Biopolymer-based functional inks for the preparation of artificial cartilage via bioprinting technology

Eva Hoch,[1] Achim Weber,[1,2] Kirsten Borchers[1,2]
[1] Institute for Interfacial Process Engineering and Plasma Technology IGVP, University of Stuttgart, Stuttgart, Germany;
[2] Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB, Stuttgart, Germany

Abstract

We present bioinks based on biopolymers from the native extracellular matrix, namely gelatin and chondroitin sulfate, which are suitable for bioprinting technology applying living mammalian cells. The bioinks can be crosslinked due to chemical modification of the biopolymers with methacrylic functions. Such insoluble hydrogels with tunable physico-chemical propertie are able to closely mimic the native extracellular matrix of biological tissues (ECM). Highly methacrylated gelatin (GM_{10}) resulted in solutions with low viscosities (e.g. 15 wt%: 6.7 ± 1.0 mPa s at 37 °C) within the inkjet-printable range and crosslinked hydrogels with high mechanical strength. Less methacrylated gelatin (GM_2) was proper for preparation of soft hydrogels and highly viscous bioinks for pneumatic dispensing technology (e.g. 15 wt%: 39.3 ± 3.6 mPa s at 37 °C). By additional acetylation of GM_2 (GM_2A_8) the solution viscosity could be significantly lowered (e.g. 15 wt%: $\eta = 5.2 \pm 0.5$ mPa s, 37 °C) and, thus, inkjet-printable bioinks with low crosslinking capacity were also gained. Consequently, a versatile bioink system for bioprinting technology was created.by adjustable twofold modification of gelatin with photochemically reactive and inert groups.

Introduction of an additional methacrylated component of the ECM, methacrylated chondroitin sulfate (CSM), further tuned the chemical and physical properties of bioink and hydrogels. GM(A)-CSM hybrid hydrogels possessed for example significantly higher swellability than pure GM(A) hydrogels of the same mass fraction. CSM also influenced bioink viscosity: For unmodified gelatin and gelatin with low degree of modification CSM induced a decrease in bioink viscosity (e.g. 15 wt% GM_2: 39.3 ± 3.6 mPa s versus 14 wt% GM_2 + 1 wt% CSM: 32.9 ± 6.5 mPa s). In contrast to this, addition of CSM to bioinks made of gelatins with high degree of modification, GM_2A_8 or GM_{10}, induced an increase in solution viscosity (e.g. 15 wt% GM_2A_8: 5.2 ± 0.5 mPa s versus 14 wt% GM_2A_8 + 1 wt% CSM: 6.5 ± 1.0 mPa s).

The developed bioinks were proven to be suitable for bioprinting with viable mammalian cells, in this case porcine articular chondrocytes, and for fabrication of tissue models with intrinsic structure. Thus, biomaterials presented in this study can be used for biofabrication of artificial three-dimensional tissues with biomimetic organization, such as articular cartilage with its hierarchical structure.

Introduction

The future vision of implants comprises the generation of artificial tissues generated from patient's own cells. Furthermore, sophisticated complex tissue models will help to perform adequate *in vitro* testing and thus avoid animal experiments.

Traditional tissue engineering (TE) uses solid scaffolds, prepared either by decellularization of donor tissue [1] or by construction of porous scaffolds applying methods like for example electrospinning, freeze drying, or 3D printing [2, 3]. Such scaffolds are then seeded with tissue-specific cells. Another approach is the encapsulation of cells into three-dimensional (3D) hydrogels [4, 5].

The quality of such artificial tissues very strongly depends on the ability to bring cells to their "right" position in these 3D construct. Any tissue consists of a variety of different cell types and extracellular matrix (ECM) compartments with different composition and/or mechanical properties. Thus, 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 3D shapes and structures.

Currently, computer-controlled 3D manufacturing techniques are being successfully adapted for TE applications in order to enable sophisticated manufacturing of artificial tissue substitutes [6]. This approach called bioprinting particularly aims for the direct deposition of biomaterials and living cells into spatial orientations and geometries [7]. One advantage of bioprinting technology is the potential to manufacture organized structures of multiple matrix materials, because material deposition can happen from multiple separate ink reservoirs (cartridges). Furthermore, simultaneous deposition of 3D matrix and cells offers the opportunity of controlled and reproducible cell distribution.

The most frequently used additive manufacturing techniques for bioprinting applications are inkjet printing and dispensing technology. Inkjet printing, a non-contact and drop-on-demand printing method, holds the advantage of a low risk of contamination [8, 9]. It is designed to process low viscous inks with viscosities from approximately 1 mPa s to 10 mPa s [10]. Several studies showed that inkjet printing allows for high resolution of 1 µm - 20 µm [11]. Dispensing technology on the other hand, often called bioplotting, allows for fabrication of 3D constructs by deposition of continuous filaments. Here, inks with higher viscosities from 30 mPa s up to $7x10^6$ mPa s are applied for processing [11]. Dispensing technologies achieve resolutions of just several 100 µm, but can realize 3D constructs in the cm range in only a few minutes.

To exploit full potential of such 3D build-up technologies, sophisticated biomaterials are additionally needed, which, besides being printable and crosslinkable, allow for tailoring of their physical, chemical, and biological properties to adapt them to the properties of native ECMs. Towards this goal, biomolecules from the native ECM constitute very promising materials as they hold for example natural signaling motifs for stimulation of cell adhesion, migration, and function.

We developed printable and photo-crosslinkable material systems based on biopolymers derived from the native ECM namely gelatin and chondroitin sulfate. Such bioinks are suitable for 3D cell printing, thereby constituting biomimetic matrices with adjustable properties for engineering complex tissue models, for instance articular cartilage.

Materials and Methods

Biopolymer Modification

Photo-crosslinkable derivatives of the ECM biopolymers gelatin (Sigma-Aldrich, Germany) and chondroitin sulfate (Sigma-Aldrich, Germany) were prepared by modification with methacrylic anhydride

(MAAnh; Sigma-Aldrich, Germany) as described elsewhere [12-14]. We prepared GM with two different degrees of modification (DM) by varying the amount of added MAAnh to give a twofold (GM_2) or tenfold (GM_{10}) molar excess with respect to free amino groups present within unmodified gelatin. Additional functionalization with acetic anhydride (Sigma-Aldrich, Germany) (GM_xA_y, with x + y = 10) was established and also published elsewhere [14]. CSM was prepared using a fivefold molar excess of MAAnh with respect to free hydroxyl groups of unmodified CS. For gelatins the DM with regard to amino groups was determined by trinitrobenzene sulfonic acid as well as by quantitative ^{1}H-NMR analysis [12]. For CS, the DM with regard to disaccharide units was determined by ^{1}H NMR spectroscopy according to Tsai *et al.* (2008) [15].

Bioink preparation

Hydrogel precursor solutions (bioinks) with biopolymer concentrations of 10 wt%, 15 wt%, and 20 wt% were prepared by dissolving GM, GMA, and CSM in physiological phosphate buffer (PBS, pH 7.2) at 25 °C to 40 °C containing either 0.5 % (w/w to biopolymer mass) Irgacure® 2959 (I2959; Ciba AG, Suisse) or 0.2 % (w/w to biopolymer mass) lithium acylphosphinat (LAP, synthesis according to [16]).

Bioink Viscosity

Bioink viscosity was determined by rotary concentric cylinder rheometry using a Physica Modular Compact MCR301 Rheometer (Anton Paar, Germany) at shear rates from 10 s^{-1} to 1000 s^{-1} at 25 °C and 37 °C.

Cell and Hydrogel Bioprinting

For the present study two printing machines were used: (1) A sSingle nozzle microdispensing system based on piezoelectric inkjet technology (NanoplotterTM 2.1, GeSiM mbH, Germany), (2) a table-top robot for pneumatic volumetric dispensing (TR300, Unitechnologies, CH).

For printing experiments with viable mammalian cells applying the inkjet microdispensing system porcine articular chondrocytes were harvested by trypsinization and suspended in sterile GM(A) bioink to give a final concentration of 1,000,000 cells per mL [14]. GM hydrogels swollen in cell type-specific culture medium served as printing substrates. Dot patterns were printed at 25 °C with piezoelectric driving voltages ranging from 30 V to 70 V. After printing, cells were incubated in a humid atmosphere of 5 % CO_2 in air at 37 °C for 3-4 h to allow cell attachment. Subsequently, cell viability was monitored by fluorescencebased live/dead staining with fluoresceindiacetat (FDA) and (PI) (10 µL of 5 µg mL^{-1} FDA in acetone + 10 µL of 0.5 µg mL^{-1} PI in PBS + 980 µL PBS).

For gradient hydrogel printing applying the dispensing robot four GMA-CSM-bioinks were prepared: 15.0 wt% GM_5A_5, 14.5 wt% GM_5A_5 + 0.5 wt% CSM, 14.0 wt% GM_5A_5 + 1.0 wt% CSM, and 13.0 wt% GM_5A_5 + 2.5 wt% CSM. With each bioink three layers were printed, i.e. 4 x 3 layers in total, and each layer was cured by UVA irradiation (385 nm, ca. 8.5 mW cm^{-2}) for 90 s. Finally, the CSM gradient was visualized by alcian blue staining using the critical electrolyte concentration approach (0.3 M) on paraffin sections (6 µm).

Bulk Hydrogel Preparation and Characterization

Hydrogels with initial protein concentration of 10 wt% and 15 wt% of GM(A) and CSM were prepared by photo-initiated radical crosslinking (10 min irradiation, ~8.5 mW cm^{-2}, 365 nm) as described elsewhere [12, 14].

For determination of the water uptake freshly prepared hydrogels were washed (≥ 5 h, 37 °C, distilled water), vacuum-dried and then weighed to determine the mass of crosslinked protein m(gel). Then, hydrogels were swollen in PBS (pH 7.2, 37 °C, ≥ 8 h) and weighed again to determine $m(gel_{swollen})$. Degrees of swelling were calculated as

$$\text{degree of swelling [\%]} = \frac{m(gel_{swollen}) - m(gel)}{m(gel)} \times 100 \qquad (1)$$

Viscoelastic hydrogel properties were analyzed by oscillatory dynamic measurements (parallel plate model, swollen in PBS, 37 °C, 2 N, 1.5 Hz, 0.01 % $\leq \gamma \leq$ 100 %) using a Physica Modular Compact MCR301 Rheometer from Anton Paar (Germany).

Results and Discussion

Biopolymer Modification

Modified gelatin was prepared by chemical coupling of crosslinkable (“reactive”) methacrylic functions and non-crosslinkable (“inert”) acetyl functions to the biopolymer that is originally derived from collagen. Free amino groups, which are present in the biopolymer, were used for the coupling reaction.

Methacrylated gelatin (GM) was synthesized using methacrylic anhydride (MAAnh) in twofold (GM_2) or tenfold (GM_{10}) molar excess with respect to free amino groups of unmodified gelatin. The successful derivatization was verified by ^{1}H-NMR spectroscopy (data not shown). The extent of total conversion of free amino groups (degree of modification DM) was determined to 85 ± 11 % (n = 4) for GM_2 and nearly 100 % for GM_{10} (n = 3) by applying the TNBS assay.

Alternatively, gelatin was reacted with both, MAAnh and acetic anhydride (AcAnh) in twofold molar excess and eightfold molar excess, respectively (GM_2A_8). Thus, in sum this also represented an overall tenfold molar excess, yet, this time combining crosslinkable and non-crosslinkable functions. The successful derivatization was verified by ^{1}H-NMR spectroscopy and within the limits of resolution of NMR spectroscopy no effect of additional acetylation on the degree of methacrylation was observed when comparing GM_2 and GM_2A_8. The DM of methacrylated CS (CSM) was determined to 22.9 ± 6.2 % (n = 3).

Thus, modified gelatin biopolymers with high and low DM can be prepared, thereby masking certain portions of the amino groups which are present within the molecule. The groups inserted can either be able to form crosslinks as in the case of methacrylic functions or remain unreactive as in the case of acetyl functions.

We will now describe how the total DM affected the gelling behavior of the biomacromolecules as well as the viscosity of the solutions (bioinks) due to the masking of the free amino functions. Furthermore, the ratio of crosslinkable functions and non-crosslinkable functions determined the potential of the biomacromolecules to form stable hydrogels with high or low degrees of crosslinking.

Bioink Viscosity

Different printing technologies have different demands on the viscosity of the inks to be processed. For piezoelectric inkjet printing the viscosity should be sufficiently low, typically between 1 mPa s and 10 mPa s [10]. In contrast, dispensing technology can process gel inks with viscosities ranging from 30 mPa s to higher than 6×10^7 mPa s [11].

Solutions of unmodified gelatin and gelatin with low DM (GM_2) formed gels at 25 °C and thus were not printable using piezo electric inkjet printers (see Figure 1A). In contrast to this, solutions of the highly modified gelatins GM_{10} and GM_2A_8 remained liquid due to the prevention of the typical macromolecule triple helix formation assumingly because of the masking of amino group and steric hindrances. At 37 °C all gelatin solutions remained in the liquid state because triple helix formation is generally less at elevated temperatures.

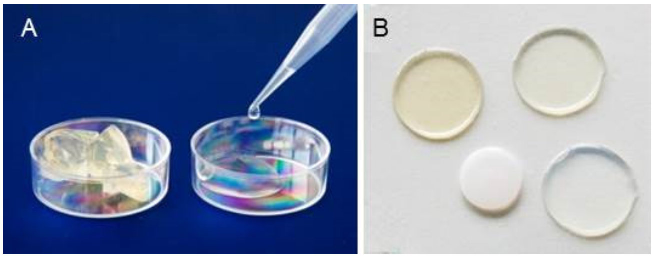

Figure 1: (A) Methacrylated gelatin with low degree of methacrylation without (left, GM_2) and with (right, GM_2A_8) additional acetylation at room temperature. (B) Chemically crosslinked hydrogels based on GM of different mass fraction (transparent) and based on GM and chondroitin sulfate (opaque).

Apart from the gelling behavior, the DM also affected the solution viscosity of gelatin solutions and mixed gelatin-chondroitin sulfate solutions.

Figure 2 shows the mean viscosity (averaged from shear rates from 10-1000 s^{-1}) of solutions made of unmodified gelatin and gelatin derivatives with and without CSM at 37 °C. Methacrylation as well as acetylation induced a significant decrease in solution viscosity, e.g. 45.3 ± 0.4 mPa s for 15 wt% unmodified gelatin, 39.3 ± 3.6 mPa s for 15 wt% GM_2, and 5.2 ± 0.5 mPa s for 15 wt% GM_2A_8. This effect was previously reported [12, 14].

Assumingly, the introduced methacrylic and acetyl groups induced weakening of the interaction between neighboring gelatin chains, thereby not only preventing gelation but also lowering the solutions' viscosity.

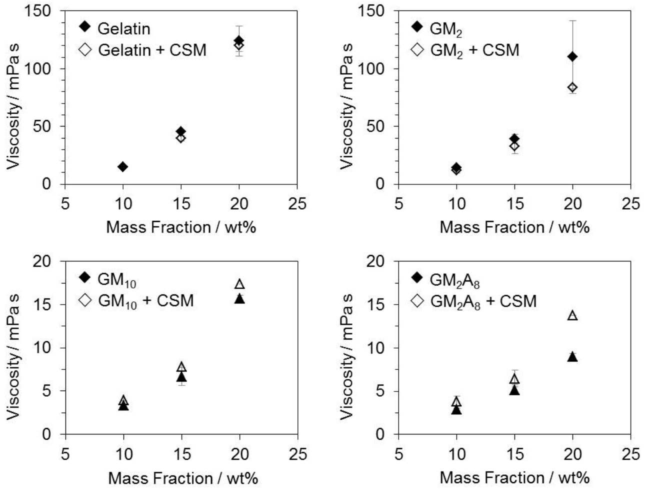

Figure 2: Mean dynamic viscosity (10-1000 s^{-1}, 37 °C) of bioinks with total biopolymer mass fraction of 10 wt%, 15 wt%, and 20 wt% comprising of methacrylated gelatin (GM_2, GM_{10}), methacrylated and acetylated gelatin (GM_2 A_8) or mixtures of GM or GMA with 1 wt% methacrylated chondroitin sulfate (CSM). Please notify the differences in the y-axis scale. Suffixes in $GM_x(A_y)$ denote the molar excess of reagent used for methacrylation and acetylation with respect to free amino groups. 1 ≤ n ≤ 5.

When comparing GM_2, GM_2A_8, and GM10 it becomes obvious that the total DM mainly determined the viscosity of the biopolymer solutions: Although gelatin derivatized with tenfold molar excess of MAAnh alone (GM_{10}) showed slightly smaller viscosities than gelatin derivatized with tenfold molar excess of MAAnh and AcAnh (GM_2A_8) in combination, these solutions behaved very much similar. In other words, viscosities of GM_2A_8 and GM_{10} solutions were in the same order of magnitude, while that of GM_2 solutions was determined to be one order of magnitude higher.

Solutions of unmodified gelatin and GM_2 with low DM, which both constituted high viscosities, became less viscous upon addition of CSM (e.g. 39.3 ± 3.6 mPa s for 15 wt% GM_2 versus 32.9 ± 6.5 mPa s for 14 wt% GM_2 + 1 wt% CSM). Apparently, CSM induced a decrease in macromonomer interaction when combined with gelatin in solution. In contrast to this, addition of CSM to gelatin with high DM (GM_{10} and GM_2A_8) induced an increase in solution viscosity (e.g. 5.2 ± 0.5 mPa s for 15 wt% GM_2A_8 versus 6.5 ± 1.0 mPa s for 14 wt% GM_2A_8 + 1 wt% CSM). Hence, in the case of solutions of gelatin derivatives with a priori reduced viscosity due to the masking of functional residues of the biopolymers, addition of an additional compound obviously increased the macromonomer interaction.

Our results showed that the chemical modification of the biomacromolecules as well as the composition of the biomolecule solution both profoundly affected the ink viscosity. By adjusting the DM of gelatin we can directly control the solution viscosity. Yet, when preparing bioinks consisting of various components the interaction between different biomolecules has also to be taken into account.

Hydrogel formation

The formation of insoluble hydrogels is achieved by addition of a photo-initiator and upon UV irradiation. The crosslinking capacity of the biopolymer solution is determined by the amount of crosslinkable methacrylic functions that are present within the solution.

We previously reported that in terms of hydrogel formation higher gelatin concentrations as well as higher degrees of methacrylation, both lead to an increase in the mechanical strength of crosslinked hydrogels. Simultaneously, the capacity of the biopolymer network to take up water (swellability) decreased. Both effects can be attributed to higher crosslinking densities, either due to the increased biopolymer mass fraction or due to the higher amount of crosslinkable groups per biomacromonomer.

Addition of CSM increased the hydrogels´ swellability while their mechanical strength remained unchanged. This effect can be ascribed to the high density of negatively charged functions in the chondroitin sulfate macromonomer and the corresponding counter ions, which generate a high osmotic pressure within the gels. The results will be published in more detail in a biomaterial oriented journal.

Bioprinting

With respect to the generation of tissue models by bioprinting technologies, we proofed that the developed bioinks were suitable for the two main printing technologies in bioprinting applications, inkjet printing and pneumatic dispensing technology.

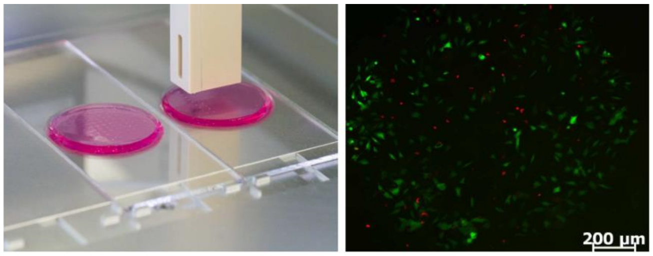

Figure 3: Inkjet printing of porcine chondrocytes suspended in 10 wt% GM_{10} bioink (1x10^6 cells per mL). Cells were printed onto swollen GM_{10} hydrogel substrates. 4 h after printing live/dead staining using FDA/PI allowed for determination of cell viability. GM = methacrylated gelatin, the suffix denotes the molar excess of reagent used for methacrylation with respect to free amino groups.

For inkjet printing, solutions with low viscosities are mandatory; therefore, we used GM_{10} bioinks with high DM for printing experiments. It is known that inks are exposed to high shear stress during drop formation and ejection [7]. In order to investigate potential mechanical damage of cells we added porcine chondrocytes to the bioink. Cell viability after inkjet printing was estimated by FDA/PI staining (see Figure 3). The inkjet deposited chondrocytes adhered to the substrate and developed the outstretched and flattened morphology that is typical for chondrocytes in 2D culture. Only very few dead cells (red) could be observed, but a high number of viable cells (green).

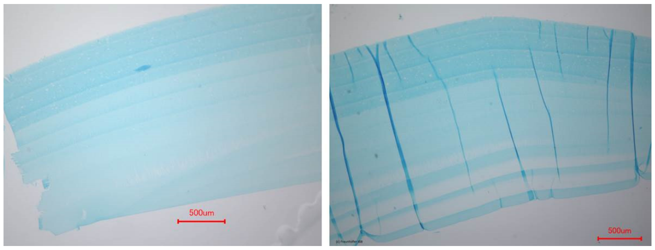

Figure 4: Alcian blue staining of 3D hydrogels with chondroitin sulfate gradient prepared by dispensing technology. 3D hydrogels were built by layer-by-layer deposition and crosslinking of four inks with different CSM content (highest content at the top, 4 x 3 layers).

These results indicate that the present inkjet printing system caused no significant mechanical damage to living chondrocytes and thus is generally applicable for processing viable cells. Furthermore, addition of cells caused no impairment of printability to the GM and GMA bioinks. Both aspects are major prerequisites for successful inkjet bioprinting of cell-laden bioinks.

For further printing experiments we used a dispensing robot. We achieved layer-by-layer assembly of 3D hydrogels with internal CSM gradient by placing bioinks with different CSM content on top of each other. 3D constructs were built by alternate printing and crosslinking by UVA irradiation. Critical electrolyte concentration staining of hydrogel paraffin sections using alcian blue allowed for visualization of the CSM gradient. Figure 4 shows that we were able to realize 3D hydrogels with discrete horizontal compartments of varying hydrogel composition, similar to the ECM of native articular cartilage.

Conclusion

Bioprinting application is a very promising approach to the generation of cell-laden matrices with defined pre-structure that will eventually mature to form functional artificial tissue. To exploit the full potential of the method sophisticated biomaterials, which are printable and crosslinkable and which hold ECM like physical, chemical, and biological properties are needed. Biomolecules from the native extracellular matrix constitute very promising materials as they hold important biological features such as natural signaling motifs to control cell behavior.

We established a versatile biomaterial system based on chemically modified gelatin and chondroitin sulfate that can be tuned to fulfill the demands of different 3D printing technologies, e.g. inkjet printing or dispensing. Twofold chemical modification of gelatin allowed for decoupling the control of the gelling behavior, solution viscosity, and the mechanical properties of the resulting chemically crosslinked hydrogels. The swellability of crosslinked hydrogels was additionally increased by addition of the highly charged glycosaminoglyvcane chondroitin sulfate.

The developed bioinks based on componants of the native ECM proved to be printable using piezoelectric inkjet printing and pneumatic dispensing. They were also non-toxic for porcine chondrocytes and allowed for fabrication of 3D hydrogel constructs with zonal intrinsic structure.

We conclude that gelatin and chondroitin sulfate based bioinks constitute promising precursors for future tissue assembly, particularly aiming at zonal cartilage tissue engineering.

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Author Biographies

Dr. Eva Hoch (1982) studied Biological Chemistry at the University of Applied Sciences in Mannheim. Her diploma thesis at the Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB in Stuttgart focused on the preparation and characterization of cell culture substrates for selective cultivation of skin keratinocytes. In 2013 she finished her PhD at the University of Stuttgart, which dealt with the development of functional biomaterials for fabrication of biomimetic articular cartilage applying 3D printing technology. Since then she continues her bioprinting activities at Stuttgart University as holder of a postdoc scholarship from the Peter and Traudl Engelhorn Stiftung.

Dr. Achim Weber, studied chemistry at the University of Stuttgart. In 2000 he joined the Fraunhofer Institute of Interfacial Engineering & Biotechnology (IGB) as a scientist and project manager, and the

Institute for Interfacial Engineering (IGVT) at the University of Stuttgart. In 2006 he became a Group Manager and since 2011 he is Deputy Head of the Department of Interfacial Engineering and Material Science at the Fraunhofer IGB. His main interest is the forming and understanding of smart and nanoscopic materials and its surfaces for applications in Pharmacy, Medicine, Environment, Material and Biotechnology.

Dr. Kirsten Borchers (1971) started her university courses with the idea to become a secondary school teacher in biology, physics and mathematics. After her exams she decided to stick to scientific work and prepared her PhD thesis at the University of Stuttgart. Since 2007 she works with the Fraunhofer Institute for Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB in Stuttgart being part of the department Interfacial Engineering and Material Science and since 2012 she gives biomaterial lectures at the University of Stuttgart. Her special interest is in the development of biomaterials for bioprinting applications and for surface biofunctionalization - in particular focusing on biomimetic biomaterials based completely on biological materials such as components from the native extracellular matrix (ECM) and cells.