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Spotlight

A Step Towards Clinical Translation of Biofabrication

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Biofabrication is a rapidly growing field with the potential to radically change current medical treatments. This vision does, however, require integrated bioprinting platforms that can process multiple materials to tissue constructs with structural integrity and of clinically relevant scales. In a recent study, Kang *et al.* [1] presented such a platform and successfully demonstrated the formation of different tissue types *in vivo*, opening the door for future steps towards the clinical translation of this technology.

Within tissue engineering and regenerative medicine (TERM), biofabrication is a rather young and promising research field that relies on the use of automated layer-by-layer deposition of biomaterials, bioactives, and cells, encompassing both bioprinting- and bioassembly-based approaches, to generate hierarchical cell/biomaterial composite structures [2]. This approach has the potential to overcome a number of classical challenges in TERM relating to organization, personalized shape, and mechanical integrity of generated constructs.

With different fabrication strategies ranging from single-cell printing to the deposition of cell-loaded hydrogels or cell spheroids, biofabrication can recapitulate the structural organization of native tissues in the fabricated construct [3]. Moreover, printing sacrificial fibers allows generating perfusable channels that enable the supply of nutrients within larger structures [3–5]. Currently available imaging technologies can yield CAD files, which can be translated to codes to run 3D bioprinters to generate patient-specific implants. Importantly, biodegradable thermoplast scaffolds can be integrated to generate implants with mechanical integrity required for surgical handling and to provide functional stability after implantation [6,7], which can even be achieved with only a few volume percent of thermoplast material [8]. However, these different strategies have so far been applied separately, rather than concurrently in a merged approach. In addition, available *in vivo* data demonstrating the efficacy of biofabricated implants is still limited.

Kang *et al.* [1] developed an elegant and effective integrated bioprinting platform (integrated tissue organ printer, ITOP). Using this, they generated – based on CAD data – perfusable tissue structures with mechanical integrity, evaluated these constructs *in vitro*, and implanted them after preculture using inductive conditions. They convincingly demonstrated *in vivo* maturation for mandible and calvarial bone, cartilage, and skeletal muscle tissue constructs. While no signs of necrosis were observed, bone and muscle constructs showed clear signs of vascularization. With this combinatorial 'toolbox', the authors have made a significant step forward and demonstrated feasibility, running through the entire biofabrication process from 3D model to *in vivo* evaluations. The work exemplified how these technologies may be able to overcome typical challenges encountered within TERM, with regard to personalized shapes, internal organization, vascular networks, and mechanical integrity of the implants.

The study by Kang *et al.* [1] has thus made substantial progress and has brought the field of biofabrication one step closer towards clinical translation. However, to achieve this final goal,

further steps and challenges remain. The efficacy of biofabricated constructs of larger sizes will have to be demonstrated in large animal models, where connecting the engineered vascular structure to the blood supply of the host will have to be ensured. Each target tissue will have its specific requirements with regard to bio-ink formulation and reinforcing strategy. As such, a broader variety of bio-inks with tailored biochemical and physical properties will be needed, and a more pronounced implementation of supramolecular and macromolecular strategies in this field appears very promising [9]. In addition, the currently applied reinforcing stiff polymers (e.g., polycaprolactone, PCL) may not be ideal for soft tissues and alternatives will have to be developed. Future work will also have to show an ideal compromise in the replication of natural tissue architecture between the resolution and the speed of production. At the moment, it is unclear which level of detail is needed for a functional maturation of a fabricated construct *in vivo*, and we anticipate that this will depend on the target tissue and thus vary from case to case.

Finally, despite the recent advances in the field and the exciting study of Kang and colleagues the fabrication of functional more complicated (combined) tissues, tissue interfaces and organs, still remains a considerable challenge. To achieve this, not only mechanical integrity but also specific function of the printed construct will have to be achieved. Nonetheless, the study of Kang *et al.* [1] illustrates the huge potential of this young and evolving field of research that we are only just beginning to unveil.

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