Biologie-inspirierte Grenzflächen- und Materialgestaltung

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Die Aufklärung der Funktionalität lebender Materie erlaubt es, bisher unerreichte Materialcharakteristika in synthetischen Polymersystemen nachzuvollziehen und damit Lösungsansätze für zentrale Herausforderungen auf den Gebieten Gesundheit, Ressourceneffizienz und Nachhaltigkeit zu entwickeln. Das IPF untersucht dazu fundamentale Wechselwirkungsprozesse an Materialgrenzflächen im Kontakt mit Biosystemen, entwickelt bioaktive Funktionsschichten sowie multifunktionelle Polymermatrices und adaptiert Ansätze der chemischen Biologie und der Bionanotechnologie für neue Biomaterialkonzepte.

2011 konnten besondere Fortschritte bei der Erkundung antiadhäsiver Oberflächen von Collembolen (hautatmenden, insektenartigen Lebewesen) erreicht werden (Helbig et al., *PLoS One* 6 (2011) e25105). Es wurde gezeigt, dass die nanoskalige Morphologie der Cuticula dieser Organismen ihre erstaunliche Resistenz gegen Benetzung und (Partikel- und Bakterien-) Adhäsion ebenso wie die mechanische Stabilität erklären lässt und damit eine interessante Vorlage für die antiadhäsive Oberflächenmodifizierung von Materialien bildet. Ein molekulares Konzept zur Minimierung der Bioadhäsion, die Immobilisierung proteolytischer Enzyme über reaktive Polymerfilme, erwies sich im marinen Milieu als äußerst effektiv, was im EU-Projekt Advanced Nanostructured Surfaces for the Control of Biofouling (AMBIO) vielfältig genutzt werden konnte (Tasso et al., *Advanced Functional Materials* 22 (2012) 39).

Die Entwicklung vielfältig anpassbarer Biohybrid-Hydrogele und deren Einsatz bildeten einen Schwerpunkt unserer Forschungsarbeiten in Verbindung mit dem Exzellenzcluster für Regenerative Therapien Dresden (CRTD) und dem Innovationszentrum für Molecular Bioengineering (B CUBE) an der TU Dresden. Die Nutzung von Kraftfeldmethoden zur theoretischen Identifizierung von Geleigenschaften (Sommer et al., *Macromolecules* 44 (2011) 981) ermöglichte hier erstmalig eine Entkopplung der biomolekularen und physikalischen Signalcharakteristik (Freudenberg et al., *Advanced Functional Materials*, in press 2012). Bioresponsive Gelmaterialien, die Wachstumsfaktoren lokal bereitstellen (Zieris et al., *Journal of Controlled Release* 149 (2011) 28) und mit deren Hilfe z. B. die Bildung kapillarer Blutgefäße (Angiogenese) in vivo stimuliert werden kann (Chwalek et al., *Biomaterials* 32 (2011) 9649), finden auch im EU-Projekt Angiogenesis-inducing Bioactive and Bioresponsive Scaffolds in Tissue Engineering (ANGIOSCAFF) bei der Erkundung neuer Therapieansätze Anwendung. Die Nutzung dendritischer Strukturen als Biomaterialien und Wirkstoffträger sowie in Hydrogelschichten wurde weiter vorangebracht (*Journal of Controlled Release* 149 (2011) 146; *Biomaterials* 12 (2011) 3903) und es wurden erstmalig photovernetzbare und stabile Polymersome als potentielle Carrier und nanoskalige Materialien für die synthetische Biologie etabliert (Chemical Communications 47 (2011) 3466).

Zu den 2011 gestarteten Projekten gehören das im Wettbewerbsverfahren der Leibnizgemeinschaft eingeworbenes Projekt Multifunctional Polymer Matrices to Direct Virus-free Cell Reprogramming (mit CRTD und B CUBE) und das EU-Projekt Human Kidney Stem Cells for Use in Drug Discovery and Regenerative Therapy (NEPHROTOOLS).

Tilo Pompe ist 2011 dem Ruf auf eine W2-Professur für Biophysikalische Chemie an der Universität Leipzig gefolgt.

Eine Reihe von Graduierungsarbeiten wurde abgeschlossen, darunter die mit dem Prädikat „summa cum laude" ausgezeichnete Arbeit *Decellularised extracellular matrices as instructive microenvironments for bone marrow derived stem cells* von Marina Prewitz (im Rahmen der International Graduate School für Biomedicine and Bioengineering, gefördert im SFB 655 From Cells to Tissues).

Biologie-inspirierte Grenzflächen- und Materialgestaltung

Generation and characterization of native extracellular matrix microenvironments to support *ex-vivo* stem cell propagation

Marina Prewitz, Philipp Seib, Jens Friedrichs, Carsten Werner

The regenerative potential of adult mesenchymal and haematopoietic stem cell populations (MSC and HSC) from human bone marrow (BM) offers great promise for regenerative medicine. To successfully expand these cells *ex vivo*, both differentiation and stem cell maintenance need to be controlled. To achieve this end, biomaterials are aiming to mimic the natural BM niche.

To investigate the complexity of the stem cell microenvironment, extracellular matrices (ECM) were generated from decellularized MSC cultures (Figure 1). Reliable stability of the MSC-derived matrices was achieved by maleic anhydride co-polymer-mediated covalent binding of fibronectin to the culture surface. The cell-secreted ECM molecules bind to the immobilized fibronectin, which serves as a coupling layer for ECM anchorage to the culture carrier. The ECM scaffolds are highly organised into suprastructures, and demonstrate very soft elastic properties. Mass spectrometric proteomic characterization of MSC-derived ECM revealed the high complexity of the ECM microenvironment. *In vitro* culture experiments with MSC and HSC in contract with the generated microenvironment allowed the control of cell fate in terms of cell adhesion, proliferation and differentiation. In summary, the mass spectrometry data provides the groundwork for a more rational design of artificial stem cell niches with defined and distinct properties, offering exciting options for the in-depth analysis and understanding of stem cell regulation by exogenous cues.

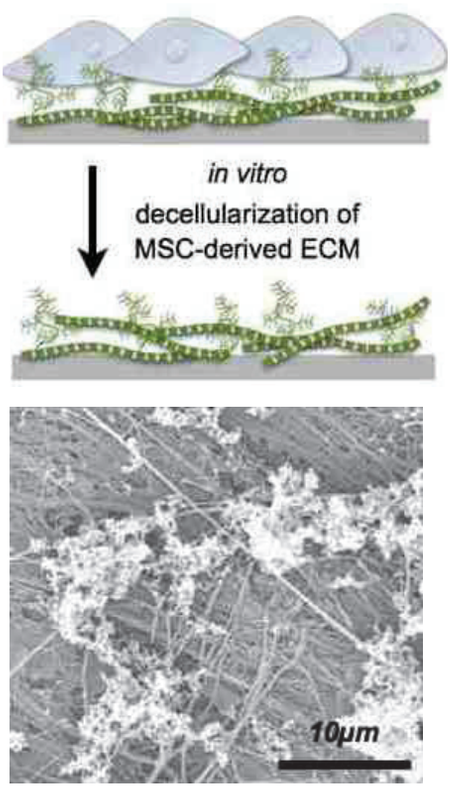

Fig. 1:
Bone marrow mesenchymal stem cells have been utilized to generate in vitro ECM microenvironments by decellularization. Scanning electron microscopy reveals the suprastructural complexity of the ECM scaffolds remaining after decellularization.

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SFB 655 - Cells into tissues.

Cooperation:
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B. Hoflack, C. Niehage (Mass spectrometry), Center for Regenerative Therapies Dresden, Technical University, Dresden

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Thrombin-responsive hydrogels: feedback-controlled anticoagulant coatings

Manfred Maitz, Uwe Freudenberg, Mikhail Tsurkan, Thomas Beyrich, Carsten Werner

Blood coagulation on foreign surfaces still presents a hazard when medical devices are used in contact with streaming blood. This problem is handled clinically by the systemic application of anticoagulants, which results in a substantial risk of bleeding complications. However, the current approach from materials science focuses on the control of physical-chemical surface properties of the materials and on the immobilization or controlled release of anticoagulants.

Surface coating with heparin to reduce blood coagulation has a long tradition. Heparin is an indirect inhibitor and catalyses the inhibition of coagulation factors like thrombin by the physiological inhibitor protein antithrombin. Steric accessibility of heparin for the two proteins is a prerequisite for the success of this type of coating. This accessibility as well as limitations in the immobilized inhibitor amount, non-controlled desorption and pre-term consumption, frequently limit the efficiency of heparin coatings [1]. Conceptually, well-accessible heparin molecules within the coating and a localized release of the anticoagulant in doses, precisely adjusted to the actual coagulation activity, could provide a more durable and efficient coating and reduce side effects of the systemic application of anticoagulants.

To address these issues, heparin was applied within a functional hydrogel coating, formed by covalent linkage of heparin to four-armed poly(ethylene glycol) (starPEG) using a thrombin cleavable peptide linker, based on the specific sequence (D)Phe-Pip-Arg-X. The cross-linking degree and mesh size in this system, and thus the accessibility of heparin for proteins can be tuned upon maintaining a constant heparin concentration in the hydrogel.[2,3]. The introduction of a cleavable peptide as a cross-linker induces a feedback control loop: Thrombin, generated during coagulation, cleaves the peptide in the gel. These causes a release of heparin into the liquid phase, where it efficiently catalyses the inhibition of thrombin by antithrombin, blocks the coagulation and terminates further degradation of the gel (Figure 1).

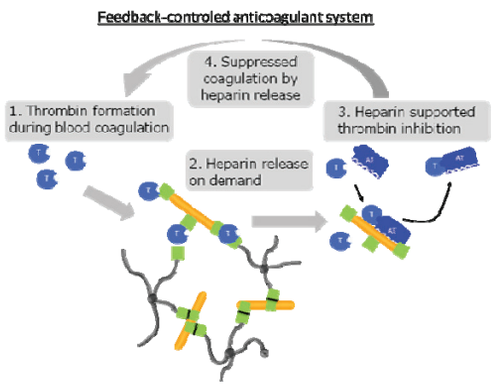
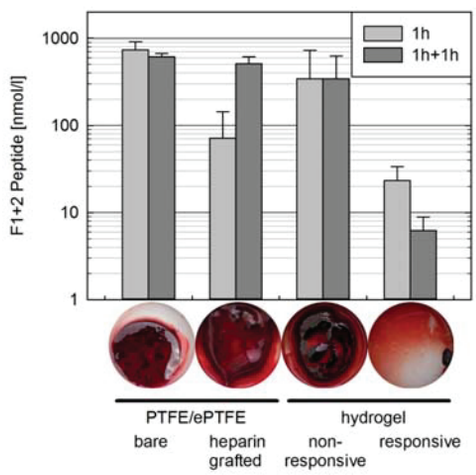


Fig. 1:
Autoregulation of anticoagulant starPEG-heparin hydrogels containing thrombin sensitive cross-linker units.

The thrombin dependent degradation of gels with the responsive peptide, at various degrees of cross-linking, was tested in physiologically relevant concentrations (from 2 to 45 nmol/l) of thrombin solutions. The release kinetics were linear for more than 12 hours, and the released heparin scaled with the crosslinking degree and with the thrombin concentration. This responsive hydrogel thus fulfills the prerequisites for the feedback loop system.

To confirm the effect of the feedback controlled material, we tested the thrombin responsive hydrogel system in freshly drawn non-anticoagulated blood in comparison to non-responsive hydrogels and clinically applied, expanded poly(tetrafluoro ethylene) grafts with or without heparin coating (Carmeda®/Propathen® and GoreTex®) during incubation times of up to three hours. The blood remained liquid in contact with the responsive hydrogel. In contrast, massive blood clots were formed in contact with the other surfaces. Furthermore, we simulated the *in vivo* situation, where material surfaces are permanently in contact with fresh blood. We exposed the surfaces to non-anticoagulated fresh blood and replaced it after one hour with fresh blood and incubated for another hour under the same

conditions. Again, after the second exposure, blood in contact with the thrombin responsive hydrogels remained liquid, whereas blood on the other surfaces coagulated. The prothrombin F1+2 fragment, a quantitative coagulation marker, confirmed the macroscopic observation (Figure 2).



The presented hydrogel system with the coagulation-responsive release of the anticoagulant heparin thus showed an outstanding performance under demanding and realistic whole-blood conditions. The subsequent transfer of the principle to other coagulation factors or other classes of coagulation inhibitors should be straightforward.

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Leibniz Association

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Fabricating microcavity arrays of biohybrid gel materials

Eike Müller, Stefan Gramm, Tilo Pompe, Uwe Freudenberg, Carsten Werner

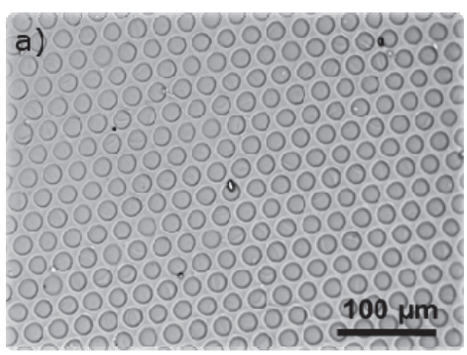
Biofunctional materials play a substantial role in advanced strategies of tissue engineering and regenerative medicine and are therefore extensively explored as functional scaffolds for cell culture applications [1]. In nature, the extracellular matrix (ECM), a highly hydrated and complex cellular microenvironment, provides mechanical and structural support as well as multiple biochemical signals that regulate cell function and fate. Synthetic materials mimicking, modulating and overexpressing specific characteristics of the ECM could improve the regenerative potential of cells and contribute towards successful therapeutic applications. Highly hydrated and modular tunable polymer networks, e.g. hydrogels, have been developed and investigated for this purpose for several years. To include spatial cues, hydrogel micropatterning has been extensively studied in the past using several different types of hydrophilic polymers and methodologies. However, most of the currently used hydrogel systems do not form well-defined micro-structures due to restrictions in chemical composition, extensive swelling and mechanical fragility.

To overcome these limitations, we have developed a novel gentle and reliable method to micropattern ECM-inspired soft biohybrid hydrogels of varying composition and mechanical characteristics. We used a chemically crosslinked hydrogel, composed of amino end-functionalized star-shaped poly(ethylene-glycol) (starPEG) and the highly sulphated glycosaminoglycan heparin [2]. As a key feature, the gelation process was performed on top of polystyrene microstructures, produced by solvent assisted micromoulding. After hydrogel formation, the polystyrene microstructures were dissolved completely. Using this approach, we were able to cast hydrogel microwell arrays of tunable stiffness in the range of 0.5-4.5 kPa (G') with

Fig. 2:
Test of the thrombin responsive hydrogel system in freshly drawn non-anticoagulated blood and non-responsive hydrogels

Biologie-inspirierte Grenzflächen- und Materialgestaltung

cavity diameters from 10 to 100 µm and well depths of up to 30 µm (Fig.1). Furthermore, the well frequency was maximized by decreasing the strip width to 3 µm without impairing mechanical stability. Subsequently the heparin component of the hydrogel was used for covalent conjugation of cell adhesion ligands (e.g. RGD-peptide) and non-covalent loading with heparin binding growth factors.



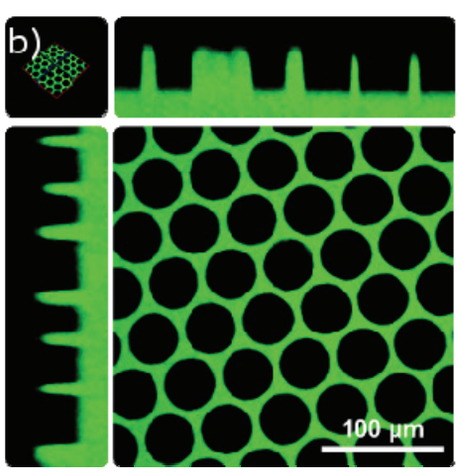


Fig. 1:
a) Brightfield microscopy image of a starPEG-heparin hydrogel microcavity array with a depth of 10 µm and a cavity diameter of 20 µm.
b) Confocal laser scanning microscopy (CLSM) image of micropatterned starPEG-heparin hydrogel containing Alexa 488 labelled heparin. The micro-well array had a depth of 10 µm and a cavity diameter of 40 µm.

Besides a systematic physicochemical analysis of the hydrogel arrays created with this micropatterning process, preliminary cell experiments were performed. Human endothelial cells as well as immunomagnetically isolated CD133 positive hematopoietic stem and progenitor cells (HSPCs) from peripheral blood of healthy donors were cultured *in vitro* on biofunctionalized microstructured hydrogel scaffolds (Fig. 2). Initial experiments indicated promising characteristics of these microstructured biohybrid hydrogel scaffolds for *in vitro* cell culture use.

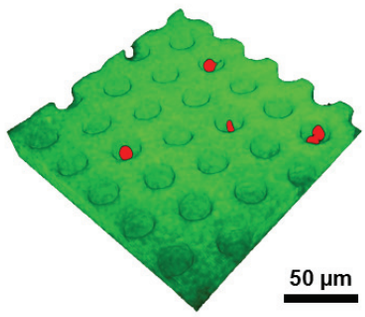


Fig.2:
CLSM image of Alexa 488 labelled micropatterned sPEG-heparin hydrogel (green) with paraformaldehyde (PFA) fixed and propidium iodide (PI) stained CD133 positive HSPCs (red) in 20 µm cavities.

Ongoing research using the presented hydrogel platform investigates the impact of the artificial bio-inspired microstructured surfaces and the presentation of growth factors on cell signalling events with a specific focus on (stem) cell fate. Proliferation and differentiation behaviour of different cells types is studied using immunofluorescence and flow cytometry.

Sponsor:
Bundesministerium für Bildung und Forschung, DFG

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Biologie-inspirierte Grenzflächen- und Materialgestaltung

Stimuli responsive polymer films to harvest human corneal endothelial cell sheets

Juliane Teichmann, Stefan Gramm, Mirko Nitschke, Carsten Werner

Corneal endothelial cells form the inner monolayer of the cornea. They regulate corneal hydration by eliciting fluid transport via ion pumps from the corneal stroma into the anterior chamber, thus maintaining corneal transparency. Corneal dystrophies and injuries (e.g. after refractive surgery) may affect the corneal endothelium and compromise its crucial function, resulting in corneal edema and opacification (blinding of the affected eye). At present, the only available therapy is the transplantation of corneal tissue (keratoplasty).

Our goal is to provide transplantable human corneal endothelial cell (HCEC) sheets by stimulated detachment of an *in vitro* generated tissue culture. For that purpose cell culture carriers with temperature-responsive polymer coatings and tunable biochemical and mechanical properties were used as a substratum for the cultivation and enzyme-free harvest of HCEC. Sheets may be used as transplants to restore a degenerated corneal endothelium, and hence may help to overcome the shortage of donor corneas.

HCEC were cultured on thin films of poly(vinyl methyl ether) (PVME, temperature-responsive component) blended with 1 wt% or 10 wt% of a reactive alternating copolymer of [PVME-*alt*-maleic-anhydride] (PVME-MA, protein/ peptide binding component) [1]. Different amounts of MA units allowed for a biomolecular functionalisation by covalent attachment of laminin/ chondroitin-6-sulfate, collagen type IV, fibronectin, or cyclic RGD peptide (cRGD). Polymer components were cross-linked by electron beam irradiation. Film thickness and degree of cross-linking were varied to tune the mechanical properties. HCEC (cell lines [2], [3]) were cultured on the polymer substrates. The aptitude of the different polymer blends to support HCEC growth and sheet harvest was compared by monitoring cell adhesion, proliferation before and cell detachment after lowering the temperature.

HCEC behaviour depended on the interplay of key properties of the polymer-coated surfaces, such as the mechanical characteristics (degree of cross linking and dry film thickness), degree of biomolecular functionalisation and type of bioactive molecule. HCEC tended to adhere better on temperature responsive polymer surfaces with a high degree of cross-linking, a low dry film thickness (approx. 50 nm), and a high content of PVME-MA in the blend (10 wt%), i.e. a high protein/ peptide coverage. In contrast, surfaces with a low degree of cross-linking, a high dry film thickness (approx. 300 nm), and a low content of PVME-MA in the blend (1 wt%) seemed to preferably support the detachment of HCEC upon temperature decrease. Likewise, while a pre-coating with laminin/ chondroitin-6-sulfate permitted weakest initial cell adhesion, cell detachment from these surfaces was superior compared to other tested protein/ peptide coating. In contrast, cRGD coating supported cell adhesion best, but diminished cell detachment.

HCEC can be grown and harvested as sheets on temperature-responsive polymer surfaces. By tuning key properties of temperature-responsive polymers we created a flexible system to control cell adhesion, monolayer formation and detachment of HCEC sheets upon temperature reduction. This technique allows for the enzyme-free harvest of cell sheets, which might be used for clinical applications to create new corneal endothelium either for transfer onto unsuitable corneal donor tissue or otherwise for transplantation into the patient eye in the future.

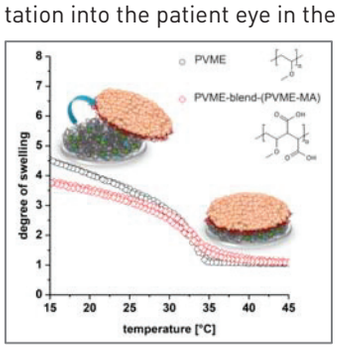

Fig. 1:
Temperature dependent swelling behaviour of immobilized thin films composed of either PVME or PVME blended with 10% wt/wt PVME-MA during heating and cooling

Biologie-inspirierte Grenzflächen- und Materialgestaltung

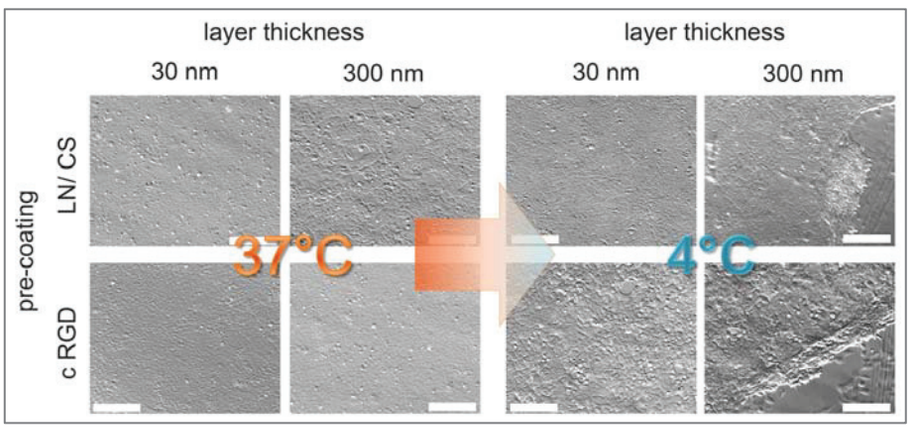

Fig. 2:
Adhesion and detachment of HCEC after four days of cultivation on polymer films of PVME blended with 10% wt/wt PVME-MA, a high degree of cross-linking and different covalent biomolecular functionalization.

Sponsor:
Deutsche Forschungsgemeinschaft: EN 168/13-1; NI 709/4-1

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Biologie-inspirierte Grenzflächen- und Materialgestaltung

Photo cross-linked and pH-sensitive polymersomes as carrier systems for bionanotechnology

Jens Gaitzsch, Mohamed Yassin, Dieter Appelhans, Brigitte Voit

In the past decade studies comprising the use of synthetic membranes to achieve a better understanding of biological processses rose considerably. For example amphiphilic block copolymers are able to form vesicles out of such membranes. These structures, so-called polymersomes, are promising and versatile candidates for applications in biomedical sciences. The formation of those specific vesicles is tailored by the right ratio of block lengths between longer hydrophobic and shorter hydrophilic block length within the amphiphilic block copolymers. Their polymeric nature is attributed by a high stability under various environmental conditions due to the great variety of monomers. In this context we are interested in designing polymersomes which are stable over a wide pH range (2-10) and addressable for swelling/deswelling behaviour to tune selective polymersomes membrane diffusion processes (Fig. 1). To achieve those specific molecular properties of our vesicles we prepared photo cross-linked and pH sensitive polymersomes, which are usable as smart targeting carriers as well as synthetic bionanorectors.

For this purpose we synthesised amphiphilic block copolymers, consisting of the biocompatible poly(ethylene glycol) (PEG) as the hydrophilic component. The basis for the hydrophobic part is the pH sensitive poly[2-(diethylamino) ethyl methacrylate (PDEAM), which is mixed statistically with a photo cross-linkable monomer. For comparison reasons, we used a benzophenone and a maleic imide based cross-linker. Within the resulting polymersomes, the PDEAM provides a pH sensitivity around pH 7 and both photo cross-linkers provide stable polymersomes against lower pH. Upon applying UV irradiation, which was optimized from 80 minutes to 30 seconds, efficient photo cross-linking of the polymersomes was achieved which depends on various parameters (UV source, spacer lengths in cross-linker unit etc.). Recent progresses allow us to incorporate various bio-active macromolecules during the polymersome formation (Fig. 1) upon final shortest UV irradiation treatment (← 1 minute) and dialysis as purification step.

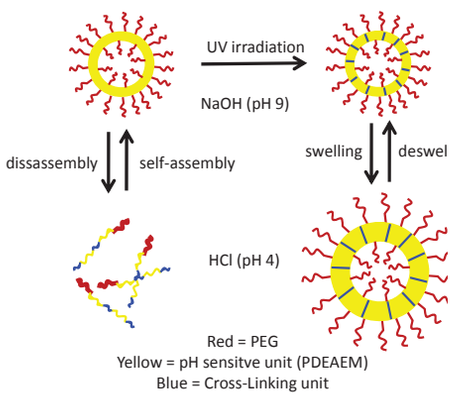

Fig. 1:
Polymersome formation starting from single block copolymer at pH 4 and final switching to pH 9 (left part). Usually, pH sensitive polymersomes disassemble upon acidification (left part), while ours remain intact and show a definite swelling/deswelling after UV irradiation (right part).

Generally our polymersomes have a size of 120 nm, if created in acidic water. In opposite to that use of electroformation yielded vesicles of up to 200 µm in diameter. Until now, only polymersomes prepared in acidic water are suited for further detailed characterization and potential application steps.

Depending on the cross-linker unit, the vesicles undergo a reversible swelling up to 160-200 nm at lower pH, due to protonation of the membrane. Consequently, controlled diffusion of dyes[1] or bio-active macromolecules through membrane could be proven. As first proof of principle, ribavirin, a component of the only available treatment for Hepatitis C virus, has been encapsulated in our polymersomes which revealed the ability to sustain the release of ribavirin.

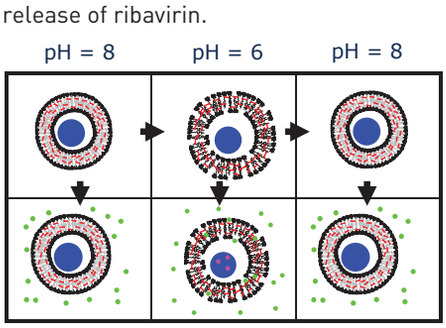

Fig. 1:
Scheme, indicating how enzymatic reactions within polymersomes can be triggered by using pH switches. Top: From left to right for pH switches from pH 8 over pH 6 to pH 8. Bottom: Upon addition of reagents at each pH state only enzyme-tic activity observable at pH 6.

Biologie-inspirierte Grenzflächen- und Materialgestaltung

Furthermore, as an example of encapsulation of a functional bioactive macromolecule, we enclosed myoglobin which does not suffer any larger damage by applying shortest UV irradiation for 30 seconds. Myoglobin functionality was assessed by treatment with guaiacol and hydrogen peroxide (Fig. 2). While activity was observed at pH 6, when the polymersome were at an acidic state and open for diffusion, no reaction was monitored for pH 8.

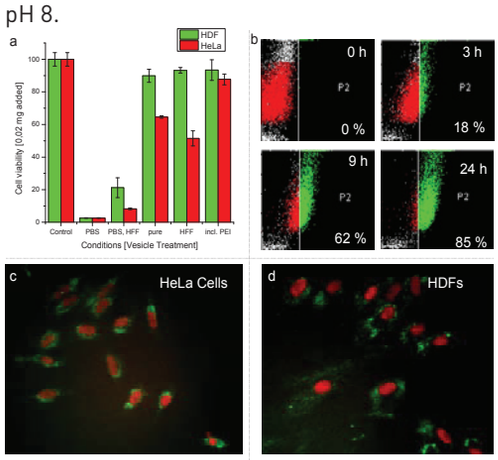

Fig. 3:
(a) MTT Test of polymersomes applied onto cells at different conditions (b) Cellular uptake analysis of polymersomes (c). Fluorescence microscopical images of polymersomes, after applied on the HeLa cell line and (d) human dermal fibroplasts

In our aim to provide a biocompatible system, our polymersomes were also applied onto cells. Here, the polymersomes proved to be non-toxic, also at higher concentrations (Fig. 3).
Finally, we created versatile polymersomes, which are capable to utilize as a drug delivery system as well as a bionanoreactor for applications in synthetic biology.

Sponsor:
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Cooperation:
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A. Temme, Universitätsklinikum Dresden
P. Schwille, Biotechnological Centre of TU Dresden

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In-situ-ATR-FTIR-Untersuchungen zur Abscheidung bioinspirierter Polydopamin-Schichten

Martin Müller, Bernd Keßler, Bernhard Torger

Muscheln haften an Oberflächen über sogenannte Byssusfäden. Byssus oder Muschelseide ist ein Sekret aus Fußdrüsen von Muscheln und setzt sich aus phenolischen Proteiden oder Proteinen mit einem hohen Anteil der Aminosäure L-Dihydroxyphenylalanin (L-DOPA) zusammen. L-DOPA kann reaktive vernetzende Biopolymerisate bilden. Das kann auch das strukturverwandte Dopamin (DA, Abb. 1), ein Neurotransmitter, welches durch Sorption aus der Lösung an einer Vielzahl von Oberflächen zu bioinspirierten vernetzten Polydopamin-(PDA)-Filmen (≈ 50 nm) mit interessantem Anwendungspotential führt [1]. Dabei wird über eine Reihe von Oxidationsschritten aus DA das reaktive Monomer 5,6-Indolchinon (IC, Abb. 1, Mitte) gebildet. Unklarheit besteht aber über den folgenden Polymerisationsmechanismus an Oberflächen und die genaue Struktur des PDA, das ähnliche Strukturelemente wie das Hautpigment Melanin aufweisen soll.
Daher wurde von uns dieser interessante und reproduzierbare schichtbildende Prozess erstmalig über zeitabhängige in-situ ATR-FTIR-Spektroskopie an Modellsubstraten unter Variation der Einflussfaktoren pH, Ionenstärke, Substrattyp und Sauerstoffangebot untersucht [2]. In der Abb. 1 ist ein Ergebnis zur pH-Abhängigkeit der PDA-Abscheidung an Germanium gezeigt, wobei bei pH=8.5 zeitabhängig ATR-FTIR-Spektren mit zunehmenden Signalen bei 1490 und 1250 cm^{-1} (Polyphenole), während bei pH=6.2 keine signifikanten Signale erhalten wurden. Die ATR-FTIR-Spektren dieser PDA-Schichten weichen aber stark von denen eines synthetischen Melanins ab. Weiterhin konnte die PDA-Abscheidung in Abhängigkeit der Zeit und der Konzentration mit dem Langmuir-Modell beschrieben werden (Abb. 1, rechts). Es zeigte sich, dass vorgebildete reaktive PDA-Partikel eine Rolle spielen.

Biologie-inspirierte Grenzflächen- und Materialgestaltung

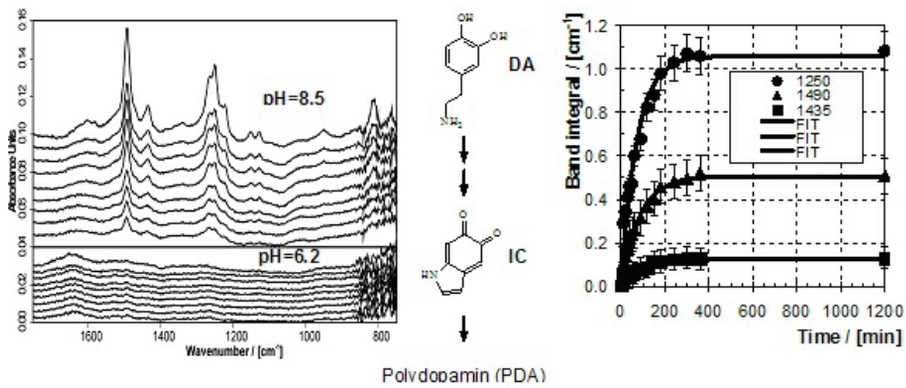

Abb. 1:
In-situ-ATR-FTIR-Spektren zur zeitabhängigen Abscheidung von Polydopaminschichten auf einem Ge-Modellsubstrat bei pH=8.5 und pH=6.2 (links). Vorgeschlagener Reaktionsmechanismus auf der Monomerebene (Mitte). Auftragung der IR-Bandenintegrale bei 1490, 1435 und 1250 cm-1 gegen die Zeit (rechts).

PDA-Schichten haben Anwendungspotential als UV-Schutz und werden von uns im Rahmen bioverwandter Depotschichten für Arzneistoffe untersucht.

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[1] H. Lee, S. M. Delatore, W. M. Miller, P. B. Messersmith, Science 2007, 318, 426
[2] M. Müller, B. Keßler, Langmuir 2011, 27, 12499