3D Bioprinting – Printing for Life
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Executive Summary
OneBeacon first covered the topic of 3D printing in a previous whitepaper published in February 2014. Since that time, technological advancements now allow us to manufacture with an increasing number of materials using a variety of different technologies. Furthermore, 3D printers continue to drop in price, operate more quickly and produce more complicated and larger structures. However, the core technology remains unchanged—additive manufacturing or depositing materials in layers to form a finished product. In this paper, we explore the emerging ability to 3D print using biological materials and thereby build biological components and subsystems.

The 3D bioprinting market was roughly $411M in 2016 and expected to rise to $1.33B by 2021.¹ Other firms estimate the global market to be $1.82B by 2022² or $1.8B by 2027.³ This increase will be fueled primarily by growth in institutional research and development (R&D), applications in the drug discovery process, toxicity testing, consumer product testing, tissue engineering and ultimately organ and tissue regeneration for transplantation (regenerative medicine). Key areas will be in medical, dental, biosensors, consumer product/personal product testing, bioinks and bioprinting of food/animal products.⁴ A variety of new manufacturing techniques has emerged and continues to evolve, which will enable such applications.

What is 3D Bioprinting?
In 2003, Thomas Boland, a bioengineering professor at Clemson University in South Carolina, filed a patent on using a custom inkjet printer capable of printing human cells using an ink where the cells were in a gel mixture.⁵ Bioprinting is defined as the “deposition of living cells in a spatially controlled manner in absence of any pre-existing scaffold and in more than a single layer,”⁶ or simply, additive manufacturing/deposition using bioinks.

Bioinks include cells and biocompatible biomaterials consisting of natural and artificial polymers such as gelatin, collagen, alginites (made from brown algae), fibrin, chitson, hyaluronic acid,⁷ nano cellulose, gelatin methacrylate and polyethylene glycol (PEG).

Bioinks serve one or more of these three basic cellular functions – matrix, sacrificial and/or support.⁸

- **Matrix** – The bioink enables developing the extracellular matrix (ECM) or scaffolding for pending cell growth. Once deposited, it solidifies with curing reagents or processes.
- **Sacrificial** – The bioink material provides temporary support and sacrificially removed once the cellular structure or tissue has developed around it. An example protocol is vasculature (e.g. veins) development. For example, various types of gelatin materials that dissolve at a certain temperature.
- **Support** – Bioink material supports the mechanical properties of the construct.

¹ www.statista.com
² www.forbes.com
³ www.marketsandmarkets.com
⁴ www.3dpbusiness.com
⁵ www.clemson.edu
⁶ www.ismar.org
⁷ www.jci.org
⁸ www.ismar.org

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A variety of novel manufacturing technologies are currently available or being developed. Each of these has its own pros and cons, and use is dependent on the material printed and the application. Examples of these technologies include:

- **Inkjet** – This is a droplet-based printer that operates very much like a standard inkjet printer but uses a specialized bioink to deliver small droplets to specified locations on the substrate. There are primarily two types of inkjets – thermal and piezoelectric/electrostatic.\(^9\)
  - In thermal, bioink is forced out of a jet through an ultra-short but rapid heating (up to 300°C) process. Due to the limited two-microsecond exposure, the cells within the bioink are minimally damaged. The temporarily heated ink is deposited or layered onto a specified area on the substrate.
  - In piezoelectric/electrostatic, a vibrating ceramic element forms an acoustic wave that disperses the bioink as a jet onto the substrate.

Although the inkjet process sounds simplistic, it is quite complex as the key concern is to ensure that the cellular material is not damaged during the printing process. The issue with inks is the shear stress that is applied to the cellular material contained in the bioink as it is propelled through the nozzle jet. Although cell viability is greater than 85%\(^1\), it is lower than other technologies. However, it has a relatively faster printing speed than other technologies. Another issue is that the nozzle jets are prone to clogging over time, resulting in additional maintenance and downtime. Overall, it does have advantages in its simplicity, agility, versatility and greater control over the deposition pattern.\(^1\)

- **Orifice Free** - This is a nozzle-free technology that is unaffected by the clogging problems found in inkjet systems. As there is practically no shear stress on the cellular material, there is greater cell viability.
  - **Laser-Induced Forward Transfer (LIFT)** – A thin film of bioink is coated onto the rear side of a transparent support substrate (a film). Next, a pulsed laser beam is focused onto this film, which heats the film to propel the bioink onto the underlying substrate in a specified pattern. Cell viability is greater than 95%.\(^12\)
  - **Surface Acoustic Wave (SAW)** – A piezoelectric substrate generates an acoustic wave that essentially results in the ejection of bioink droplets from the carrier onto the substrate. It offers a faster fabrication speed and since cells are unexposed to nozzle shear stress, high pressure or heat, cell viability is high at 89.8%.\(^13\)

- **Syringe/Extrusion** – Bioink in syringes is dispensed either mechanically or pneumatically onto the substrate. These printers extrude bioink as filaments rather than droplets, and are used for certain types of bioprinting. Fabrication speed is much slower than inkjet and cell viability is within the 80-90% range.\(^14\)

- **Magnetic Levitation** – In this method, cells are tagged with magnetic nanoparticles, which make the cells magnetic. External magnetic fields are applied to create specific patterns and these can be layered to form 3D structures. The magnetic field is used as an invisible scaffold to rapidly aggregate cells to form the extracellular matrix. In this method, there is no need for an artificial substrate. It is an effective tool in creating vascular smooth muscle cells and other tissues, which can then be used for screening cardiovascular drug toxicity.

- **Micro-valve** – This is a variant of a droplet-based printer and uses a solenoid controlled plunger valve that allows bioink to be ejected onto a substrate. Cell viability is greater than 90% as there is no mechanical stress on the cells during ejection.\(^15\)

- **Emerging Methods** – There is ongoing improvement and development of new technologies as well as the adaptation of methods from other manufacturing processes for bioprinting. Some of these include electrospinning and microscale continuous optical bioprinting.

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- **Electrospinning** - This is an existing manufacturing technology where a polymer in a syringe pushes through a metallic needle or spinneret. An electrical voltage is applied to the tip and collector plate, which results in the formation of nanofibers on the collector plate. Bioinks are now being used in place of polymer with this technology to layer cellular fibers onto a substrate.\(^{16}\)

- **Microscale Continuous Optical Bioprinting (uCOB)** – This new technique uses UV light to rapidly cure a bioprinted hydrogel (gel with a water liquid component) to form complex tissue with a network of vasculature (blood vessels to transport blood, nutrients and waste).\(^{17,18}\) Researchers recently used uCOB to culture a vasculature network in vivo (outside of the body) and then graft this onto the skin wounds of mice. After two weeks, researchers observed that the network had grown and merged with the host’s blood vessel network. Currently this remains a research project, as it is not yet fully functional.\(^{19}\)

### Bioprinter and Bioink Manufacturers

Existing and new firms worldwide are venturing into the bioprinting space, given its high growth and market potential. Firms either are developing the bioprinters, the bioink materials, or providing services such as developing bioprinted tissue for research and industrial applications. The following offers a brief overview on some of the major firms in this industry:

Bioprinter manufacturing firms include Envisiontec, Gesim, Biobots, Cellink, RegenHU, Ourobotics, Dilab, Cyfuse, Organovo,\(^{20}\) Hewlett Packard (HP) and others. Universities and research institutions worldwide are also modifying traditional inkjet printers from firms like HP and Canon by for use in 3D bioprinting. Lastly, universities are developing R&D models of such products primarily for internal research, but may also market these to other research institutions.

Firms manufacture bioinks as proprietary or non-proprietary formulations. Proprietary formulations are used for either owned bioprinter equipment or are custom-developed for others. Stock on non-proprietary bioinks can be used by bioprinters from various manufacturers. Some of the bioink manufacturers include Biokon Solutions, CELLINK, RegenHU, Biobot\(^{21}\) and others.

### Medical Applications

The main application for bioprinting is the medical field. The importance of this technology in medical advancements cannot be overstated. There is significant research underway with transplantation success in animal models.

- 3D bioprinting has been used for the generation and transplantation (in animals) of several tissues, including multilayered skin, bone, vascular grafts, tracheal splints, heart tissue and cartilaginous structures.\(^{22}\)
- Recently, "Wake Forest staffers have implanted bioprinted skin, ears, bone and muscle on laboratory animals, where they grew successfully into the surrounding tissue."\(^{23}\)
- Anticipated significant advancements in 3D bioprinting include the generation and development of tissue for bone, heart valves, tissue for ear-reconstruction, and bacterial cultures for advanced studies in virology.\(^{24}\)
- In 2016, Czech scientists developed a model of a human lung used to simulate asthma and paving the way for new treatments for chronic lung diseases.\(^{25}\)
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- In late 2016, Organovo started selling bioprinted kidney and liver tissue for use by pharmaceutical companies to test for molecular and drug toxicity during early stage and pre-clinical trial drug development.26
- In October 2016, they introduced a 3D bioprinted human liver as a therapeutic tissue in preclinical development. It will take three-to-five years for them to develop an IND (investigational new drug) for the FDA and numerous years thereafter before its approval for human use.27
- Bioprinting technologies will soon enhance the self-repair capabilities of tissues in the craniofacial area.28

Challenges 3D bioprinters deposit rows or filaments of living cells in layers onto a substrate to form tissue, muscles and eventually organs. The major challenge in the development of complex tissue or organs is the vasculature (blood vessels) needed to transport oxygen, nutrients and waste to and from the printed substitute product. This process is quite complicated and requires significantly more research and study before transplant-worthy organs can be mass developed.

Additionally, regulatory hurdles worldwide require investigation, review and approving the product before its use for human transplants. Within the U.S., the FDA would ideally regulate such products as a biologic, but depending on the application, it could be additionally construed as a drug or medical device, prompting different regulatory thresholds. Significant clinical trial data will likely be required especially since this is a brand new technology where the efficacy and safety of the device or biologic is unknown. There currently is no specific standard on 3D bioprinted biologics. The FDA released draft guidance on Additive Manufactured Devices29 30 (3D printed) in May 2016 but it does not specifically address bioprinted products.

The FDA did approve a 3D printed biodegradable airway splint made of PCL (polycaprolactone – a biodegradable polyester), for use in an infant under the emergency-use exemption, along with written consent of the patient’s parents.31 This was a one-off approval, however, and similar one-time signoffs for emergency-use are likely. However, for general clinical use, the FDA will require significant clinical trial data before approval. Until then, much of the hype surrounding 3D bioprinted materials will be primarily for research or trials with animal models.

Beyond regulatory hurdles, there could also be potential concerns from religious and other ethical groups arguing that bioprinting organs or using biomaterials from other animals (e.g. collagen scaffolding from pig hearts) in this process is unnatural. Such groups could exert pressure on governmental bodies and impede—or even ban—the bioprinting of such materials. An example is the case of the U.S. ban on the use of fetal stem cells. These arguments could negatively affect this field and greatly undermine the technology’s benefits.

Insurance Concerns Insurability of this technology remains a challenge due to safety, use of newer materials with unknown lifespans, and potential long-term quality and efficacy issues. For now, the leading exposure is likely to be from R&D use, drug/molecule toxicity testing applications and potential early stage clinical trials. There will be an increase in exposure once transplantable, bioprinted tissues and organs are approved and commercially available in the market. However, it will take time to fully understand the exposures associated with such products.

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Due to projected market growth in this industry, it is likely we will continue to see a plethora of startups and investments, as well as existing firms venturing into this field. Opportunities for insurance coverage, for both new firms as well as new exposures, are already present and will continue to emerge. Remaining abreast of 3D printing technology will be incumbent on those servicing the life sciences industry and will present an exciting opportunity to appreciate the many benefits afforded by this process.

Conclusion

Imagine a world where sick or dying patients are saved by generating organs, tissues and muscles through 3D bioprinting. There have been major strides with this technology but we are not there yet. It may take up to ten years before FDA approved products are commercially available. Even then, these biologic products may be limited to simple organs such as skin and bladders. Complex organs such as livers, kidneys and hearts may take even more years before being commercially approved for the market.

For now, this technology can aid in various areas that will improve our lives. This can range from toxicity testing in drug development to ongoing R&D in existing and completely new areas. There are many unknowns regarding the success of this technology but the benefits should outweigh the concerns.

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References


4 Ibid 2


6 Ibid 3


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10 ibid 9, page 3
12 ibid 9, page 3
13 ibid 9, page 3
14 ibid 9, page 3
15 ibid 11, page 23
20 ibid 9, page 5
21 ibid 9, page 6
23 ibid 5
31 ibid 9, page 37

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