Current state of 3D printing in tissue engineering

“As our understanding of stem cell biology, biomaterials and rapid prototyping technology gets more advanced, we expect to see a bigger and a more exciting role of 3D printing in the realm of tissue engineering and regeneration. We also anticipate that 4D printing will be the next frontier in this rapidly evolving field...”

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3D printing, also referred to as additive manufacturing (AM), is an emerging technology driving major innovations in healthcare, engineering and the arts. In medicine, 3D printing is being used to fabricate patient-specific anatomical models for presurgical planning and to design customized prosthetics [1], medical devices [1,2] and drug delivery systems [3,4]. Moreover, recent advances have enabled 3D printing of complex tissues using biocompatible materials, cells and supporting components [5–9].

3D printing creates objects by adding layers of material. Most 3D printers follow similar principles. The 3D structures (organ model, tissue scaffold or prosthesis) can be either designed using a computer-aided design (CAD) software or acquired through imaging sources such as CT and MRI as 3D-reconstructed objects. CAD software prepares the final object with relevant dimensions and generates an STL (stereolithography) file – a standard file-type widely used by most 3D printing devices. The structure is sliced into a stack of 2D layers and the sliced data are relayed to the printer, where the material is laid down layer by layer. Depending on the design of the object, material used and the 3D printing device, specific post-processing steps are required. Currently, a variety of materials are available in the market with unique properties related to strength, flexibility, ease of printing, biocompatibility and biodegradability [10]. Moreover, newer

generations of 3D printers are capable of using multiple materials including biological substrates and cells, which is of particular interest for tissue regeneration [11]. These features will allow for printing organs with natural compartmentalization of different cell types.

The ability to integrate medical imaging with 3D printing enables production of personalized and anatomically correct scaffolds, tissues or devices. Jeremy Mao and his team at Columbia University Medical Center have developed a way to replace knee menisci using 3D printed scaffolds seeded with growth factors [12]. The anatomic contours of the meniscus are obtained using knee MRI and reconstructed using CAD software. The meniscus scaffold is manufactured using a biodegradable polyester and seeded with growth factors. After implantation, regeneration of the cartilage occurs via cell homing. On *ex vivo* analysis in a sheep model, they showed that the regenerated menisci have structural and mechanical properties similar to the native meniscus. In another study, Glenn Green and his group at University of Michigan used 3D printing technology to develop patient-specific external airway splints for the treatment of tracheobronchomalacia (TBM) in three infants [2]. DICOM images of the airway from patients' CT scan were used to create a 3D model of the airway and imported into a CAD software. Measurements of airway diameter and length for the design of the

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device were obtained. The patient-specific splint was subsequently fabricated using PCL, a biocompatible and biodegradable polyester. The splint was placed external to the airway allowing the diseased airway wall to be suspended to the device using sutures. All patients demonstrated increase in airflow attributable to the increase in airway diameter.

Our team has created a customized bioengineered graft to repair and/or replace large tracheal defects with a goal to develop a tracheal graft that can provide longitudinal flexibility as well as radial rigidity. This graft maintains airway patency while concurrently supporting chondrogenesis, neovascularization and re-epithelialization. Using 3D printing technology, biologic collagen membrane and mesenchymal stem cells, we have achieved encouraging preliminary results in large animal models. We generate 3D reconstructions of the tracheobronchial tree extending toward the carina and the major bronchi using CT scan images of neck and chest. Large tracheal defects, long segment airway stenosis or TBM can then be corrected virtually using CAD software. The corrected anatomical 3D image is converted to a (.STL) file and the tracheal scaffold is 3D printed. The latter is combined with a biological membrane and subsequently seeded with mesenchymal stem cells. These stem cells are allowed to proliferate and differentiate into chondrogenic progenitor cells in a bioreactor *in vitro*. We incubate the stem cells in growth media containing a specific mixture of chondrogenic factors to induce the formation of chondrocytes. With this approach, we have seen cellular growth and differentiation of the stem cells into

chondrogenic progenitors *in vitro* and chondrocytes *in vivo* in the animal model. We have successfully shown that the implanted tracheal graft is capable of maintaining airway patency [13]. Currently, we are working on understanding the airway dynamics, mucosal epithelial function and long-term effects of the bioengineered trachea.

As our understanding of stem cell biology, biomaterials and rapid prototyping technology gets more advanced, we expect to see a bigger and a more exciting role of 3D printing in the realm of tissue engineering and regeneration. We also anticipate that 4D printing will be the next frontier in this rapidly evolving field – time being the fourth dimension. The next generation of biomaterials will be able to self-assemble, self-repair and respond to the environmental cues such as heat, water and pressure as the conditions change within the living system [14]. Substantial information remains to be discovered and technical challenges [15] to be overcome in the quest to design and fabricate customized complex organs; now is the prime time for tissue engineering, which promises to be the new frontier in medicine.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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