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Editorial

3D Skin Bioprinting: A Novel Tool for Dermato-Pharmacology, -Toxicology and Drug Development

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The topical drug administration is an emeging route of application of pharmacologically active substances with different therapeutic indications (dermatological disorders, pain, inflammation, hormone replacement, nicotine, central nervous system indications etc). The main advantages of transdermal drug delivery route are that (1) it has local and/or systemic effect, (2) lower dose level can be given than in case of the enteral dosage form, (3) reduced side effect spectrum, (4) long term absorption profile, (5) non-invasive administration, (6) simple selfadministration, (7) lack of first pass metabolism and gastrointestinal degradation and irritation. There are several *in vitro* and *in vivo* approaches for the investigation of transdermal absorption and pharmacokinetics of topically applied drugs. As a traditional first approach to study topical drug release and permeation, arteficial membranes are used in Franz diffusion cells. The next step in the biological complexity is the *ex vivo* investigation of drug absorption in animal skin preparation. However, the most relevant and predictive approach for characterisation of human transdermal drug absorption is the diffusion study performed of course in human skin. However, in many cases the availablity of human skin from e.g. plastic surgery is not so simple because of bioethical considerations and burocratic permission processes. In such cases drug testing on human skin substituents can be an alternative and these models might have a high importance in drug development [1]. The emerging 3D bioprinting technology makes it possible to construct human skin substituents from human cells. There are several types of technologies used. One is the extrusion based technique, the second one is the droplet based technology by bioinks and a third possibility is the laser based technique [2]. All fabrication methods need the basic cell types of the skin: fibroblast, keratinocytes and melanocytes. These cells should be mounted on a scatter (building block) prepared from biopolimers with natural (fibrin, collagen, gelatin, chitosan, alginat etc) or sythetic (polyethylene glycol (PEG), polyacrylic acid (PAA), polyacrylamide (PAM), poly (2-hydroxyethyl methacrylate) (PHEMA) etc) origin [2-4]. More advanced skin substituents includes vascular elements, immunological cells and innervation as well. The secretory properties of the skin should also be considered by including the appendages (hair follicles, sweat glands, etc). Regarding the complicated cell culturing and mixing technologies, ensuring of the proper conditions during the bioprinting process and afterwards has a crucial role. The post-processing of the bioprinted materials is essential to get fully functional biomimetic skin. To reach the proper stucture and mechanical properties of the skin construct the dermal fibroblasts and epidermal keratinocytes should be left to proliferate and then the keratinocytes need time to differentiate. After the process of construction there exist different methods for evaluation of the skin equivalents. From biologial point of view the viability of the cells should be tested and also the biomarkers of extracellular matrix, various cell types and basal membrane can be studied by immunostainings. The structural morphology and heterogeneity of artificial skins can also be investigated in histological sections. Beside the biological factors the functional properties of the artificial skins should also be tested by mechanical and pharmaceutical techniques. The human skin exhibits viscoelastic properties and anisotropy. For tailoring the material some biodegradable synthetic products like polycaprolactone (PCL) and poly(L-lacticacid)-co -poly(ϵ -caprolactone (PLACL) can be added to the constructs to improve the strenght and the flexibility. To test the absorptive properties and optimize the different pharmaceutical formulations Franz diffusion cells and microfluidic lab-on-a chip devices are suggested to be used.

Beside the biological, histological, mechanical and functional characterizations for preclinical use and for pharmacological and pharmacokinetic purposes [1], further and more advanced goal of the preparation of 3D bioprintinted skins is to gain implantable materials in humans. The bioprinted skins are designed to be used to help wound healing and regeneration [5] and for skin replacement in burning injuries or in other dermatological or cosmetological indications. The application possibilities depend on the biological complexity of the human skin substituents. The correlation between the utilization and the models is presented in figure 1.

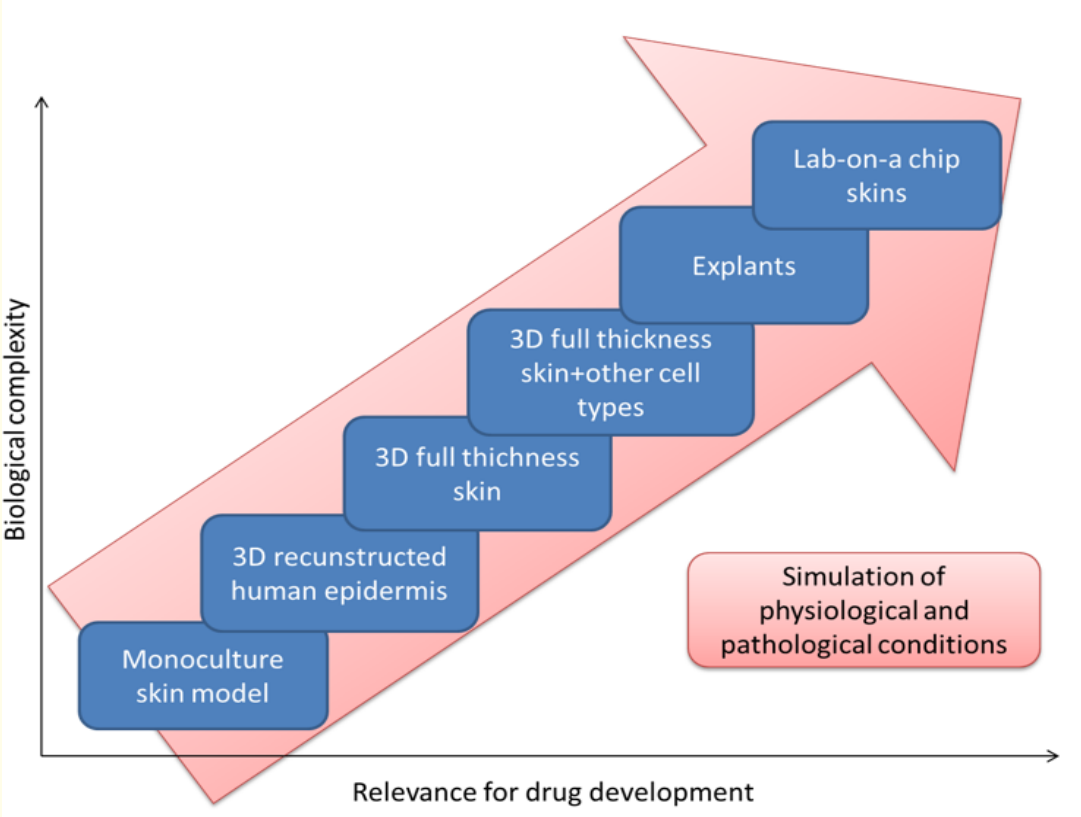

Figure 1: *The application possibilties and the relevance of the in vitro models of human skin highly depend on the complexity of the system (After Yan., et al. 2018, with modifications [1]).*

Taken all together, the wide spectrum of technologies of 3D skin bioprinting provides promising tools both for the topical drug development in pharmaceutical industry and for medical and cosmetological applications. A breakthough in this field and in the quality and biocompatibility of bioprinted artificial human skins can be predicted within some years.

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