Title: Manufacturing and Scale Up Challenges of Bioprinted Tissues

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Abstract

More than 110,000 patients are currently in the organ waiting list in the US alone and about 20 patients die every day waiting for a transplant [1]. Due to the limited availability of organs and the requirements for donor matching and compatibility, the demand for replacement organs far exceeds supply. Therefore, large-scale manufacturing of transplantable organs and tissues are necessary.

Bioprinting is a promising technology to generate functional tissues and organ systems that has the potential to solve this critical unmet need. The last decade has seen significant developments in this field with innovations in printing technique, bioink materials, and robotic systems that allow for precise dispensing of bioink at a subcellular scale. Yet, the field is far from clinical translation as among other challenges ahead of large-scale manufacturing is the requirement for scalable packaging systems for bioinks needed for clinical environments.

Characterization of critical quality attributes of bioprinted constructs is a major hurdle for clinical scale tissue manufacturing. Currently used characterization methods in the research environment are often destructive tests and not amenable for production for use with clinical applications. Non-contact and non-destructive characterization methods need to be developed for ensuring quality of manufactured tissue. Long term preservation and transportation of the living cell containing bioinks and manufactured tissue products is another significant challenge in clinical translation of bioprinting. Tissue cryopreservation techniques as well as supporting devices and infrastructure would be necessary. Furthermore, the lack of standards and guidance documents for bioprinting workflow are also hindering the progress of bioprinting towards clinics.

CGMP-grade containment systems including cartridges and syringes that can maintain container closure integrity under cryogenic temperatures are required to ensure cells remain viable when frozen, stored and thawed for delivery through a bioprinter. Current commercial bioink products remain primarily intended for research use only and therefore they are not manufactured or filled in CGMP environments. The limited CGMP-grade bioink materials available require additional steps in formulation by the end user increasing risks of contamination and batch-to-batch variability. Therefore, CGMP grade syringes, cartridges and containment systems must be designed specifically for clinical bioprinting. Elastomeric stopper and rigid cyclic olefin polymer (COP) based container systems have previously been investigated as a solution in long term preservation of biological therapies in cryogenic conditions [2]. The container system should also have an acceptable range of particulates, extractables and leachables for clinical application. The use of such container systems may enable the commercialization of cells premixed with CGMP-grade bioink, which can accelerate the research to clinic translation of bioprinting.

Overcoming these critical manufacturing challenges can result in bioprinting technology implementation of for the fabrication of replacement tissues and organs at a large scale, which may eventually eliminate the organ shortage crisis that the current world is facing.

References

1. Organ donation statistics (https://www.organdonor.gov/learn/organ-donation-statistics) Date of Access: 01/31/2021
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