

The Future of Printed Organs and Other Tissue Engineering Methods

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Introduction

According to McGowan (2017), tissue engineering is the use of a combination cells, engineering materials and processes, and certain biochemical factors in the pursuit of improving clinical procedures for repairing damaged organs. Tissue engineering, and particularly printed organs, has become particularly popular in the public conscious for being cutting edge and potentially revolutionary. As an emerging field of research, much of the contemporary body of research falls into two categories: the research done on pushing the field forward, and the research done on feasibility, ethics, and other secondary research categories. The promise of printed organs, in a perfect world, means the elimination of wait-lists for kidney or liver transplants, among many other organs. An ideal printed organ is a perfect replacement for someone suffering from, for example, renal failure, and thereby drastically reducing the patient's reliance on dialysis for blood filtering.

The implications of applying engineering concepts to biology also bring the implied focus on efficiency and cost-effectiveness. A printed organ is theoretically cheaper to produce and more quickly available as opposed to the similar method of growing tissue over a decellularized scaffold, such as a cadaver or xenograft (Brown and Massachusetts General Hospital, 2016). The major questions that remain to be answered specifically for 3D printing organs generally fall into 3 categories; how to speed up the organ-printing process, how to increase organ complexity and scale said organs to clinically viable sizes, and how to maintain standards and protocols in order to maintain quality assurance and garner FDA approval.

For the purposes of this literature review, 3D organ printing does not necessarily refer specifically to traditional "ink and paper" analogous methods. In the field of tissue engineering

and regenerative medicine, replacement organs are traditional sources from cadavers for crucial organs and donor for non-critical organs, and sometimes an alternative species (xenograft). The body of research examined in this review focuses on alternative, non-anthropogenic sources that involve alternative, lab-grown systems for producing viable replacement organs.

Methods

I used several data parsing methods to gather relevant articles for a wide but topical snapshot of the tissue engineering field as a whole. For primary data collection, I started with Virginia Tech's *Summon* search system, in which I searched broadly for "tissue engineering". After refining the search results to articles only published within the last 6 months. Because the field of 3D organ printing is a subfield of tissue engineering, I then scanned the titles of the articles for mentions of key terms that indicate that the research is pertinent to 3D printed organs. Terms such as "bioink", "scaffolds", "membranes" and "regenerative medicine" all indicated that the articles were possibly related to 3D organ printing and therefore collected into the primary pool of articles. Articles ranked highly on Summon in terms of relevance but didn't have any of the "marker" terms in the title were also added to the preliminary pool.

As a check for article relevance, I ran the abstracts through a natural language processing program, which gave me key terms and topics for the abstracts. The results of the processing gave me a vague idea of the relevance of the article and whether I should include it into my final selection.

I then read the abstracts of all the articles. As with all sciences, there are a variety of different styles of research articles. In the last six months, Summon found an approximately equal distribution between articles focusing on original research and review and commentary

articles. While the exploration in the differences in approach articulated by original research provides the most technically accurate snapshot of organ printing and tissue engineering, the distribution between original research and review articles give insight into the landscape of the field.

Finally, I read the articles. During the reading process when I felt that the text was explaining a major topic, I wrote down the key term, and marked how many times it came up in the article. I did this across all of my articles, generating a “heat map” of sorts for the relative importance of a particular subject across my snapshot of the 3D organ printing field.

Parallels and Trends in Organ Printing Research

Organ printing poses itself as the answer to the long standing issue of a shortage of organs for transplants. According to the U.S. Department of Health and Human Services’ Organ Procurement and Transplantation Network, someone is added to the national transplant waiting list every ten minutes, and that on average, twenty-two people die each day while waiting for a transplant. While current research involving decellularizing and regenerating an existing organ using stems cells in order to prepare for transplant shows promise, the process still depends on an existing, fully grown, functional organ. In the future, organ printing could reduce or eliminate the need for organ donors, greatly reducing the number of people stuck on the waiting list for a suitable replacement organ.

Similarities in research aims. Much of the original research being done in organ printing in the last six months involves determining the best materials for scaffolding and membrane production, and advancements in printing methods. The examination of a material for

suitability in organ production hinges on multiple factors, including the toxicity of the material, whether the recipient body can replace structures over time for eventual incorporation, and the relative ease and speed of the production of various tissues using that particular material. The research being done in printing methods examines the bioavailability of printed materials using established materials and composition methods, looking instead at that production process itself.

For example, the research of Gabriel, Rodrigues, Macedo, Jardim, and Filho (2017) focuses on whether electrospun polyurethane would make a suitable, bioavailable organ scaffolding material. The speed of production of electrospun polyurethane coupled with its suitable micro-structure makes it suitable for scaffolding for printed organs. The scaffolding was tested for its physical properties in terms of similarity to organic tissue, but the crux of the research focuses on the bioavailability of the material by testing the toxicity of the material using cultured cells. The research concluded that the material had desirable physical properties for organ production and that the inherent toxicity of the material was not significant enough to disqualify it as a possible bioavailable material for future research.

Similarly, the work of Courtenay et al. (2016) focuses on other possible materials for organ production. Their research was aimed at determining whether electrically charged, bacterial cellulose membranes could serve as a possible platform for organ membranes in organ production. The research similarly concluded that the cellulose matrix membranes could serve as viable organ membranes in particular to the high degree of control over the chemical composition, and therefore physical properties of the material as a way of modifying artificially-produced organs to be tailor-made to the recipient.

Furthermore, research done by Elomaa and Yang (2017) investigates the usage of hydrogel printing for vascular tissue production. Their work focused on the bioavailability of the material. Their survey of several different parties' research examined how human cells reacted in said hydrogel vascular tissues. The survey of research included variations in printing methods, including whether the tissue was printed into a calcium chloride solution, the temperature of printing, and the density of cell deposition, among other factors. The research aggregated the results of the other research in regards to the response of the cells, including cell viability and vascular tissue inflammation to determine which printing methods using hydrogel yielded the best results.

The work of Guo, Lembong, Zhang, and Fisher (2017) looks instead at possible advancements in the printing process itself. The research looks at the differences in bioavailability of bone and ligament grafts when using current and experimental methods. The research focuses on different avenues of artificial ligament production, and the advantages and disadvantages between post-printing cell seeding an empty print matrix versus a pre-mixed, cell-laden print matrix. The work also looks at the various functional strength of different production methods in the context of a high-stress application such as replacement or repaired ligaments. The research concludes that new advancements in bioprinting allow for more complex and functional tissue to be produced, but that the need for future materials that both stronger and more flexible in function is a crucial step in the advancement in regenerative tissue production.

Similarities in research conclusions. While original research focuses particularly on possible new materials for regenerative medicine, both new research and research focused on commentary and meta-analysis both came to similar conclusions. All of the collected articles

either mention the limitations of current research and where they expect the field to progress in the future in order to solve these problems, or describe the precautions and potential issues when the field of regenerative medicine, organ printing in particular progresses enough to be faced with the need to scale up in production while maintaining quality standards.

For example, Kaushik, Leuten, and Khademhosseini's (2016) research commentary on the advancements in the field in draws conclusions in multiple problematic areas. The research comments on the need for increased complexity in artificial tissue production, citing the current differences between an engineered organ and its native counterpart in both structural and functional capabilities. The research also stresses the future need to combine top-down and bottom-up organ production methods to help reduce the shortcomings of both methods, combining the specificity and precision of bottom-up techniques and the macro-scale scaffolding provided from top-down production methods. Not all of the conclusions drawn by Kaushik et al.'s research are grim, however, as they note the emerging usefulness of printed organs for *in vitro* testing of emerging and currently-developing drugs. The availability and relative cheapness of printed organs could be a potential avenue to reduce the exorbitant costs of developing new drugs.

Hui, Nowicki, Fisher, and Zhang's (2016) research commentary offers a similarly cautiously optimistic perspective on the future of organ printing. The research comments on the need for improvements in printing methods and research into new materials to support organ development. The research also mentions that the current state of organ printing, namely the relatively simple composition of bio-inks used in the printing process, as a limiting factor due to the fact that no organ is comprised of entirely one kind of cell. Similarly to the research done by

Kaushik et al., Hui et al. stress the need for the incorporation of different organ printing methods and more specialized bioinks to begin to approach the complexity needed for a functioning replacement of a complex organ such as a heart. Hui et al.'s research also touches on similar potential pharmaceutical benefits of engineered organs, specifically the ability to have direct control of drug administration and easy observation of the effects.

The research of Park, Jang, Lee, and Cho (2016) summarizes the state of research similarly to the other collected research: like Hui et al., the research indicates that the next steps of research need to be in addressing the current shortcomings in the production methods used. One prominent concern of Park et al., is the need for better bioinks and printing systems; currently high-resolution printing techniques are limited by bioink viscosity, producing low-strength results. To augment the strength of the produced material, synthetic polymer is added as a way to reinforce the material. However, the downfall of this is that soft tissue render the use of the synthetic polymer reinforcing is unsuitable, severely limiting the options for organ production.

Hussein, Ohya, and Puri (2017) offer a macro-scale review of the challenges of current research. The research mentions both outward-facing challenges such as garnering FDA support for approval of future research, as well as the need for organizations like the FDA to act as regulatory bodies to ensure the highest standards are met in the organ production process. Hussein et al., also touch on conclusions drawn by other collected research by reiterating the potential uses of printed organs in pharmaceutical testing applications, and the urgent need for

improvements in printing technologies, bioinks, and materials for printing to allow for suitably complex organs.

Conclusions

The majority of the research in the last six months in the field of regenerative medicine, and in particular, organ production, has been enormous. However, as such a young field of bioengineering, the advancements all face the same conclusions. The consensus is that while research may find that material A is very well suited for organ scaffolding, it is not suited for diverse, nano-precise tissue that is needed for the whole organ. On the flip side, material B may be very well suited for complexity and diversity, but is lacking in 3D organ production, instead being more useful for 2D organ and other organ-on-a-chip applications (Hui et al., 2016).

Several research articles envision future research to incorporate both material A and material B - the dream being the ideal mix of precision in production, speed of production, bioavailability, and patient-specific tailoring, all while maintaining and scaling the ethics and standards needed to bring printed organs to the mainstream.

Future research in the field is likely to focus on more of the same; that is, more materials research for potential macro- and microstructure development, with a stronger emphasis on printing technologies in particular. As defined by McGowan, the field of tissue engineering is the mixture of biological, medical, and engineering processes to produce anthropogenically identical tissues, vascular structures, and organs. The current limitations reported by much of the research in this review focus heavily on the limitations of the engineering aspect of tissue engineering. Future research ideally will address issues with current printing methods and bioinks by advancing the printing technology to allow for inkjet precision with more complex and

specialized bioinks, where current printing methods are limited to simpler bioinks. Furthermore, there is likely to be a similar level in commentary and meta-analysis research due to the very young nature of the field, leading to a need in peer review and “state-of-the-field” reports. The research, without exception, is optimistic about the future prospects of the field, and the apparent energy and public support they have push their research towards the ultimate goal of fast, tailor-made, printed replacement organs and tissues for those that need them most.

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