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3D bioprinting of cell-laden hydrogels for advanced tissue engineering

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3D bioprinting is an emerging tissue engineering technique that enables the additive fabrication of different cell types and materials with a defined three-dimensional arrangement. This review provides an overview of different 3D bioprinting techniques, highlights their capabilities, and reveals limitations which still exist. Based on the described techniques we show how bioprinting can potentially impact patient care in the future following two different routes. We distinguish between the fabrication of tissue substitutes for implantation and the printing of tissue models as a platform for drug and toxicity screening. This review offers a state-of-the-art view of both of these fields of application, including the targeted tissue types, their stage of development as well as their initial applications, and provides an outlook on possible future developments in the field of 3D bioprinting.

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Introduction

3D bioprinting is an emerging Tissue Engineering (TE) tool that applies additive manufacturing technology with the goal of generating three-dimensional, tissue-resembling structures [1]. The printing process constitutes the layer-wise deposition of cell-laden hydrogels, referred to as bioink, according to a predefined 3D model. Following the printing process, cellular structures are cultured in an *in vitro* or *in vivo* environment to form functional tissues. The main advantage of 3D bioprinting is its capability to build up multicellular structures with a high degree of spatial organization and a defined material composition [2].

While the technology of bioprinting itself has been the focus of research for the past 13 years [3–7] and will continue to be for years to come, e.g. technical, biological, and material related advances, the first signs of its evolution towards a tissue engineering tool with preclinical relevance can be observed today. This article provides an overview of the latest advances in this rapidly evolving field. In the first part, a review of the characteristics of different bioprinting techniques is offered and the second part focuses on the preclinical application of bioprinted tissue units.

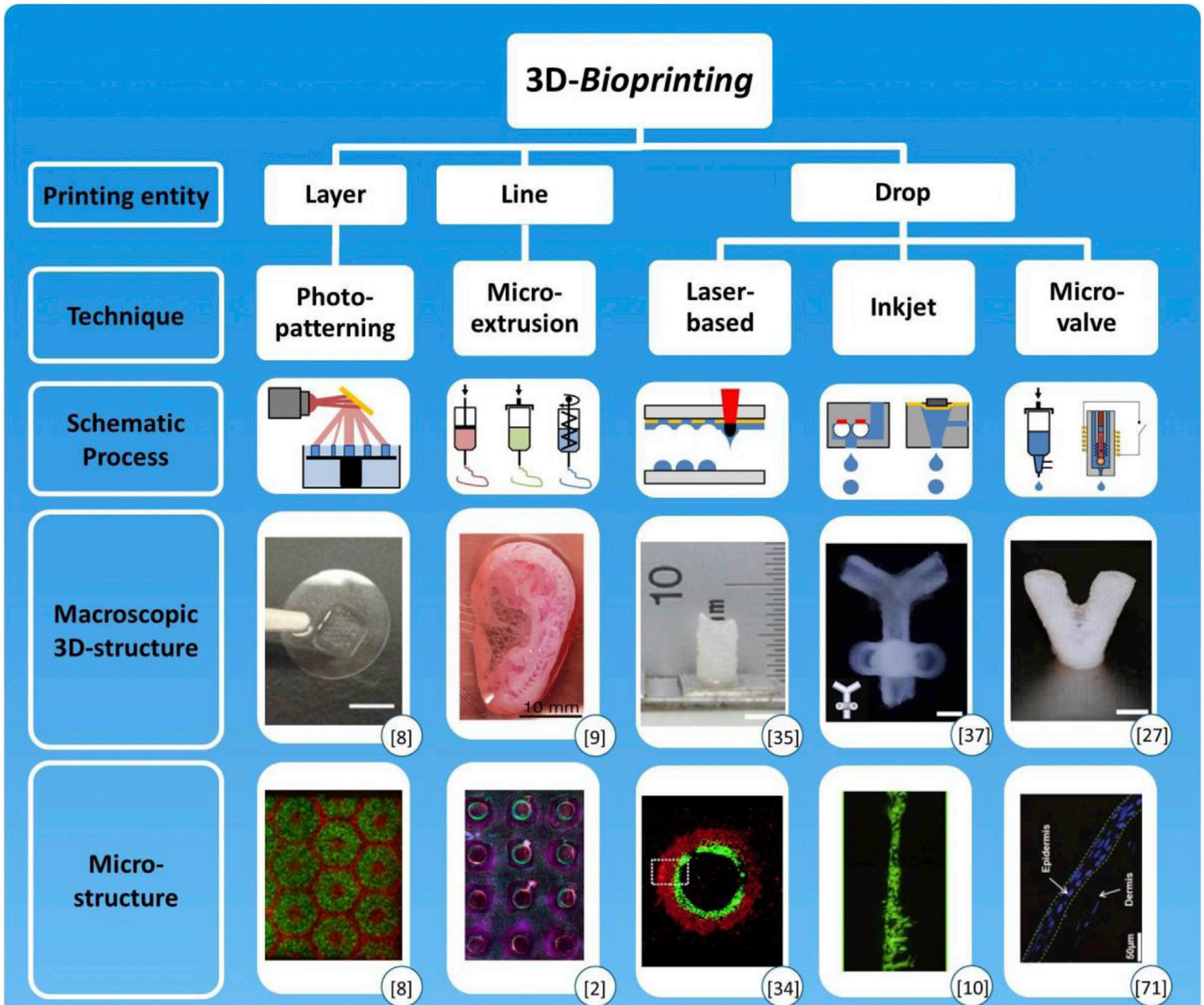
Bioprinting technologies

From its beginnings, dating back to Mironov and Boland in 2003 [3] until today a panoply of bioprinting methods have evolved. Based on the smallest printable entity, these techniques can be divided into three classes (Figure 1). Bioink can either be printed layer-wise (e.g. photo patterning [8]), continuously plotted (e.g. microextrusion [9]), or dispensed drop by drop (e.g. inkjet bioprinting [10]). In the following section we describe the general methodology of frequently used techniques and point out their most important technical characteristics (printing resolution, viscosity range of printable fluids, post-printing cell viability). In addition, we evaluate the techniques' ability to generate both large, free-standing objects and small, micropatterned structures.

Layer-wise bioprinting

Recently, new bioprinting strategies have been developed that allow for the manipulation of a full layer of bioink in one step. Instead of generating an object drop by drop or line by line a complete layer is structured according to a predefined pattern. A prominent example of this strategy is photo-patterning of photocrosslinkable bioinks. Using automatically exchangeable photo masks [8] or a beam projector [11], each "printed" layer exhibits an individual curing pattern. In initial studies, bioink could be patterned with a resolution of less than 50 μm and a post-printing survival rate of 80% [8] to 90% [12]. So far this technique has shown itself to be more eligible for the patterning of planar microstructures

Figure 1



	Layer-wise	Line by line	Drop-on-Demand		
	Photo-patterning	Microextrusion	Laser	Inkjet	Microvalve
Droplet volume (nl)	**n. a.**	**n. a.**	**0.01-7** [33]	**0.01-0.13** [10,69]	**2-720** [27,32]
Resolution (μm)	**< 50** [8]	**45-1,200** [4,14]	**45-140** [28,35]	**70-100** [70]	**200-1,000** [29,71]
Viscosity (mPas)	**n. a.**	**1-960,000** [17]	**22-8,279** [28,33]	**1.5-5** [69]	**1-1,500** [27,72]
Viability (%)	**80-90** [8,12]	**61-97** [14,18]	**80-98** [73,74]	**69-92** [31,37]	**71-99** [27,40]
Printing of...					
• free-standing 3D-structures	+	+++	+	++	+++
• planar micro-structures	+++	+++	+++	++	+
	[8,11,12]	[2,4,14,17,18]	[28,33–35,73,74]	[10,31,37,69,70]	[27,29,32,40,71,72]

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Overview of different 3D bioprinting techniques [69–74].