Bioink Development for Additive Manufacturing of Artificial Soft Tissue

K. Borchers2, C. Bierwisch5, S. Engelhardt3, C. Graf4, E. Hoch6, B. Huber6, R. Jaeger5, P. Kluger2, H. Krüger1, W. Meyer1, E. Novosel2, O. Refle4, C. Schuh2, N. Seiler3, G. Tovar2, M. Wegener1, T. Ziegler5
1Fraunhofer Institute for Functional Polymersystems IAP, Potsdam, German; 2Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB,Stuttgart, Germany; 3Fraunhofer Institute for Laser Technology ILT, Aachen, Germany; 4Fraunhofer Institute for Manufacturing Engineering and Production IPA, Stuttgart, Germany; 5Fraunhofer Institute for Mechanics of Materials IWM, Freiburg, Germany; 6University of Stuttgart, Germany

Introduction

The future vision of implants comprises individually tailored prostheses and the generation of artificial tissue and organs generated from the patient's own cells. Furthermore, sophisticated complex tissue models will help to perform adequate *in vitro* testing and avoid animal experiments. In order to develop artificial, biomimetic structures which perform as well as natural ones, we need fabrication processes that do not set any limits to the generation of shapes, and materials that allow for tailoring of their physical, chemical, and biological properties.

We introduce new biocompatible materials for the manufacturing of flexible structures by freeform fabrication methods.

Methods

We develop printable and photo-crosslinkable material systems, either based on bio-polymers derived from the native extracellular matrix, e.g. gelatin, or fully synthetic resins. We use e.g. (meth)acrylation of the precursor polymers to achieve photo-crosslinkablility. Further chemical modifications and additives are applied in order to achieve inkjet-printable resin viscosities. Inkjet-printing combined with UV laser or twophoton-polymerization (TPP) in inert atmosphere is developed for 3D material structuring. Computational fluid dynamics are used to find optimal geometries for specific functions. Using bio-based materials inkjet-printing and 3D encapsulation of cell-laden bio-ink is performed.

Results

We provide synthesis of cytocompatible polymers suitable for additive manufacturing processes. Different types of non-degradable synthetic polymers were tailored to be non-cytotoxic. Surface biofunctionalization of the polymers with cell-adhesion anchor molecules enables proper cell adhesion and proliferation to confluent monolayers. UV laser curing and TPP were applied to generate e.g. tubular systems with respect to future nutrient supply of large *in vitro* tissue constructs or blood vessel substitutes. The viscosity of the materials was tailored to the inkjet-printable range and the E-modulus of the crosslinked synthetic materials can also be adjusted. Modelling and computational fluid dynamics allows for prediction of the correlation of structure and function, e.g. for biomimetic bifurcations with optimized wall shear stress for endothelial cell growth in blood vessel like systems. Gelatin-based biomaterials constitute both, printable non-gelling precursor solutions and crosslinked hydrogels with tunable physico-chemical properties. Such bioinks can be used for 3D encapsulation of cells and cell printing, thereby constituting biomimetic matrices with adjustable properties for engineering of complex tissue models.

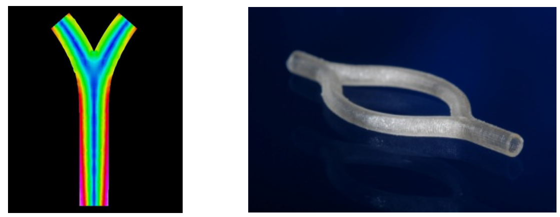

Figure 1. *Left: Computational evaluation of shear stress. Right: prototype of an elastic branched tube, fabricated from newly developed cytocompatible ink by UV laser curing.*

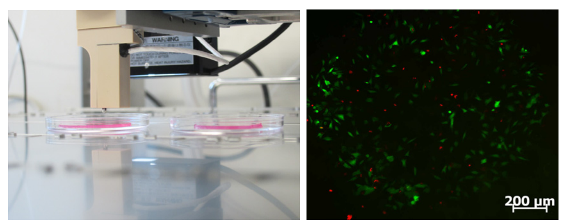

Fig. 2: *Left: inkjet-printing of cell-laden gelatin-based bioink onto hydrogel substrates. Right: viable porcine chondrocytes after inkjet printing (green: live cells, red: dead cells).*

Conclusion

Additive manufacturing can be opened up for processing both, bio-based and synthetic precursors for future generation of complex soft tissue substitutes.

Publications

E. Hoch, C. Schuh, T. Hirth, G.E.M. Tovar, K. Borchers, "Stiff gelatin hydrogels can be photo-chemically synthesized from low viscous gelatin solutions using molecularly functionalized gelatin with a high degree of methacrylation", J Mater Sci: Mater Med 11 (2012) pp.2607-2617.

W. Meyer, S. Engelhardt, E. Novosel, B. Elling, M. Wegener, H. Krüger. Soft Polymers for Building up Small and Smallest Blood Supplying Systems by Stereolithography. J. Funct. Biomater. 3 (2012) 257-268

Acknowledgements

The Authors thank Fraunhofer, European Union (Artivasc 3D, 263416) and Max Buchner Foundation for funding.