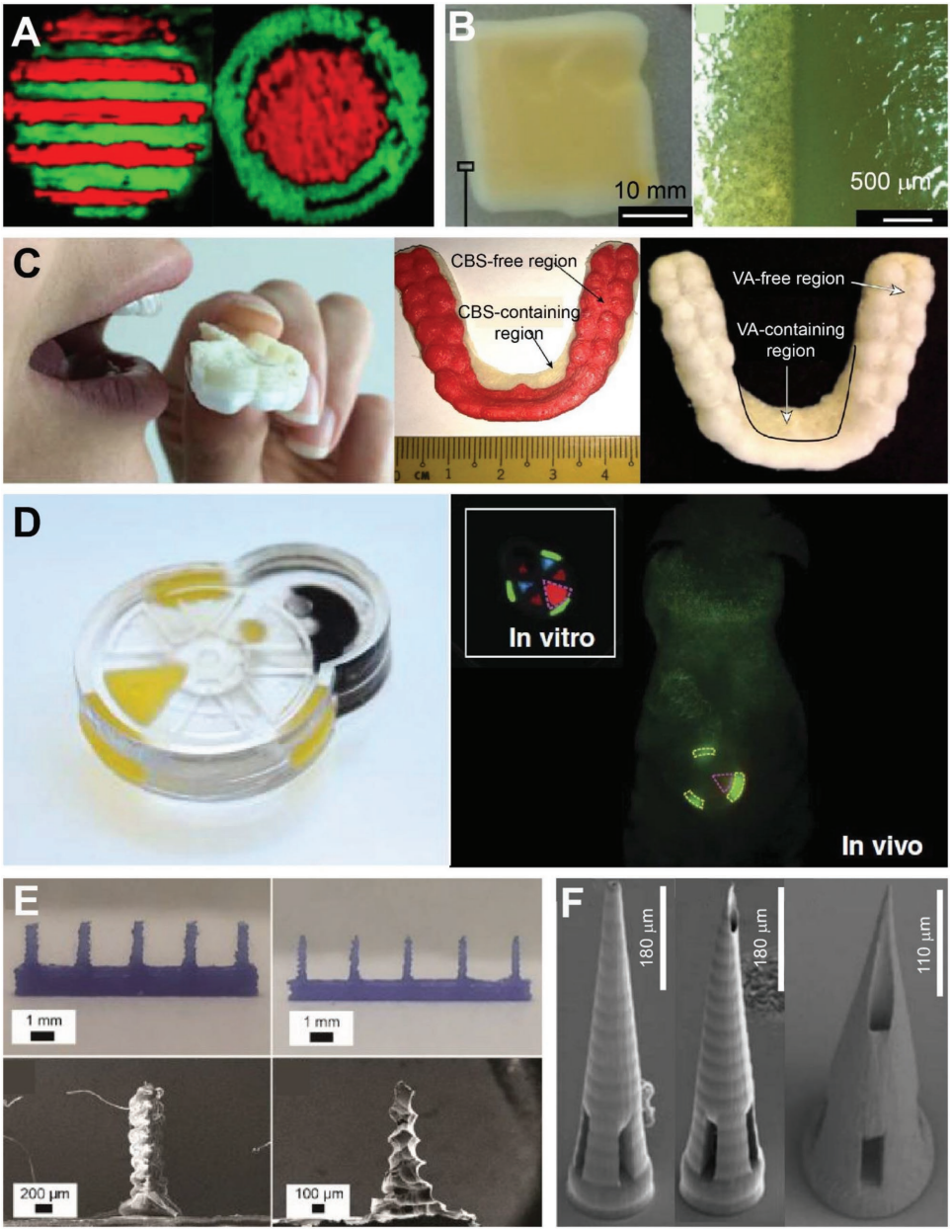

Figure 5. 3D printing for designing novel drug delivery systems. A) 3D-printed multidrug containing tablets with complex configuration and unique drug release profile. Raman spectroscopy technique shows cross-sectional mapping of multilayer drug tablets (caffeine in green and paracetamol in red). Reproduced with permission.[63] Copyright 2015, American Chemical Society. B) Shalev et al. used vapor jet printing to deposit nanostructured films of small molecules onto different substrates. This film printing method will help to accelerate drug screening and achieve dosage accuracy. The two pictures shown here are fluorescein on listerine. Reproduced with permission.[59] Copyright 2015, IOP Publishing. C) Personalized oral drug delivery mouth guard (left figure). A 3D-printed mouth guard consisted of a CBS-free top (red) and CBS-containing base (off-white) fabricated using PLA filament and PVA CBS-loaded filament, respectively (middle figure). A mouth guard comprising VA-free top (white) and VA-containing base (off-white fabricated using PLA/PVA filament and PVA VA-loaded filament, respectively) (right figure). Reproduced with permission.[137] Copyright 2018, American Association for the Advancement of Science. D) An implantable microdevice with a locking mechanism for precise movement and actuation control developed using 3D printing technology (left figure). The wirelessly controlled microdevice is implanted on a mouse (right figure) for controlled release of drug (doxorubicin). Reproduced with permission.[112] Copyright 2017, American Association for the Advancement of Science. E) A biodegradable microneedle for transdermal drug delivery fabricated using fused deposition modeling (FDM) to achieve improved feature size. Reproduced with permission.[66] Copyright 2018, the Royal Society of Chemistry. F) Microneedles with distinct architectures are fabricated with two photon polymerization using Ormocer. Reproduced with permission.[16] Copyright 2007, Wiley-VCH.

in green and paracetamol in red). In contrast, the DuoCaplet structure (Figure 5A, right) design allows the modulation of the release rate by tailoring the architecture and materials of the printed shell (green) that is encapsulating the drug (red).[63] In a recent demonstration, Shalev et al.[59] leveraged the solvent-free vapor jet printing technique (OVJP)[133–135] to create nanofilms of

molecular pharmaceutical ingredients (Figure 5B) which significantly enhanced the dissolution rate in comparison to powder-formed particles.

In addition, 3D printing can create ingestible dosage forms as a solution to medication nonadherence. "Drugs don't work in patients who don't take them." (US Surgeon General, C. Everett Koop, quoted in 1985). Yet, ≈ 50% of patients in the developed country do not adhere to their prescription. Moreover, the compliance rate is lower for patients who are prescribed multiple drugs with complex dose regimes.[132,136] Nonadherence has a substantial financial cost and leads to drug resistance and preventable losses.[132] 3D printing can simplify drug regimens by either combining multiple drugs in one dosage form or providing a method to provide long-term sustained release drug delivery for a specified period of time. In both the cases, this technology can reduce medication nonadherence and improve treatment outcomes.

In addition to ingestible devices, oral drug delivery has also been demonstrated with a 3D-printed personalized wearable mouthguard-shaped drug delivery device (Figure 5C).[137] Liang et al. created drug-loaded FDM filaments via hot-melt extrusion technique. Specifically, clobetasol propionate (CBS) or food-grade flavor vanillic acid (VA) was blended with poly(L-lactic acid) PLLA and poly(vinyl alcohol) (PVA) to formulate a drug delivery system with tunable release kinetics.[137] The authors have also demonstrated the ability to deliver desired dosage in a human clinical trial.

5.2. 3D-Printed Implantable Drug Delivery Microdevice

3D printing introduced a potential opportunity for developing personalized, controlled, and precise drug delivery systems. This technology achieves precise control of dosage in accordance with the size and dispensary mechanism of the design. Biocompatible material also allows for long-term implantation or retention while continuously dispensing controlled volumes with the potential to evolve into a highly efficient sensor-controlled drug dispensing system. Chin et al.[112] used photolithography with *z*-axis control to create a biocompatible and implantable drug delivery microdevice which can be wirelessly controlled on demand. They exploited unique mechanical properties of hydrogels and proposed a locking mechanism for actuation of freely moving parts (Figure 5D). Interestingly, on a mouse model of osteosarcoma, the authors demonstrated the triggered release of drug (doxorubicin) for 10 days and observed 1/10th of the toxicity of the standard chemotherapy regimen.[112]

5.3. 3D-Printed Needle

The hypodermic needle is a prime example of a clinical application of a novel drug delivery system. However, patients are aversive to the system due to the pain they may experience.[138] In addition, hypodermic needles generate biohazardous waste and require rigorous training on its administration.[66] In contrast, polymeric microneedle (MN) is an attractive alternative that can provide a less invasive and more cost-effective method to achieve drug delivery.[139,140] Furthermore, recently developed polymeric MN has low immunogenic response, improved shelf life, and flexibility in their material composition.[66] However, the MN fabrication with micromolding process typically requires expensive photolithography and etching equipment. Alternatively, Luzuriaga et al. recently produced polymer MN using FDM 3D printing with polylactic acid as a rapid and facile fabrication approach to create biodegradable MN (Figure 5E).[66] In another example, hollow MNs with a variety of geometry have been fabricated with two photon polymerization printing process using commercially available Ormocer material to achieve transdermal delivery of drug, as shown in Figure 5F.[16] We anticipate that the continuous advancements in 3D printing technology will allow for cost-effective, rapid, and on-demand fabrication of novel drug delivery systems in future.

5.4. 3D Printing in Drug Synthesis

In addition to the development of the drug delivery, the versatility of 3D printing approach has been explored in the area of drug synthesis. A new concept of reactionware spring boarded from the high cost and complexity of the design and fabrication process of new drug delivery systems. Kitson et al.[141] invented a versatile reactionware that can print molecular configurations to assist in the chemical design process. This approach offers a cheap and automated chemical discovery platform to accelerate the drug manufacturing process without the need for special facilities. Using both reactionware and 3D printing, new drug design and development will become more accessible and faster than what was previously attainable.

5.5. 4D Printing in Drug Delivery

The term "4D printing" signifies tailoring of 3D objects which can change shape over time in response to external stimuli.[9] Although this technique is similar to 3D printing, 4D printing adds time as the fourth dimension.[142,143] Within the last decade, botanical inspired 4D biofabrication emerged as a new field that allows complex morphing of bioprinted materials in response to external stimuli, such as hydration,[73] temperature,[9] magnetic field.[143,144] These shape-changing structures can be designed to morph into complex shapes in different environments that can provide solution for forward and inverse design problems. Applications of this technique in biomedicine can mediate difficult geometric shapes not amenable to normal 3D printing methods. Drug delivery devices, in particular, can benefit from another layer of complexity and specificity. For example, drug delivery devices can be tailored to adopt a different conformation or drug release profile depending on the biological environment. Shape memory polymer has the ability to temporarily adopt a programed shape and recover the original shape upon exposure to a stimulus.[145] Future material research can leverage these characteristics in 4D printing to create multimaterial constructs to accommodate more complex medical necessities. For further application of 4D printing in biomedicine, the reader is referred to this review article[143] for detailed discussion.

6. Tissue-on-a-Chip

Tissue/lab-on-a-chip, synonymous to biomedical application of microfluidics, is an advantageous and cost-effective way to investigate basic research questions.[146–148] Analyzing fluids at the micrometer scale using microfluidic device holds immense promises for biological research.[147,149] Current tissue-on-a-chip research aims to create tissue chips that can accurately model the structure and function of a specific organ and diseases for drug screening and drug toxicity evaluations. 3D printing technology has been the ideal tool to facilitate these efforts. For example, recent advances in SLA-based 3D printing enable the creation of a biocompatible, elastomeric, transparent, gas-permeable, and water-impermeable resin possessing Slygard 184 properties. This allow for rapid prototyping of microfluidic device as an alternative to the soft lithography–based technique.[147,150,151]

In another example, Homan et al. recently designed a novel 3D bioprinting method to recapitulate human proximal tubules in a perfusable tissue chip (**Figure 6**A).[152] These 3D proximal tubules are surrounded by extracellular matrix and proximal tubule epithelial cells (PTECs) to form a lumen architecture. They demonstrated that these 3D proximal tubules (PTs) showed higher albumin uptake than 2D models due to the enhanced cell polarity and brush border cells. Additionally, the epithelial barrier of 3D-printed PTs can be disrupted by introducing the nephrotoxin and cyclosporine in a dose-dependent manner, suggesting the potential for 3D PTs to be used for investigation of nephrotoxicity.

The liver is a critical organ involved in drug metabolism. A tissue-on-a-chip model of the liver has considerable potential to act as a drug effect screening tool. Bhise et al. presented a liver-on-a-chip system where 3D-bioprinted liver spheroids are used to assess drug toxicity.[153] They designed a novel bioreactor interfaced with a 3D printer that can generate bioresponsive and biodegradable hydrogel-based HepG2/G3A hepatic spheroids. Hepatic functionality and concentration of secreted biomarkers were maintained for one month. Moreover, the authors show that the bioreactor responds to acute drug toxicity, consistent with previously reported animal drug toxicity studies.

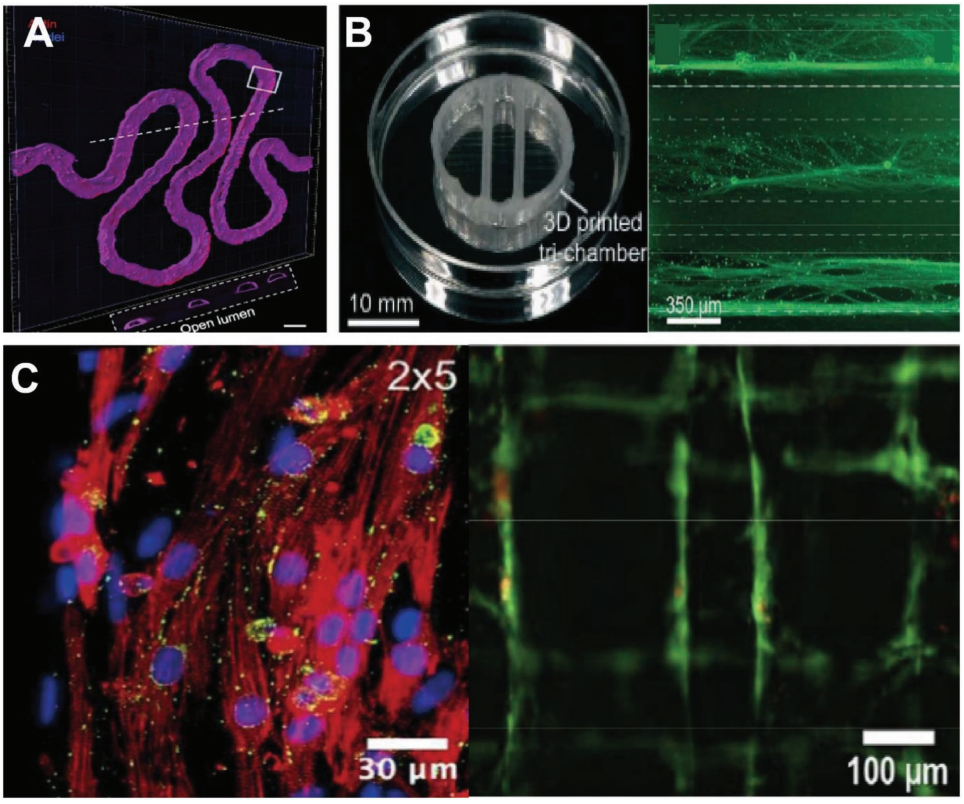

Figure 6. 3D-printed organs or tissues-on-a-chip for fundamental medical research. A) 3D-printed in vitro human renal proximal tubules embedded within an extracellular matrix and housed in perfusable tissue chips. This is an efficient method that can be applied in drug screening and disease modeling. Reproduced with permission.[152] Copyright 2016, Nature Publishing Group. B) Customizable 3D-printed nervous system-on-a-chip (3DNSC). The circular pattern of 3D-printed silicone tri-microchannels designed for axonal guidance (left). The image shows the schematic of a representative 3DNSC for peripheral nervous system research applications. A microscopy image shows three parallel microchannels of neurons and axons (green) in a chamber (right). Reproduced with permission.[154] Copyright 2016, the Royal Society of Chemistry. C) Zhang et al. placed endothelial cells within microfibrous hydrogel scaffolds to generate a 3D-bioprinted endothelialized myocardium. Immunofluorescence staining of sarcomeric α-actinin (red) and connexin-43 (green) of cardiomyocytes seeded on bioprinted microfibrous scaffolds (left). The schematic shows a scaffold seeded with neonatal rat cardiomyocytes. Microscopy image of bioprinted cardiac organoids in bioreactors shows high cell density and viability (right). Reproduced with permission.[18] Copyright 2016, Elsevier.

This indicates the potential for this liver-on-chip platform to be used as an alternative method for drug toxicity analysis.

Cardiac tissue engineering has been a challenge due to the complicated hierarchical structure of the myocardium and the challenge for vascularization of muscle tissues to maintain oxygenation and energy supply.[18] Zhang et al. recently presented a novel method to fabricate endothelialized myocardium using bioprinting technology. After bioprinting the 3D endothelialized microfibrous scaffold, cardiomyocytes were seeded on an aligned structure to form the myocardium. They further launched a pharmaceutical compound screening test by combining this printed endothelialized myocardium with a microfluidic perfusion bioreactor. They found that perfusion of the scaffolds during bioreactor culture significantly increased survival of cardiomyocytes (Figure 6C). This study highlights the flexibility and complexity afforded by bioprinting technologies that allow tissue engineering to overcome major limitations, such as tissue vascularization.

The nervous system is one of the most anatomically as well as functionally complex systems within the human body. The 3D environment for cells of the nervous system significantly contributes to their cellular responses and physiology. Current methods are very limited in their ability to recapitulate disease states and study connectivity as well as disease processes, such as neurodegenerative and psychiatric diseases. Hence, the complexity of nervous system diseases makes in vitro nervous system models a valuable tool for drug screening for the understanding of neural physiology. Johnson et al. created a nervous-system-on-a-chip using DIW printing technology to help assess viral infection.[154] This 3D nervous-system-on-a-chip (3DNSC) consists of a 3D architecture with microchannels and compartments that permits axonal alignment and cell segregation (Figure 6B). They found that while Schwann cells play a vital role in axon-to-cell viral spread, they also cause a bottleneck in viral transmission. This suggests that a customizable nervous-system-on-a-chip successfully achieved by 3D printing can mediate further applications to facilitate advancements in medical research. Furthermore, in vitro 3D neuronal models have made considerable steps to capture the cortical layers[155] by utilizing microfluidics[156,157] or silk scaffolds.[158] However, the process is long and inefficient. To simplify 3D neuronal models, Lozano et al.[159] used bioink consisting of peptide modified biopolymer, gellan gum-arginine-glycine-aspartic acid (RGD-GG) combined with cortical neurons. The group creates layers of neurons cells using hydrogel to establish different cortical layers. The material and flexibility of current 3D printing technology provide a promising avenue in brain tissue engineering to help recapitulate the complexity of human neuroanatomy and neuroarchitecture.

7. 3D Printing in Cancer Research

3D-printed in vitro cancer models can serve as a platform to advance cancer[160–162] research by 1) emulating tissue microenvironment to further understanding of cancer metastasis, 2) identifying molecular markers for drug discovery, and 3) streamlining future drug screening trials. Particularly, cancer metastasis is a dynamic and complex process whereby the primary tumor leaves the original tumor site and spreads to another region of the body. Its dependence on the microenvironment and various mechanical factors poses a major challenge for cancer researchers. While previous 2D models were able to measure cell proliferation, matrix metalloproteinase (MMP) protein expression and chemoresistance, the 3D model enabled improved physiologic measurements with more accurate morphologic observations. In one method, gelatin/alginate/fibrinogen hydrogels were loaded with HeLa cells to 3D print cervical cancer cell spheroids.[19] The flat and elongated cell morphology–observed 2D cell cultures appear as spheroids with smooth surfaces and compact cell–cell connections in the 3D hydrogel model. Indeed, major strides are currently being made, but several challenges remain. First, 3D printing has not been able to generate the mechanical forces directly exerted on cancer cells that can alter their metastatic potential. Shear and solid stresses affect cancer pathophysiology by directly changing the tumor morphology and by deforming blood and lymphatic vessels through which tumor cells can spread.[163] Moreover, in regards to drug testing, different 3D printing techniques result in different drug responses, indicating that the increasing complexity of this technique compromises the reproducibility of these cancer spheroids.

Typically, the natural 3D environment for cancer is modeled using immunodeficient mice with human cancer cell xenographs. However, immunodeficiency compromises the natural microenvironment the model attempts to recapitulate. Huang et al.[164] sought to understand the migration of cancer cells using 3D-printed in vitro microchip in hydrogel. They used digital micromirror device–based projection printing biofabrication system to print complex PEGDA biomimetic vascular scaffolds and microstructures to study the vascular migration of tumorigenic 10T1/2 cells (**Figure 7**A). However, even with a scaffold, these models lacked appropriate cell density and control over spatial distance between cell types. To address this issue, Xu et al.[165] used 3D printing technique to co-culture human ovarian cancer (OVCAR-5) cells and normal fibroblasts (MRC-5) micropatterned on Matrigel to achieve the appropriate cell density (Figure 7B). With high-resolution 3D printing technology, it is now possible to investigate cancer cell migration in a high-throughput manner.

Bone, the most common site for cancer metastasis, is a mineralized connective tissue with complex structure and sensitive microenvironment. Bone tissue–engineered 3D constructs are more advantageous than 2D cell cultures due to the structure and mechanical composition 3D printing can produce to mimic the bone tissue microenvironment. To better understand the propensity for metastasis to bone, Zhu et al.[14] proposed a stereolithography-based 3D printing technique using nanoink, customized by hydroxyapatite nanoparticles suspended in hydrogels, as a cost-effective method to artificially fabricate a tunable biomimetic nanocomposite bone matrix. The ability to easily create bone scaffolds that resemble the tumor microenvironment allows scientists to better study microenvironmental influences of cancer metastasis and proliferation at various stages of disease (Figure 7C). Improved biomimicry of the bone microenvironment underlines the potential of using 3D-printed bone tissue as a platform for drug discovery and to test cancer therapies at the early stages of drug development.

For further readings, the readers are referred to these reviews[119,129,147,166,167] for detailed discussions of the application of 3D printing in cancer research.

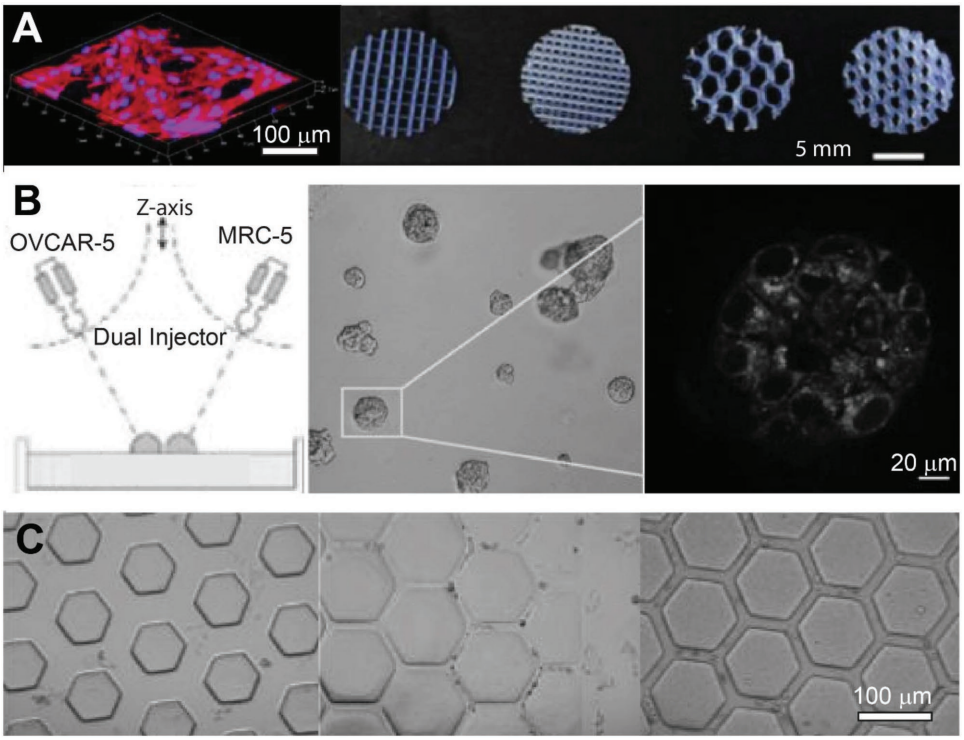

Figure 7. 3D printing for cancer research. A) A novel 3D-printed bone-specific biomimetic environment developed for evaluating breast cancer bone invasion. The left confocal image shows 3D views of MSC monolayers grown on the 3D bone matrix; actin and DNA are stained red and blue, respectively (left). The images on the right show the final printed bone matrices with various pore structures. Reproduced with permission.[14] Copyright 2016, Elsevier. B) A 3D-printed ovarian cancer model was fabricated with cancer cell and normal fibroblasts. The left schematic reveals an automated three-axes stage with nanoliter dispensing valves controlled by a pulse generator. The two right images are two-photon autofluorescence images showing the 3D structure of 3D acini formed from ovarian cancer cells seven days post printing. Reproduced with permission.[165] Copyright 2011, Wiley-VCH. C) The effects of geometric cues on healthy cells and cancer cells (HeLa cells) were compared using a biomimetic microchip. The honeycombs with 25 μm wide channels (left), 45 μm wide channels (middle), and 120 μm wide channels (right) are designed to mimic the structure of human blood vessels. Reproduced with permission.[164] Copyright 2014, Springer Nature.

8. 3D Printing for Tissue or Organ Regeneration

Tissue engineering is a rapidly expanding field aimed to fill in the gap left by the shortage of donor tissues and the consequences of transplant rejection. Tissue regeneration, achieved by combining cells and bioactive factors in a biomaterial scaffold to produce an implantable construct, is capable of replacing and restoring damaged tissues. The biomaterial scaffolds can provide the factors and environment necessary for cell differentiation and proliferation in order to restore tissue structure and function. Traditional methods in tissue engineering, such as gas foaming, solvent casting, fiber bonding, phase separation, particulate leaching, and freeze-drying have limited ability to form complex geometries required for anatomical defects. 3D printing technologies, however, can be used as an accelerator to go from tissue engineering concepts to fast and inexpensive clinical interventions.

8.1. 3D Printing for Ear Cartilage Regeneration

The application of 3D printing technologies in tissue regeneration has been gaining scientific interest. Its customizability is a major advantage for engineering tissue structures and architectures with precision. One particular application researchers have explored is to use 3D printing to reconstruct artificial ears. For example, Zhou et al. recently developed an in vitro patient-specific cartilage for the ear using 3D printing technology to treat microtia, a congenital condition that leads to an underdeveloped external ear (**Figure 8**A).[168] This study adopted 3D printing to fabricate a resin ear model, which was used to form negative molds with clay and silicone. Biomaterial scaffolds were then placed into the negative molds prior to seeding chondrocytes for three months. Cartilage constructs grown with this method were implanted in five patients who had very positive long-term outcomes. The ability of 3D printing technologies to integrate with previously established research in tissue engineering highlights another advantage of 3D printing to fast-forward the current progress in tissue regeneration.

8.2. 3D Printing of Heart Valves

Although heart valve disease has increased in prevalence over past years, valve replacement remained the only treatment option for a majority of patients. Previous prosthetic replacement technologies could not replicate the anatomical

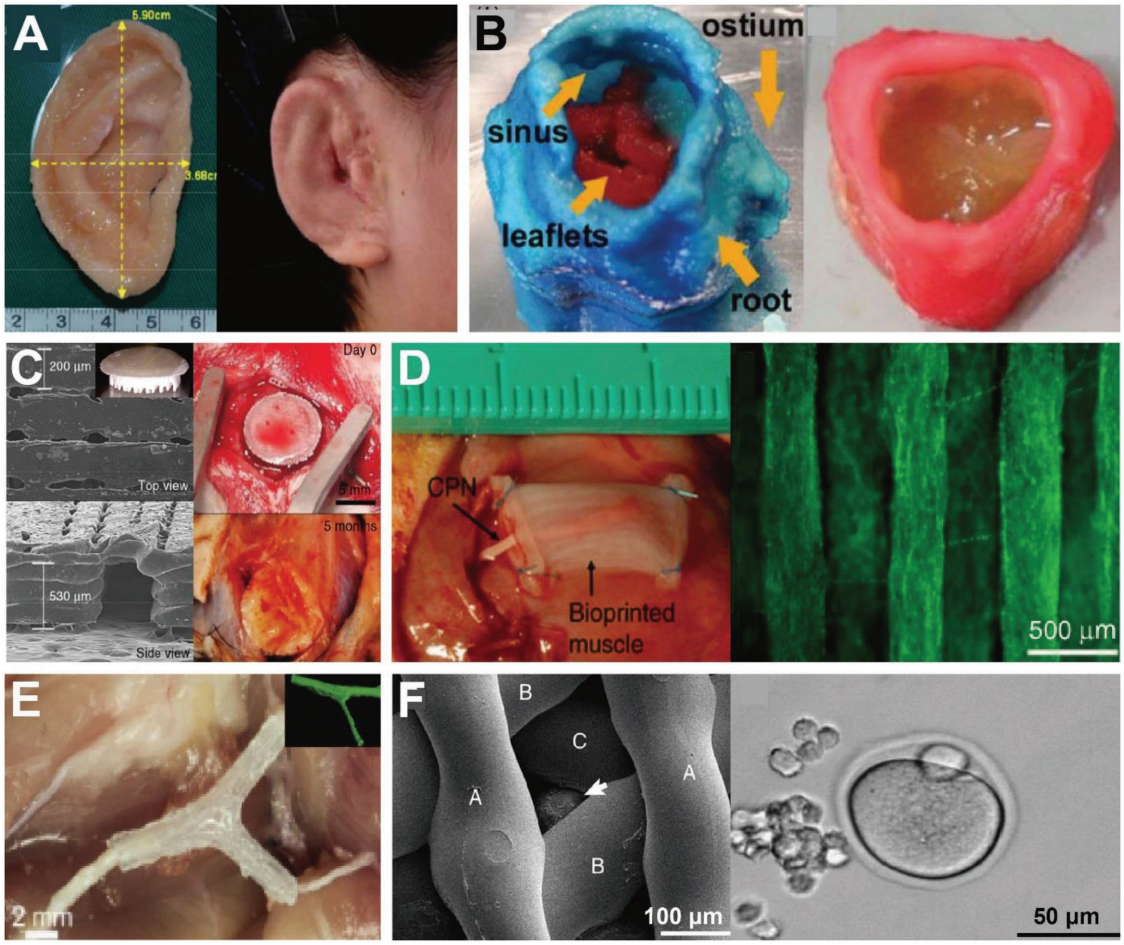

Figure 8. 3D printing for tissue or organ regeneration. A) A personalized ear-shaped cartilage using expanded microtia chondrocyte scaffolding fabricated by 3D printing (left). The cartilage was used to treat five microtia patients. Two and a half years after the procedure, patients reported mature cartilage formation and satisfactory outcomes (right). Reproduced with permission.[168] Copyright 2018, Elsevier. B) 3D-bioprinted valve conduits fabricated with dual cell types. Reproduced with permission.[74] Copyright 2012, IOP Publishing. C) An integrated tissue–organ printer (ITOP) was recently employed to perform calvarial bone reconstruction. Scanning electron microscope images (left) show the printed calvarial bone construct. Images show the printed bone constructs implanted at day zero (top right) and after 5 months (bottom right). D) Skeletal muscle reconstruction can also be fabricated using this integrated tissue–organ printer. Staining (right) showing high cell viability after subcutaneous implantation of the bioprinted muscle construct into mice (left). Reproduced with permission.[176] Copyright 2016, Nature Publishing Group. E) A novel 3D-printed network of pathways functionalized with physical cues and path-specific biochemical gradients provides a mechanism for regenerating damaged nerve plexuses. Reproduced with permission.[20] Copyright 2015, Wiley-VCH. F) Different scaffold angles in a 3D-printed microporous hydrogel scaffold can significantly affect the survival of ovarian follicles. Ovarian function was completely restored after implanting follicle-seeded scaffolds into the surgically sterilized mice. A scaffold at 60° provides corners that surround follicles on multiple sides (left). An oocyte with polar body was released from a follicle cultured in scaffold at 60° (right). Reproduced with permission.[178] Copyright 2017, Nature Publishing Group.

complexity and cellular heterogeneity in biological tissue. To address this problem, Hockaday et al. created heterogeneous heart valve conduits using bioink (Figure 8B), a mixture of alginate and gelatin hydrogel encapsulating two different cell types, aortic root sinus smooth muscle cells, and aortic valve leaflet interstitial cells.[74] After geometric reconstruction of the aortic valve conduits by micro-CT images, a dual cell type bioprinting process allowed heterogeneous cell distribution in the printed tissue layers to fabricate it. After seven days of in vitro culture, both the cell types exhibited robust cell viability and confirmed by alpha smooth muscle actin (αSMA) and vimentin protein staining. Additionally, Nakayama et al.[169] also successfully created trileaflet heart valve mold using 3D printing technology. The mold was assembled using two conduit parts and three sinus parts and designed with highly specialized systemic circulation in vitro and in vivo. Using this mold, a biovalve can be generated from seeding autologous connective tissue. The realization of trileaflet human valves with complex geometry and physical properties by 3D bioprinting depends on the availability of biocompatible and printable hydrogel materials.[170] To add to the repertoire of biocompatible and printable materials, Duan et al.[170] formulated a hybrid hydrogel combining methacrylated hyaluronic acid (Me-HA) and methacrylated gelatin (Me-Gel) that can be used to encapsulate human aortic valvular interstitial cells (HAVICs) for trileaflet heart valve bioprinting. This hybrid hydrogel, designed to regulate cellular response, expands the library of biomaterials for printing 3D living components and biomimetics.

8.3. 3D Printing for Skin Tissue Replacement

Patients with contour defects resulting from tumor resections, trauma, and congenital deformities require adipose tissue to restore adequate volume for a normal cosmetic appearance.[171] In plastic and reconstructive surgery, tissue printing offers the possibility of restoring normal function and appearance.[172] Pati et al. used decellularized adipose tissue (DAT) matrix bioink to successfully print precisely defined and flexible dome-shaped structures.[172] These bioengineered soft tissue grafts are more advantageous than analogous tissue grafting or synthetic material replacements. Tissue grafts using adipose tissue can only fill in the contours visible on the skin. Very few medical interventions existed to replace the skin after burn injuries or other skin tissue damages.[173] Recent advancements in bioprinting using polymers to encapsulate stem cells (SCs) introduce new strategies for restoring skin appearance and functionalities. For example, Ng et al.[174] investigated chitosan-based biomaterials for 3D bioprinting of skin tissue. Chitosan is a particularly desirable material for skin bioprinting due to its good antimicrobial properties, high geometric fidelity, and biocompatibility with skin fibroblasts. Chitosan can also serve as a scaffold to guide SCs to achieve their final shape. In a review based on recent innovation, Ventola et al.[129] reported the existing inkjet to bioprint keratinocytes and fibroblasts with unparalleled precision. These advancements help to overcome the common pitfalls associated with single-cell inkjet bioprinting[175] and exhibit immense potential for the future of skin tissue engineering.

8.4. 3D Printing for Bone and Muscle Regeneration

While 3D printing has the advantage generating complex anatomic tissue constructs using successive layers of cell-laden hydrogels, it is deficient in providing substantive structural integrity, mechanical stability, and high flow rates. To address this issue, Kang et al. designed a novel integrated tissue–organ printer capable of forming stable tissue constructs of any shape. They applied this method to print circular calvarial bone constructs that were then cultured in osteogenic media for ten days (Figure 8C). The investigators implanted these constructs in a calvarial bone defect region in rats and observed that these bioprinted constructs presented newly formed vascularized bone tissue throughout the implants after five months.[176] They extended this technology further and used PCL pillars to align muscle cell growth into organized muscle tissue.[176] After confirming cell viability (Figure 8D, left), the constructs were implanted into nude rats near the peroneal nerve to improve integration of the transplanted muscle with the surrounding tissue.

8.5. 3D Printing for Nerve Regeneration

3D printing technologies have been applied to nerve regeneration as a potential therapeutic option for peripheral nerve damage. Granted, nerve regrowth is a complex and protracted process that requires both physical cues and biochemical molecules to ensure successful regeneration. In a study by Johnson et al., the researchers restored nerve function through nerve regeneration across a 10 mm nerve gap in rats. Using a DIW 3D printing technology, they created a guiding scaffold with silicone rubber ink. This in vitro study demonstrated a proof of concept for the ability of 3D-printed physical and biochemical cues to guide axonal regeneration (Figure 8E).[20] 3D printing technology is an invaluable tool that can incorporate established and future medical research on proteins and molecules required for nerve regeneration to accelerate recovery and improve patient outcome.

8.6. 3D Printing for Whole Organ Regeneration

At a larger scale, application of bioprinting in whole organ regeneration has promising potentials. The ability to construct personalized biocompatible tissues and organs provides the means for individualized treatment without the need to harvest autograft from the patient. One current barrier to reaching this goal, however, is designing cell-laden hydrogels with the proper mechanical properties.[177] The framework material determines the nature of the microenvironment and currently, very few materials are biocompatible while still comprising of the desired mechanical properties. In one study by Lee et al.,[177] the authors used PCL to encapsulate three different cell types, including hepatocytes (HCs), human umbilical vein endothelial cells, and human lung fibroblasts in collagen bioink. This method allowed them to successfully mimic the natural microenvironment, paving the way toward whole liver regeneration. Interestingly, the geometry of the microenvironment is also an important factor for tissue regrowth. Laronda et al.[178] found that the micropore hydrogel geometry affects the survival of ovarian follicles. Selection of the correct geometry allowed vascularization and complete restoration of ovarian function after implantation of follicle-seeded scaffolds in nude mice (Figure 8F).[178]

Many of the foundations for applying 3D printing to whole organ regeneration are currently being laid. Further, the development of novel 3D printing technologies such as surface tension–assisted additive manufacturing[179] could provide versatile platforms that can fabricate multicomponent biomaterials. The reader may be interested to refer to the in-depth discussion on 3D printing on tissue or organ regeneration in these excellent review papers.[91,119,129,172,180–206] In summary, current research involves understanding the geometry, composition, and biochemical factors needed for 3D printing–assisted whole-organ regeneration. The potential for 3D printing to expedite this process will be instrumental for the financial feasibility in future clinical applications.

9. Outlook: Toward 3D-Printed Bioelectronics

The incorporation of electronics into biomedical devices and biological scaffolds is a foundational concept, which when applied, can mimic and even augment the complex functionalities of biological systems. However, the degree of such integration demonstrated by conventional manufacturing technologies has been limited. For example, electronic integration into 3D constructs typically requires innovative strategies such as transfer printing processes,[25,207–209] and/or assembly

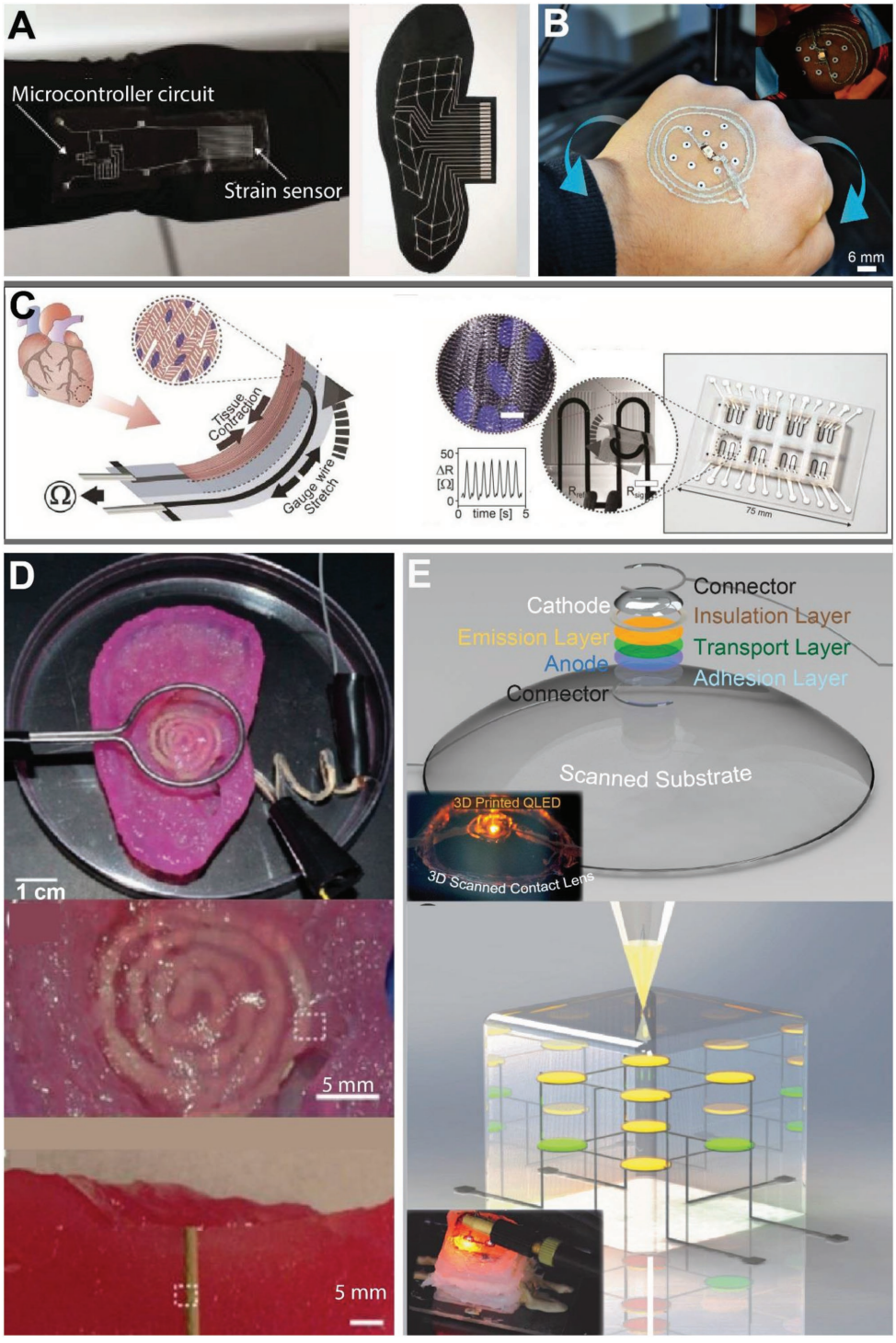

Figure 9. 3D-printed bioelectronic devices. A) Valentine et al. reported a hybrid 3D printing technique that integrates direct ink writing with automated pick and place mechanism. Electronic components were integrated into a printed pattern used conductive electronic ink and insulation matrix. Reproduced with permission.[215] Copyright 2017, Wiley-VCH. B) Adaptive 3D printing of electronics on a moving free-form surface. The image shows the integration of wireless electronics with the 3D-printed conductive path on a moving hand. LED power is provided via a wireless power transmission system. Reproduced with permission.[216] Copyright 2018, Wiley-VCH. C) 3D-printed cardiac microphysical organ-on-a-chip devices designed to integrate with soft strain gauge sensors. The left graph shows the sketch of the device principle. Contraction of an anisotropic engineered cardiac tissue deflects a cantilever substrate, which stretches a soft strain gauge embedded in the cantilever. The resistance changes proportionally to the contractile stress of the tissue. The fully printed final device is shown on the right. Confocal microscopy shows immunostained laminar neonatal rat ventricular myocyte (NRVM) cardiac tissue on the cantilever surface. The second inset shows a cantilever deflecting in response to tissue contraction. Reproduced with permission.[27] Copyright 2017, Nature Publishing Group. D) Functional "bionic ears" are fabricated by co-printing an alginate hydrogel matrix seeded

of prefabricated devices,[210] to accommodate for the geometric and material incompatibilities.

Recent advancements in 3D-printed electronics potentially enable the creation of hybrid bioelectronics. In contrast to the "top down" fabrication approach of microelectronics that involve harsh chemical and temperature processing conditions, 3D printing of electronics is typically performed under ambient conditions via a bottom-up assembly process. This permits a multiscale manufacturing approach to ingeniously incorporate electronics in 3D-printed constructs.

The seamless integration of electronic systems paves new frontiers for optimized smart prosthesis, drug delivery devices, and tissue-engineered bioelectronic constructs that can address urgent clinical needs.[211] Here, we highlight the recent progress of printed electronics that can provide 3D printing with this capability.

3D printing of conductive traces is a promising solution for the planar constraints of the conventional electronic fabrication approach. Ahn et al.[212] demonstrated the impressive ability to direct-write 3D conductive traces using highly concentrated (>70 wt%) viscoelastic conductive ink with silver nitrate, diethanolamine, and poly(acrylic acid). In contrast to prior inkjet printing approaches, DIW creates microscale 3D interconnects to fabricate flexible microelectrodes. Further extending the previously established soft material–based printing methods, Valentine et al.[215] demonstrated a hybrid 3D printing technique that integrates direct ink writing with automated pick-and-place technology of surface mount electronic components (**Figure 9**A). Conductive electrode inks and insulating matrix can be specifically patterned and cointegrated with electronics components. The elasticity of the printed conductors was achieved with the addition of thermoplastic polyurethane (TPU).

McAlpine and co-workers recently demonstrated an autonomous, adaptive 3D printing technology that enables the direct printing of conductive inks on moving free-form surfaces.[216] Specifically, this hybrid fabrication approach leverages an integrated robotic system aided by computer vision to create a closed-loop 3D printing fabrication approach. The authors demonstrated the ability to 3D print a wireless device on a moving human hand (Figure 9B) with an integrated and wirelessly powered light-emitting diode (LED) chipset (inset of Figure 9B). This development demonstrates the ability to create on-the-fly wearable electronics on moving biological targets, rendering it a powerful technique that could enable the direct integration of electronics components on a living biological organism, for instance, in a surgical setting.[216]

In addition to 3D-printed soft electronics, fabrication of passive electronics, such as strain gauges, imparts hybrid biological constructs with sensing capabilities to provide valuable feedback information. For example, a hybrid prostate model–integrated sensor[217] created with patient-specific anatomical details was shown to assist surgeons during the preoperative planning process. These recent advances demonstrate the ability to combine bioprinting with 3D-printed electronic fabrication approaches to create hybrid biological constructs. Impressively, Lind et al.[27] developed cardiac microphysical organ-on-a chip devices integrated with soft strain gauge sensors. As described in the schematic in Figure 9C, the associated strain gauge enables real-time monitoring of anisotropic engineered cardiac tissue contractions, where the change in resistance of the strain gauge is proportional to the contractile stress of the tissue.

Furthermore, the multimaterial electronics 3D printing approach can also be integrated with whole organ 3D printing. For example, Mannoor et al. used a chondrocyte-seeded alginate hydrogel matrix with conducting silicone to print a circular antenna.[26] The printed circular antenna is a proof of concept for the crude yet functional electronic "bionic ear" (Figure 9D). Importantly, the authors demonstrated the biocompatibility of the printed electronics with a biological construct. The fluorescent image (bottom) of Figure 9D shows the viability of the neocartilaginous tissue in contact with an electrode (top).

To date, demonstrations of a seamless bioelectronics 3D printing have been limited to passive electronic components, such as conductive traces and capacitors. The integration of active electronic devices could impart an otherwise passive construct with optical, sensing, and computational capabilities.[218–220] However, the complexity of incorporating diverse classes of materials exhibiting disparate properties makes a fully 3D printable active electronic device a formidable challenge.[28] For example, as demonstrated by Kong et al., the 3D printing of LEDs requires the integration of a cathode, an anode, printable substrate, an emission layer, and charge transport layers (Figure 9E) with varying viscosities, surface energies, tribological and mechanical properties.[221] However, overcoming this challenge will liberate the device from the constraints of conventional microfabrication processes. For example, this approach can allow the incorporation of 3D scanning technologies to 3D print electronics on a 3D substrate, as shown in the direct printing of a quantum dot light-emitting diodes (QD-LED) on a 3D-scanned contact lens (Figure 9E, top image). Critically, this approach also conceptualizes hybrid 3D constructs embedded with active electronics, such as silicone cube embedded with light-emitting diodes (Figure 9E, bottom image).

We anticipate that similar approaches can develop 3D printing strategies of various classes of active electronics.[222] Nevertheless, the biocompatibility of such approach must be critically assessed to ascertain a full translational result from the bench to the bedside. Overcoming this obstacle could endow us with a powerful ability to integrate electronics onto a variety of biological constructs. We expect that this capability will ultimately allow healthcare providers and researchers to directly print biomedical electronics devices and bioelectronics

with chondrocyte cells and conducting silicone. The fluorescent image (bottom) shows the viability of the neocartilaginous tissue in contact with the electrode (top). Reproduced with permission.[26] Copyright 2013, American Chemical Society. E) 3D printing of LEDs requires the integration of a cathode, an anode, printable substrate, an emission layer, and charge transport layers. The top image presents a QD-LED directly printed on 3D scanned contact lens. The inset presents electroluminescence output from the printed QD-LED on 3D scanned contact lens. The bottom image is representative of 3D printing of a $2 \times 2 \times 2$ multidimensional array of embedded QD-LEDs. Reproduced with permission.[221] Copyright 2014, American Chemical Society.

to address unmet clinical demands with novel strategies in areas such as regenerative medicine, drug delivery, and fundamental medical research.

10. Clinical Potential

3D printing technologies are becoming more widely adopted in the clinical setting. Educational applications[223] of 3D printing include the fabrication of anatomical models used as a teaching tool in the clinic. Moreover, surgeons can extract anatomical information from magnetic resonance imaging (MRI) images[224] to generate anatomically accurate models to guide precise surgical planning that can reduce operating room time and improve surgical results.[98,126] As 3D printing is making its way into operating room to improve surgical outcomes, the more ambitious current progress aims to integrate functional 3D-bioprinted tissues and organ systems into the human body. Although this is conceivable within the next coming decade, we are still limited by the inventory of biocompatible materials and tissue engineering capabilities. Research to further understanding of heterogeneous cell types in the tissues, cell proliferation, reproducible source of cells will be required for developing the inventory of bioprinting material.[181] Additionally, for normal tissue function, innervation and vascularization will be needed to fabricate human-scale bioprinted organs suitable for transplantation. With the advent of 3D printing technology, on-demand bioprinting, where materials and cells are directly deposited in or on a patient, may become feasible.[181] Bioprinting of skin directly onto wounds and bones to correct calvaria defects in mice[225] has already been attempted and future developments to improve resolution, speed and biomaterial composition can potentially lead 3D bioprinting towards on-demand tissue regeneration during surgical procedures.[181]

Some current challenges of biomedical devices and bioprinted constructs in progress include degradation in the harsh gastrointestinal environment for a long-term oral drug delivery platform, inflammatory responses to foreign implants, as well as sustainability of devices and bioprinted tissues over a long period time. Current trials are promising but still in their infancy. Further research should be done to ensure the biocompatibility and sustainability of 3D printing–assisted systems. Once we do achieve electronic communication with the implanted devices via personal electronics, a method to protect personal health information must also be instituted. Future endeavors will require the knowledge from a variety of different expertise in radiology, medicine, material science, computer science, and biomedical engineering to streamline the work flow from imaging to implantation.

11. Conclusion

In summary, we highlighted the recent progress in 3D printing technologies to potentially address a number of clinical challenges. Novel 3D constructs and devices with an unprecedented level of complexity, properties, and functionalities are now conceivable. The ability to create highly customized and optimized 3D physical configurations from digital designs is essential to the free-form fabrication of smart prosthetics, robust support structures, and enhanced medical devices. Such technologies simplify the fabrication of tissue/organ-on-chip platforms that can provide critical insights to advance fundamental medical research. Similarly, by replicating the 3D microenvironment critical for organ and tissue regeneration, 3D bioprinting fosters future advancements in the field of regenerative medicine. Finally, the development of a multimaterial, multiscale 3D printing approach will expedite the synergistic integration of active properties and functionalities of distinct classes of materials. We envision that future developments of this approach would fuse various electronic components with biological construct and/or medical devices to provide better diagnostic tools and treatment strategies to ultimately address unmet clinical needs.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

3D printing, additive manufacturing, bioelectronics, biomanufacturing, biomedical devices

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