Medtech Insight
Pharma intelligence

Market Intel: Cornea, Bio-Drugs, Artificial Hips On Track For 3D Printing

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ANALYSIS

Executive Summary
Although certainly not a given, many researchers and companies are pursing the eventual goal of bioprinting human organs, starting with the three-dimensional printing of a structure that has cellular function. If organ function via bioprinting becomes a reality for the skin, bone, lung, liver, eye and/or kidney, among other potential organs, the market opportunity could be in the billions. But challenges, including cost and ethics, stand in the way of this milestone in regenerative medicine.

Fact or fantasy? The bioprinting of a human organ.

For many, it is the holy grail of health care, beginning with establishing cellular function, which is already a reality. Cellular function would be followed by tissue function and hopefully, eventually organ function.

According to Aakanksha Kashyap, team lead of medical devices and health care information technology (IT) research at Grand View Research, Inc., the pursuit of bioprinting organs globally is expected to witness significant growth and attention from health-care researchers over the forecast period from 2017 to 2024. “This is due to rising incidences of chronic illnesses, leading to organ and tissue transplants, coupled with an increasing human life span and a limited number of organ donors,” Kashyap told *Medtech Insight*.

Advancements in technology and incorporating IT within the health care industry, along with a rising geriatric population and improved R&D efforts, are also catalysts, Kashyap said. Kashyap noted that several research institutes and

universities analyze the prospects of bioprinted implants, organs and tissue reconstructions.

Among them, she said, is Heriot-Watt University of Scotland, which has created a bioprinter capable of printing pluripotent stem cell cultures that may be applied for drug testing. The increasing prevalence of cancer is one of the key factors behind the growth in this market.

Market Estimates

Grand View Research estimates that the global bioprinting market for the pursuit of organs was worth $800m in 2017, and will grow at a CAGR of nearly 20% by 2024.

Cellink's CEO Erik Gatenholm estimated the current market value between $300m and $400m, reaching about $1.8bn by 2021, citing different market reports.

Precise Bio's **CEO Aryeh Batt** believes the potential US market for the company's products could exceed $10bn.

"Bioprinting of biomimetic microstructures can be used for cancer cell migration studies," Kashyap said. Most of the market players have formed alliances with research institutes and universities that focus on grafting and organ regeneration technologies.

"Though organ bioprinting is a far-fetched goal, there has been a considerable and commendable progress in the field of bioprinting that could be used as transplantable tissues in regenerative medicine," Kashyap said.

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The New Prescription: Bio-Drugs

"Medical pills are the latest development in the bioprinting organ market and are expected to witness lucrative growth over the forecast period," Saiprasad Mahadev Bhise, a research analyst at Grand View Research, told *Medtech Insight*. "This growth may be attributed to the increasing need of medicines and the advantage of fast and cost- efficient production of bio-drugs using bioprinting" (Also see "Market Intel: Nanorobots, Digital Tracking, Dose Printing: Innovative Drug

Delivery Systems Will Make Precise Drug Dosing A Reality" - Medtech Insight, 18 Dec, 2017.)

Bhise said 3D printing combines the efficiencies of digital design to production stage with a combination of oral scanning, computer-aided designing and 3D technology.

“Dental labs now have the capacity to produce crowns, stone models and a range of orthopedic appliances,” he said.

For instance, Stratasys Ltd., a manufacturer of 3D printers and 3D production systems, has developed dental printers and laboratories, “which offer maximum hygiene,” Bhise noted.

Biomaterial Innovation

In short, bioprinters can generate skin tissue, heart tissue and blood vessels and other indications.

For example, Swansea University in the United Kingdom has developed advanced technology for printing of soft tissues and artificial bones, which are used in reconstructive surgeries.

Cellink LLC (based in the US, Sweden and Japan) is the first "bioink" company and the leading bioprinter provider worldwide that focuses on the development and commercialization of bioprinting technologies that allow researchers to 3D-print human tissues and organs for developing pharmaceutical and cosmetic treatments, according to Cellink's CEO and cofounder Erik Gatenholm.

“Cellink’s innovative and patent-pending bioprinting technology is a biomaterial innovation that enables human cells to grow and thrive such as they would in the natural human body environment,” Gatenholm told *Medtech Insight*. Today, the company’s disruptive technology platform is being used to print tissues like cartilage, skin, liver, pancreas, and even fully functional cancer tumors that can then be used to develop new cancer treatments.

Founded in January 2016, Cellink has sold products in more than 50 countries and installed its systems at hundreds of prestigious labs, including at Harvard, Massachusetts Institute of Technology (MIT), Princeton and US FDA.

The technology uses a 3D printer that has been specifically designed to print soft materials as opposed to standard 3D printers that print hard materials such as plastics.

“The soft material is what we refer to as 'bioink', a biocompatible material that can provide human cells with an ideal environment where they thrive and multiply,” Gatenholm explained. “The entire technology platform is developed so that it provides the human cells with all the right signals to do what they are supposed to do inside the body. This means that we can construct human tissues, containing a wide range of human cells.”

Gatenholm said leading research institutes use Cellink's technology to develop new medical products and technologies and pharmaceutical and cosmetic firms use it to print skin, liver, kidney and other tissues. For instance, the technology can be used to print patient-specific cancer tumors that replicate the patient’s own tumor. The printed tumors can then be used for testing of new drugs to determine their efficacy.

"In the future, the idea is to use this technology to print implantable tissues,” Gatenholm said. “The whole industry is working toward developing systems that can reduce the organ donor market and reduce the waiting time for new organs and tissues.”

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The Future Of Lung Transplants

Earlier this month, Israeli-based CollPlant Holdings Ltd. said it signed an exclusive license, development and commercialization agreement with Silver Spring, Maryland-based United Therapeutics Corp. for bioprinted lung transplants.

“We have developed an rhcollagen [recombinant human collagen-based] bioink, which is used in the 3D-bioprinting process of lung transplants manufacturing,” said CollPlant's CEO Yehiel Tal. “We are collaborating with United Therapeutics

to optimize the BioInk formulations in order to achieve optimal physical and biological properties needed for lung scaffold printing."

The lung blueprint is loaded on the bioprinter, which prints the lung, layer after layer, with the *rhCollagen BioInk*. Ultraviolet (UV) light being used to photo-cure or crosslink each layer after its deposition. The printed construct is then moved from the printer to a bioreactor where the relevant cells are applied to the construct using perfusion technique. The final organ will also be developed in the bioreactor.

"CollPlant's rhCollagen is biocompatible and it supports viability of different cell types, which is important for building a new organ," Tal told *Medtech Insight*. The material is plant-derived, so it does not elicit immune response. In addition, the lung manufacturing technology will enable the use of cells from the patient, thus reducing the risk of immune response or rejection of the implant.

"In the US alone, there are only 30,000 life-saving transplants per year, whereas 900,000 people are dying every year from organ impairment," Tal said. "We estimate that the number of patients in the US that might benefit from lung transplant is above 100,000 per annum. Overall, we believe our technology represents a multi-billion market potential."

A New Vision

In the ophthalmic space, Precise Bio Inc., which has offices in Winston-Salem, North Carolina and Shoham, Israel, is the first company to transplant a 3D-printed cornea graft in animals (rabbit), said the company's CEO and Cofounder Aryeh Batt.

“We are also pursuing several other programs using 3D-printed tissues, including other ocular implants," Batt told *Medtech Insight*.

Precise Bio believes that its proprietary 3D biofabrication technology (pictured to the right) is particularly well-suited for ophthalmology, in part, because the eye is structured as discrete layers of different cells that are particularly amenable to 3D printing.

“There are a limited number of cell types involved in these layers, which have been extremely well characterized,” Batt said. Critically, precise deposition of specific cell types in specific spatial relationships is essential for normal eye function. He feels that the company's technology has a significant advantage compared to ink jet or extrusion and other bioprinting technologies. Furthermore, ocular transplant procedures are commonly used to treat a variety of ophthalmic conditions, “which obviates the need to develop new surgical techniques for implantation of biofabricated organs,” Batt said.

“We intend to become the leader in the 3D printing of ocular organs," he added. Precise Bio employs a broad scope of technologies, including proprietary biomaterials, cell technology, bioengineering and 4D-bioprinting, which together combine a platform for biofabricating human tissues and organs.

“Human tissue is comprised of cells and other biological materials, which are the building blocks for biofabrication,” Batt said. “The cells are obtained from the patient or a donor, based on the specific tissue requirements.”

The cells are then combined with the bioink, which is a combination of materials that structure the tissue and enable fabrication. Afterward, the bioink is streamed in the Precise 3D bioprinter to be deposited, cell by cell, droplet by droplet, to create an anatomical structure that mimics what is found in nature. A curing process is performed after each layer is printed, followed by a maturing phase in which the tissue develops the integrity needed for normal tissue function. For patients with corneal diseases, there is a huge shortage of donor corneas.

Worldwide, it is estimated that over 12 million people are on waiting lists for donor corneas, according to an article in the journal *JAMA Opthalmology*.

“The ability to biofabricate corneas would enable these patients to receive immediate care rather than waiting for a donor cornea to become available,” Batt said. “In addition, printing can provide a significant advantage in quality control and improvement of certain graft properties, as well as enable personalization of the tissue to meet each patient’s unique needs.”

Precise Bio expects to begin a clinical study of its 3D-printed cornea graft as early as the end of 2019. Besides the corneal market, the company is exploring other potential indications in the ophthalmic space. Combined, the technology could benefit hundreds of millions of patients, Batt said.

“That number could be even larger when we include potential applications of our technology in cardiac diseases and other types of tissue within the body," he said. (Also see "SCAI2018: New Study Shows 3D Printing Helps Prevent Leaks In Heart-Valve Patients" - Medtech Insight, 26 Apr, 2018.) Overall, Batt believes the potential U.S. market for the company’s products could exceed $10bn.

‘We believe that highly accurate 3D bioprinting technology is a key enabling technology that has tremendous potential to solve many of the challenges of lab-grown organs for clinical use,” Batt said. “Clearly, though, some of these challenges are unrelated to the printing itself or require the development of complementary technologies, several of which Precise Bio is pursuing in collaboration with other world-class organizations.”

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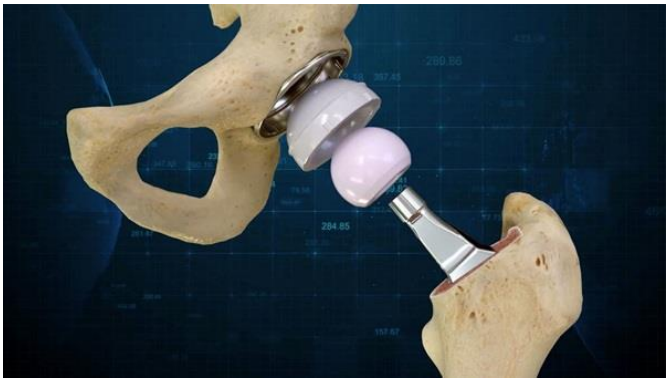
Personalized Joints

Another forerunner to bioprinted organs is the *Conformis Hip System* from Billerica, Maryland-based ConforMIS Inc.: the first 3D-designed primary total hip replacement system (pictured below), which uses industry-standard materials, some consisting of cobalt and chromium alloys.

Since July, orthopedic surgeon Gregory Martin, has implanted 10 cases. "Once a patient is indicated as a candidate for hip replacement based on history, physical examination and X-rays, a CT scan is ordered," said Martin, founder of Personalized Orthopedics of the Palm Beaches in Boynton Beach, Florida (Also see "Market Intel: Innovation Drives Growth, Draws Younger Patients In Joint Replacement Implants Market" - Medtech Insight, 21 Sep, 2018.) "A surgical plan is then produced based on that information using proprietary software called the *iView*."



The Iview provides anatomical views, with and without the Conformis implants,

"so we see how the implants interact with the patient's anatomy," Martin told *Medtech Insight*. "The design process provides the 'best fit' implant components with certain patient specific geometries designed into the implants."

The iView also offers advanced anatomical information that cannot be obtained from traditional 2Dtemplating.

"Surgeons are able to request changes to the plan, based on their preferences," Martin said. "The final design is then presented for approval. 3D-printed jigs are also provided to facilitate proper implantation of the device."

Most artificial hips are available in only a certain number of sizes, lengths and angles.

“The Conformis system leaves no patient behind,” Martin said. “By providing the surgeon with a precise plan, instrumentation and customized implants to recreate the patient’s individual anatomy, the system has the potential to eliminate leg length discrepancies and implant malposition. Both of these are common sources of dissatisfaction after hip replacement.”

The projected global market for primary total hip replacement in 2019 is $7.1bn, according to market research.

“3D-printing of medical devices and interventions is the future,” Martin said. As one of his patients told him, “I wouldn’t buy a pair of shoes that is one size too big or too small, so why would I want a hip or knee implanted that is not the correct size? It just makes sense,” Martin said.

Reprint For Treating Liver Disease

Over the past 11 years, San Diego-California-based Organovo Holdings, Inc. has developed a set of technologies that allows for bioprinting of tissue, beginning with living human cells as the building blocks. Liver has become the company’s primary focus over the past two years.

“We have a therapeutics program that is ramping up to take these bioprinted tissues and implant them into humans to treat a range of rare liver diseases,” Oragnovo's CEO Taylor Crouch told *Medtech Insight*.“We also have a drug discovery and partnering capability to use these same tissues in the laboratory to explore how drugs interact with human-like liver constructs in an *in vitro*environment.”

Organovo chose to focus on to liver, because of the feasibility of seeding an otherwise healthy liver with a healthy patch construct that can slowly regenerate.

In addition, all drugs pass through the liver in some manner. The company has created a bioprinter that is able to lay down different kinds of cells in various combinations into a dish, where living tissue can be formed and thrive outside of a living environment for up to 30 days. The liver can then be used for in vitro experimentation or for tissue to be implanted in animals, or ultimately humans for a longer-lasting effect.

“Our technology platform starts with the ability to isolate cells from donated organs,” Crouch explained. Then, after cryopreserving the cells, combine them when necessary in a configuration that closely resembles human tissue. “We are therefore able to manipulate these tissues outside of the body and ultimately implant them into the body to treat a range of rare liver diseases,” he said.

Organovo expects to bring its liver patch, comprised of living human cells that form a tissue, into human clinical trials by 2020. The company envisions laparoscopically implanting these patches onto the surface of the liver, culminating in a surface area of roughly a one-dollar bill.

"This should be of sufficient size to either replace missing function in these genetic diseases, which are caused by the absence of a fundamental enzyme, or to supplement the function of a failing liver,” Crouch said. The first clinical study

will target patients on liver transplant lists with end-stage liver disease to assess the safety of the patch.

“In our animal studies, we have already shown that the patch is effective for the rare liver disease alpha-1 antitrypsin deficiency (A1AT),” Crouch said. Crouch said today more than 6,000 liver transplants are performed every year in the US, discounting tens of thousands of patients with liver disease who do not receive a transplant.

“Limiting the market to just A1AT, for which there are about 100,000 patients currently diagnosed, we estimate the market opportunity to be over $1bn yearly,” he said. Going forward, the definition of an organ may change, based on the combination of science and technologies, Crouch said. "But replacing a full organ function using bioprinting is not out of the realm of possibility,” he said.

A Long Way To Humans

Frank Rybicki, professor and chair of the Department of Radiology at the University of Ottawa in Ontario, Canada, who is considered a world’s leading authority on medical modeling – the use of nonbiological material to improve patient quality of life – said there are several companies that are pursuing "the important intersection between bioprinting and genetic engineering."

Rybicki told *Medtech Insight* he's thrilled that bioprinting can generate cellular function and living tissue. Although he believes that the generation of tissue constructs and replacement organs remains five years out.

“While there is incredible potential, we must remain cautionary, as marketing and hype can show an organ such as a heart or kidney in a 3D-printing device ,” Rybicki said.

“Bioprinting is an essential part of medical research, but we should dispel the fantasy that the process is simple and that a live organ can exist on a simple printing platform.” Concerning bioprinting and bioengineering, there is solid, validating literature that supports the future, he noted. However, to make the leap from cellular to tissue, cells need to be organized and act like a tissue, which is challenging.

“The environment needs to be highly controlled,” he said. “The cells also need to work and function together while alive.”

Rybicki, who is editor-in-chief of the journal 3D Printing in Medicine, also noted that the peer-review literature is scare with articles addressing costs.

“Bioprinting is an expensive investment, with scientific and pecuniary obstacles for success,” he said. “One can imagine as well ethical risks related to printing organs and tissues, although in my opinion, the benefit of having shorter transplant lists and tissues available for people who need them will greatly outweigh the risk.”

AI Improves 3D Printing, Cost Remains High

As Adjunct Technology Furthermore, he points to artificial intelligence (AI) as an adjunct technology that will improve 3D printing in general, specifically focusing on image segmentation in medical image processing. “This will potentially save time, effort and render more accurate image quality,” Rybicki said.

Additionally, the FDA has been extremely receptive in adapting new technologies like bioprinting into clinical workflows (Also see "Podcast: US FDA's James Coburn Chats About 3D Printing" - Medtech Insight, 25 Sep, 2017.)

“What has emerged from boots on the ground is a strong partnership between scientists, clinicians, and regulatory bodies such as the FDA to bring technologies to market that are safe and efficacious,” he said.

Recently, the American Medical Association approved new Category III coding for 3D printing.

“The details of those codes will be released by the AMA in the near future,” he said.“However, personally, I believe it is too early to develop and present coding options for bioprinting, based on the fact that such billing codes are developed after clinical experience has permeated US health care, and the peer-review literature is stronger,” Rybicki says.

Health Canada also recently issued a new draft guideline on 3D printing (Also see "Canada Consults On Licensing Of 3D-Printed Device Implants" - Medtech Insight, 13 Nov, 2018.)

Rybicki predicts that skin will be the first organ to be successfully printed, although it may be five years before skin banks can depend on 3D printing. “Skin is almost two-dimensional,” he explained. “One dimension is very thin, which makes it amenable for bioprinting.” There is also a strong need for skin

banks, which are expensive to maintain. Skin grafting for burn and postoperative patients holds the most potential. “If organs could be printed, the market value would be in the billions for sure,” Rybicki noted. “But I would not want to rely on that bank account just yet.”