Advanced Manufacturing Technology (TechVision)

3D Printed Medical Implants and Organs
Improving lives through 3D printing technology

D718-TV
April 8, 2016
## Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Slide Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innovations in 3D Printing of Medical Implants and Organs</td>
<td>3</td>
</tr>
<tr>
<td>3D Bioprinted Vascularized Tissues, Harvard University, USA</td>
<td>4</td>
</tr>
<tr>
<td>3D Printed Ear, Cornell University, USA</td>
<td>5</td>
</tr>
<tr>
<td>3D Printed Prosthetic Ovary, Northwestern University, USA</td>
<td>6</td>
</tr>
<tr>
<td>3D Printed Liver Tissues, Organovo Holdings Inc., USA</td>
<td>7</td>
</tr>
<tr>
<td>Strategic Insights</td>
<td>8</td>
</tr>
<tr>
<td>Appendix</td>
<td>9</td>
</tr>
<tr>
<td>Key Patents</td>
<td>10</td>
</tr>
<tr>
<td>Industry Interactions</td>
<td>13</td>
</tr>
</tbody>
</table>
Innovations in 3D Printing of Medical Implants and Organs
A group of researchers at the Wyss Institute for Biologically Inspired Engineering at Harvard University has successfully demonstrated a method for three-dimensional (3D) printing vascularized tissues.

- This vascularized tissue was made by creating a custom designed multi-material 3D bioprinter.
- The bioprinter was equipped with four print heads mounted on a three-axis, motion controlled gantry. The gantry was designed for a build volume of 725 mm x 650 mm x 125 mm.
- The entire tissue was built on perfusion chips, which were printed in the beginning of the bioprinting process.

This novel multi-material 3D bioprinting method enables printing of thick human tissues (more than 1 cm thick). Perfusing these tissues in the human body and using this key innovation as a foundation for organ printing are some of the future plans of the university.

Innovation Attributes
- This vascularized tissue was made by creating a custom designed multi-material 3D bioprinter.
- The bioprinter was equipped with four print heads mounted on a three-axis, motion controlled gantry. The gantry was designed for a build volume of 725 mm x 650 mm x 125 mm.
- The entire tissue was built on perfusion chips, which were printed in the beginning of the bioprinting process.

Competing aspects
- This vascularized tissue was made by creating a custom designed multi-material 3D bioprinter.
- The perfusable chips are 3D printed using silicone ink, which is the substrate on which the tissue is printed.
- As soon as the substrate is ready, nozzles containing different ‘bio inks’ are sequentially coprinted to create a matrix of different cells to create vascular tissue structure.

Application Potential
- Drug screening
- Wound healing
- Stem-cell research
- Organ printing

Technology Convergence
- 3D bioprinting
- Bioinks
- Tissue printing

Wide-scale Adoption
The successful bioprinting of vascularized tissue is a unique feat. The research team is still finding new materials and inks for printing various kinds of tissues. Hence, adoption of this technology may extend beyond the near-term.
A group of physicians and bioengineers at Cornell University have 3D printed a human ear using synthetic materials that functions like a natural human ear.

- After setting, the collagen acts as a scaffold inside, upon which the cartilage cells would proliferate and grow to produce a ear structure that looks like the human ear.
- According to the researchers, the entire ear printing process, starting from mold designing to printing and setting of gel takes less than two days.
- The ear is then left in a medium consisting of nourishments for several days cartilage cells to culture.

This novel 3D printed ear is a key innovation in printing cartilage-based organs such as an ear. The same printing technology can be replicated in the near future to ‘print’ cartilaginous non-vascularized parts such as trachea, joints, spine, and nose.
A research team in Northwestern University in Illinois, USA, has successfully printed a functional bioprosthetic Ovary.

**Innovation Attributes**
- The feat of printing of an ovary was achieved by a research team led by Monica M. Laronda.
- The team used a 3D bioprinter to print a scaffolding that will hold and help in culture of hormone producing cells and oocytes (immature egg cells).
- The scaffolding was printed using biogels created utilizing collagen proteins obtained from animal cells.

**Tech Profile**

**Application potential**
- Ovary implants in humans with fertility issues.
- The new implants will also be used for implanting ovaries in ovarian cancer survivors and childhood cancer survivors.

**Competing aspects**
- After printing scaffolds, they were filled with ovarian follicles and hormone producing cells and left to culture.
- The 3D printed ovary was tested by implanting into a female mouse.
- The mouse was able to successfully ovulate and give birth to a litter of young mice.

**Technology Convergence**
- 3D bioprinting
- Bioinks
- Tissue printing
- Bio-engineering

**Wide-scale Adoption**

The novel method of 3D printing ovaries is a key innovation in fertility treatment. Intense clinical trials will be needed for commercializing this method.

**Future Plans**

The researchers, who have tested their 3D printed ovary technology in mice, are planning to apply it in humans, especially survivors of childhood cancer. They hope that their technology will become an important part of infertility treatments after commercialization of 3D printed ovaries.
3D Printed Liver Tissues
Organovo Holdings Inc., USA

**Innovation Attributes**
- Organovo owns a proprietary bioprinting platform for printing human tissues, the exVive™ platform.
- exVive3D™ Liver Model is a 3D bioprinted liver tissue that can remain fully functional for 40 days *in-vitro*.
- The liver models cannot be used for transplantation, but are designed for using *in-vitro* conditions.

**Market Opportunity**
- Evaluation of liver for drug exposure.
- Studying liver cell metabolism.
- Gene/protein expression profiling
- Histological tissue assessment

**Wide-scale Adoption**
Organovo’s 3D printed Liver model has been approval by the US Food and Drug Administration (FDA) and has been commercialized. Commercialization is expected to bring more customers from the field of medical and pharmaceutical research.

**Tech Profile**
Organovo is a US-based 3D bioprinting company that has successfully commercialized it’s 3D printed liver called ‘exVive3D™ Liver Model.’

**Competing aspects**
- exVive3D Liver Model tissue can be used for *in-vitro* testing of liver cells for drug reactions.
- The design of liver model is precise and has a reproducible architecture ensuring structural and functional stability for up to 40 days.

**Market Strategies**
- 3D human liver testing services.
- Supply of 3D printed human tissues for medical research and therapeutics.

**Company Profile**
Organovo is based in California, USA. The company has been involved in 3D bioprinting research since 2007 and subsequently developed it’s first 3D bioprinter, the “NovoGen MMX Bioprinter” In 2014, Organovo announced its first product, the 3D printed Liver, for research purposes.
**Strategic Insights**

### Need for Improved and Customized Implants

- 3D bioprinting is a transformational technology in the medical industry. 3D bioprinting has enabled the medical industry to approach the possibility of creating organs for the human body.
- 3D bioprinting has changed the landscape of implants. Advancements in material science have aided 3D bioprinting technology to print bones, cartilages, and other body parts with similar compositions as they appear in the body.
- 3D bioprinting technology’s ability to print parts in desired shapes, composition and structures has enabled production of implants that can be highly customized for a patient’s needs.

### Materials for 3D bioprinting

- Material science is the key driver behind the evolution of the 3D printing industry. As the 3D printing industry has grown, there are still opportunities for improved and novel materials, 3D bioprinting still suffers from material limitations.
- 3D bioprinting is predominantly used in printing tissues and implants. Therefore, the materials used for 3D bioprinting need to mimic or often have properties similar to the ones present in living beings.
- While there has been many innovations reported in using materials extracted from living cells for bioprinting, development of synthetic materials that mimic biological cells will help enable the 3D bioprinting industry to grow at a rapid pace.
- There are also opportunities for materials, such as biodegradable polymers and ceramics, for use in supporting or forming artificial organs, or possibly as bioprinted substitutes for bone.

### Growth Potential

- Opportunities for 3D bioprinting beckon in the medical industry.
- The number of start-up companies offering customized implants of different compositions for various ailments is on the rise.
- Successful research programs outlining achievements in 3D bioprinting of delicate organs present a key opportunity for new companies that will eventually commercialize these technologies for the benefit of humankind in the future.
- 3D bioprinting has opportunities in the military arena, where bioprinting techniques are looked up on as solutions for treating wounded soldiers effectively.

### Challenges

- 3D bioprinted organs and implants go through a rigorous testing phase and rather long approval cycles before commercialization. This effectively increases the time for 3D bioprinting techniques and bioprinted products to reach the market.
- Bioprinting materials are scarce; and with the growth of bioprinting technology comes more demand for materials that will help mass production of organs and implants.
Appendix
## Key Patents - World

<table>
<thead>
<tr>
<th>No.</th>
<th>Patent No.</th>
<th>Publication Date</th>
<th>Title</th>
<th>Assignee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>WO/2016/049345</td>
<td>31.03.2016</td>
<td>Three-dimensional bioprinted artificial cornea</td>
<td>The Regents of the University of California</td>
</tr>
</tbody>
</table>

An artificial cornea is fabricated by separately culturing live stromal cells, live corneal endothelial cells (CECs) and live corneal epithelial cells (CEpCs), and 3D bioprinting separate stromal, CEC and CEpC layers to encapsulate the cells into separate hydrogel nanomeshes. The CEC layer is attached to a first side of the stromal layer and the CEpC layer to a second side of the stromal layer to define the artificial cornea.

<table>
<thead>
<tr>
<th>No.</th>
<th>Patent No.</th>
<th>Publication Date</th>
<th>Title</th>
<th>Assignee</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>WO/2015/173020</td>
<td>19.11.2015</td>
<td>3D cell printing of bioglass-containing scaffolds by combination with cell-containing morphogenically active alginate/gelatin hydrogels</td>
<td>Müller, Werner E.G.</td>
</tr>
</tbody>
</table>

The present invention relates to a combined system for three-dimensional (3D) bioprinting of cells, especially bone-forming cells, that comprises (i) a bioprintable and biodegradable cell-containing alginate hydrogel/alginate/gelatin hydrogel, surrounded by (ii) a printable bioglass-containing matrix. The morphogenic activity of the alginate hydrogel/alginate/gelatin hydrogel, supplemented with the (bio)polymers, polyphosphate-calcium complex or biosilica, is increased in a synergistic way by the bioglass integrated into the inventive bioglass-(bio)polymer-alginate/gelatin hydrogel scaffold, providing this new scaffold with enhanced morphogenetic activity for bone implants.
### Key Patents - China

<table>
<thead>
<tr>
<th>No.</th>
<th>Patent No.</th>
<th>Publication Date</th>
<th>Title</th>
<th>Assignee</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>CN 104490489</td>
<td>08.04.2015</td>
<td>Method for preparing tissue engineering blood vessel based on 3D bioprinting technology</td>
<td>Huaian Haoyun Biotechnology Co., Ltd.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>The invention provides a method for preparing a tissue engineering blood vessel based on a 3D (3-Dimensional) bioprinting technology. The method comprises the following steps: alternately printing a blood vessel shape by virtue of a high-polymer material and a human renascent skin fiber cell column, and removing the high-polymer material after fusion to structure a tissue engineering blood vessel; filling late-outgrowth endothelial progenitor cells into the blood vessel, and performing in-vitro dynamic culturing for 7 days in a bioreactor to obtain a differentiated tissue engineering blood vessel, wherein the high-polymer material is one of pluronic F127, poly(N-isopropylacrylamide), methyl cellulose and sodium alginate. The blood vessel obtained by the method is high in biocompatibility and higher in mechanical property, thrombus formation resistant and platelet adhesion resistance, and can be used for repairing and replacing a damaged or disease blood vessel.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>CN 104494151</td>
<td>08.04.2015</td>
<td>Hydraulic extruding material supplying system and hydraulic extruding material supplying method for 3D bioprinting</td>
<td>Shanghai University</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>The invention relates to hydraulic extruding material supplying system and a hydraulic extruding material supplying method for 3D bioprinting. The hydraulic extruding material supplying system comprises a pressure source, a liquid pipe, a spray head device, a liquid storage box, an electrohydraulic proportional overflow valve, a controller and an upper computer, wherein the pressure source comprises a micro-injection pump and a medical injector; the liquid pipe is connected with the spray head device, the liquid storing box and the electrohydraulic proportional overflow valve to form an extruding circuit and a pressure regulating circuit; the controller is connected with the micro-injection pump and the electrohydraulic proportional overflow valve through data wires and is used for controlling the work of the whole hydraulic material supplying system through the upper computer. With the adoption of the hydraulic extruding material supplying system and the hydraulic extruding material supplying method for 3D bioprinting, the material extrusion can be controlled in real time and can quickly respond; the system and the method are applicable to various extrusion molding 3D bioprinting devices and are not limited by materials and processes.</td>
<td></td>
</tr>
</tbody>
</table>
### Key Patents - USA

<table>
<thead>
<tr>
<th>No.</th>
<th>Patent No.</th>
<th>Publication Date</th>
<th>Title</th>
<th>Assignee</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>US 20160024154</td>
<td>28.01.2016</td>
<td>Biocompatible protein, biocompatible protein gel and biocompatible conducting protein gel comprising the protein and method for preparing the same</td>
<td>Research &amp; Business Foundation Sungkyunkwan university</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>An external force judgment method including a reference value acquisition step of acquiring a reference value of a relative position or angle of a second member with respect to a first member when a robot on which no external force is acting or on which a known external force is acting is assumed to be operated by a predetermined command in advance; a measured value acquisition step of acquiring a measured value of a relative position or angle of the second member with respect to the first member when the robot is operated by the predetermined command; and a judgment step of judging the presence or absence of an external force acting on the robot based on a difference between the reference value and the measured value and a predetermined threshold value.</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>US 20120190078</td>
<td>26.07.2012</td>
<td>Three-dimensional bioprinting of biosynthetic cellulose (BC) implants and scaffolds for tissue engineering</td>
<td>Gatenholm Paul</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A novel BC fermentation technique for controlling 3D shape, thickness and architecture of the entangled cellulose nano-fibril network is presented. The resultant nano-cellulose based structures are useful as biomedical implants and devices, are useful for tissue engineering and regenerative medicine, and for health care products. More particularly, embodiments of the present invention relate to systems and methods for the production and control of 3-D architecture and morphology of nano-cellulose biomaterials produced by bacteria using any biofabrication process, including the novel 3-D Bioprinting processes disclosed. Representative processes according to the invention involve control of the rate of production of biomaterial by bacteria achieved by meticulous control of the addition of fermentation media using a microfluidic system. In exemplary embodiments, the bacteria gradually grew up along the printed alginate structure that had been placed into the culture, incorporating it. After culture, the printed alginate structure was successfully removed revealing porosity where the alginate had been placed. Porosity and interconnectivity of pores in the resultant 3-D architecture can be achieved by porogen introduction using, e.g., ink-jet printer technology.</td>
<td></td>
</tr>
</tbody>
</table>
## Industry Interactions

<table>
<thead>
<tr>
<th><strong>Jennifer Lewis</strong></th>
<th><strong>Lawrence Bonassar</strong></th>
<th><strong>Dr. Monica M. Laronda</strong></th>
<th><strong>Steve E. Kunszabo</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Wyss Professor,</td>
<td>Professor, Dept. of Biomedical Engineering, 149 Weill Hall, Cornell University, Ithaca, NY 14853.</td>
<td>Postdoctoral Fellow, Woodruff Lab, Northwestern University, 303 E Superior Street, Suite 10-121, Chicago, Illinois 60611.</td>
<td>VP, Corporate Communications, Organovo Holdings Inc., 6275 Nancy Ridge Drive, San Diego, CA 92121.</td>
</tr>
<tr>
<td>Wyss Institute for Biologically Inspired Engineering, Pierce Hall 2213 Blackfan Cir, Boston, MA 02115.</td>
<td>Phone: +1-607-255-9381 E-mail: <a href="mailto:LB244@cornell.edu">LB244@cornell.edu</a> URL: <a href="http://www.cornell.edu">www.cornell.edu</a></td>
<td>Phone: +1-312-503-2530 E-mail: <a href="mailto:m-laronda@northwestern.edu">m-laronda@northwestern.edu</a> URL: <a href="http://www.northwestern.edu">www.northwestern.edu</a></td>
<td>Phone: +1-858-224-1092 E-mail: <a href="mailto:skunszabo@organovo.com">skunszabo@organovo.com</a> URL: <a href="http://www.organovo.com/">www.organovo.com/</a></td>
</tr>
<tr>
<td>Phone: +1 617-496-0233 E-mail: <a href="mailto:jalewis@seas.harvard.edu">jalewis@seas.harvard.edu</a> URL: wyss.harvard.edu</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>