How can 3D printing be a powerful tool in nanomedicine?

Wei Zhu¹, Thomas J Webster² & Lijie Grace Zhang^{*,1,3,4}

¹Department of Mechanical & Aerospace Engineering, The George Washington University, Washington, DC 20052, USA

²Department of Chemical Engineering, Northeastern University, Boston, MA 02115, USA

³Department of Biomedical Engineering, The George Washington University, Washington, DC 20052, USA

⁴Department of Medicine, The George Washington University, Washington, DC 20052, USA

* Author for correspondence: Tel.: +1 202 994 2479; Fax: +1 202 994 0238; lgzhang@gwu.edu

“The nanoscale structure of 3D printed objects confers the unique desired medical effects, such as the control of drug release with optimal temporal and spatial distribution, the simulation of the native 3D environment for improving cell functions for tissue engineering applications, as well as the fabrication of small size nanodevices for diagnostics.”

First draft submitted: 8 December 2017; Accepted for publication: 8 December 2017; Published online: 17 January 2018

Keywords: 3D printing • drug delivery • nanodevice • nanomaterial • nanomedicine • tissue engineering

3D printing refers to engineering a 3D object by using layer-by-layer additive manufacturing strategies. The origin of 3D printing can be traced back to the emergence of stereolithography (SLA) in the 1980s [1], which utilizes UV light to scan and cross-link photosensitive liquid in designed patterns. Following the fruition of SLA, many types of 3D printing techniques, including selective laser sintering, inkjet printing and fused deposition modeling, have been developed in the last few decades. 3D printed objects beginning from 3D models can assume almost any conformation or architecture. This inherent fluidity in 3D design has revolutionized the scopes of many areas of research and engineering. One such area where 3D printing technology boasts notable advantages is for biomedical applications. This is due to its (3D printing) ability to fabricate customized patient-specific devices and implants [2]. In regard to the use of 3D printing in nanomedicine, it involves the introduction of nanotechnology to 3D printing for medical diagnostics and therapeutics. This can be either embedding nanostructured materials into 3D printed objects or directly printing 3D objects at nanoscale resolution. The nanoscale structure of 3D printed objects confers the unique desired medical effects, such as the control of drug release with optimal temporal and spatial distribution, the simulation of the native 3D environment for improving cell functions for tissue engineering applications, as well as the fabrication of small size nanodevices for diagnostics.

3D printing technique at nanoscale resolution

Classic 3D printing techniques, such as SLA, selective laser sintering, inkjet printing and fused deposition modeling, barely produce objects with resolution lower than a few microns. Although some lithography-based techniques can achieve high resolution, they are limited to produce high-aspect ratio 2D structures instead of complex 3D architecture. Currently, one intriguing 3D printing technology that can produce objects at nanoscale resolution is two-photon polymerization (TPP) based 3D printing. TPP-based 3D printing technique utilizes a near-infrared femtosecond laser to solidify photoresist for the fabrication of ultraprecise 3D nanostructures. The resolution relates to the laser power, exposure time and is largely determined by the efficiency of TPP initiators [3]. Even though TPP-based 3D printing has been employed in many fields due to its high spatial resolution, the time-consuming fabrication process and lack of water soluble initiators are a hindrance to its application in broader biomedicine.

3D printing nanocomposite for medical applications

Direct 3D printing at nanoscale resolutions is limited by the development of advanced 3D printing methodologies, and as such, a more comprehensive strategy is to directly add nanomaterials into printable inks by which to fabricate 3D nanocomposites. Supplementing host matrices with nanomaterials, such as carbon nanotubes, graphene,

quantum dots and other nanoparticles, enables the printed nanocomposites to hold both properties of bulk matrices and nanomaterials simultaneously. Simply put, the addition of nanomaterials can improve mechanical properties, alter thermal and electrical conductivity, as well as many other biological properties. In order to successfully 3D print nanomaterials, the ink should display good printability, high-resolution potential, as well as ease of processing and maintenance. With this in regard, the properties like stability, viscosity and wettability should be adjusted to achieve best printing performance and reproducibility. The major challenge, which should be overcome while printing nanomaterials, is the ease of aggregation and precipitation of nanomaterials when they are in the printable inks. Therefore, stabilization procedures to evenly disperse nanomaterials, such as addition of stabilizing agents, are usually required for printing nanomaterials.

3D printing nanostructured scaffold for tissue engineering

Natural tissues or organs reside within environmental surroundings with nanostructured extracellular matrices (ECM), making the nanomaterial a unique tool to manipulate artificial scaffolds for successful tissue regeneration [4]. By integrating nanomaterials within 3D printed constructs, it is feasible to simultaneously assert control over the scaffold's shape and manipulate part dimensions, such as the creation of nanostructured surfaces. The incorporation of nanomaterials could improve cell function and facilitate new tissue formation by altering the biological, mechanical, thermal and electrical properties of scaffolds [5]. When the 3D printed nanocomposite scaffolds are used *in vivo*, the customized shape fits the requirement of specific patients, while nanomaterials modulate the cell fate to enhance tissue regeneration. Most nanomaterials modulate cell growth and/or differentiation by providing an appropriate nano-biointerface and recapitulating the function of natural ECM [6,7]. Specifically, the nano-biointerface inside 3D printed nanocomposites influences the interactions between cells and the ECM. These interactions further dictate cell adhesion, proliferation and differentiation, and determine tissue formation. In addition to repairing injured tissues, 3D printed nanostructure scaffolds could be used as *in vitro* tissue/organ models for the study of disease progression and drug discovery [8]. The *in vitro* engineered 3D models possess the cells and nanostructured ECM, in combination with other biological components, making it possible to achieve a biologically relevant environment. This engineered *in vitro* model closely mimics the microenvironment of the native *in vivo* system, which can help to ease the need for animal models in research.

3D printing for pharmaceuticals & drug delivery in nanomedicine

Compared with conventional solid dosage forms which carry limited discrete dosage, 3D printing allows for the manufacture of nondiscrete personalized dosage forms for individual patients. The benefit of 3D printed dosage forms is that it can be customized per gender and age to meet specific administration requirements. Personalized medicine has been a long-pursued goal in therapeutics, which is particularly significant for pediatric and geriatric patients. This is due to the fact that the physiological and metabolic functions of children change rapidly, while elders might display various co-morbidities, as well as changes to renal clearance and within the GI tract [9]. In addition to the customized dosage forms, the 3D printing of nanosuspensions composing of drug nanoparticles has been encouraging to overcome the problem relating to the dissolution of poorly soluble drugs [10]. Approximately 40% of new drugs identified through screening programs have poor solubility in water, resulting in low oral bioavailability and fluctuation in absorption [11,12]. Various methodologies to account for the depreciated bioavailability and absorption of novel drug compounds have been explored, such as the dissolution of compounds in aqueous mixtures, solubilization using surfactants, as well as the formation of novel drug complexes [11]. However, the results are usually less than ideal. Drug nanoparticles, which are pure solid drug compounds of small size, have been suggested to be a successful delivery strategy to improve drug bioavailability and increase drug exposure for oral and parenteral dosage forms. Therefore, the integration of drug nanoparticles within the 3D printing process will likely show notable promise in not only the development of personalized dosage administration, but also facilitate the delivery of insoluble drugs.

3D printing nanodevice for diagnostics

Since many nanomaterials such as carbon nanotube, graphene and metallic nanoparticles have a unique conductive feature, they could be utilized to print electronics for the development of novel nanodevices for use in diagnostics. In this context, one popular area of research is the development of electrochemical sensors for monitoring cell or tissue vitality. These sensors have been extended for use from research areas to clinical applications including oncology, neurobiology and pharmacology, which enable the real-time monitoring of living cells. However, the

current most commonly used three integrated electrode platform (reference, working and auxiliary electrodes on the same substrate) requires tedious processing in which cells are detached and re-attached onto the electrode surface, which leads to reduced cell response and lowered signal to noise ratios. With the assistance of 3D printing, an advanced 3D sensing system could be obtained. This system would possibly have the sensing electrodes and the electrical contacts positioned vertically on opposite sides of the same chip to permit the sensor to intimately contact cells or tissues under test [13]. The sensor design could also be tailored according to specific tissues or organs with tunable sizes and shapes. Importantly, by introducing 3D printing with nanoscale resolution, the sensing system would be able to be made in millimeter or micron scale, avoiding the issues associated with large systems such as the diffusion limitation.

Challenges & future perspective

Whereas it is evident that 3D printing offers great potential for applications in nanomedicine, there remain several challenges to overcome before it becomes a viable, mainstream technology. To achieve the nanoscale printing resolution, advanced 3D printing methodologies and facilities need to be developed. Meanwhile, researchers need to engage in the development of more products that could be applied in nanomedicine by means of extant 3D nanoprinting techniques. This also requires allotting more effort to seeking novel 3D printable biomaterials that possess both excellent printability and biocompatibility for medical applications. For the printing of nanocomposites, stabilization processes should be optimized to avoid the formation of large nanomaterial aggregation and precipitation. In addition, postprinting processing could also be introduced to functionalize the 3D printed objects.

Financial & competing interests disclosure

This work was supported by NIH Director's New Innovator Award 1DP2EB020549-01 and NSF BME program grant # 1510561. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

- 1 Hull CW. US4575330 (1986).
- 2 Cui H, Nowicki M, Fisher JP, Zhang LG. 3D bioprinting for organ regeneration. *Adv. Healthc. Mater.* 6, 1601118 (2017).
- 3 Xing J-F, Zheng M-L, Duan X-M. Two-photon polymerization microfabrication of hydrogels: an advanced 3D printing technology for tissue engineering and drug delivery. *Chem. Soc. Rev.* 44, 5031–5039 (2015).
- 4 Zhang L, Webster TJ. Nanotechnology and nanomaterials: promises for improved tissue regeneration. *Nano Today* 4, 66–80 (2009).
- 5 Zhu W, O'Brien C, O'Brien JR, Zhang LG. 3D nano/microfabrication techniques and nanobiomaterials for neural tissue regeneration. *Nanomedicine* 9, 859–875 (2014).
- 6 Nel AE, Mädler L, Velegol D *et al.* Understanding biophysicochemical interactions at the nano–bio interface. *Nat. Mater.* 8, 543 (2009).
- 7 O'Brien CM, Holmes B, Faucett S, Zhang LG. Three-dimensional printing of nanomaterial scaffolds for complex tissue regeneration. *Tissue Eng. B Rev.* 21, 103–114 (2014).
- 8 Zhu W, Holmes B, Glazer RI, Zhang LG. 3D printed nanocomposite matrix for the study of breast cancer bone metastasis. *Nanomedicine* 12, 69–79 (2016).
- 9 Florence AT, Lee VHL. Personalised medicines: more tailored drugs, more tailored delivery. *Int. J. Pharm.* 415, 29–33 (2011).
- 10 Cheow WS, Kiew TY, Hadinoto K. Combining inkjet printing and amorphous nanonization to prepare personalized dosage forms of poorly-soluble drugs. *Eur. J. Pharm. Biopharm.* 96, 314–321 (2015).
- 11 Pardeike J, Strohmeier DM, Schrödl N *et al.* Nanosuspensions as advanced printing ink for accurate dosing of poorly soluble drugs in personalized medicines. *Int. J. Pharm.* 420, 93–100 (2011).
- 12 Merisko-Liversidge EM, Liversidge GG. Drug nanoparticles: formulating poorly water-soluble compounds. *Toxicol. Pathol.* 36, 43–48 (2008).
- 13 Ragonis H, Schreiber D, Inberg A *et al.* Disposable electrochemical sensor prepared using 3D printing for cell and tissue diagnostics. *Sensors Actuators B Chem.* 216, 434–442 (2015).