Biologie-inspirierte Grenzflächen- und Materialgestaltung

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Multifunktionelle Polymermatrices sind für neue Therapieansätze der regenerativen Medizin von entscheidender Bedeutung. Arbeitsgruppen des IPF konnten hierzu in den letzten Jahren zell-instruktive Biohybrid-Hydrogele auf Glykosaminoglykan-Basis entwickeln, die es erlauben sowohl biophysikalische als auch biomolekulare Matrixeigenschaften systematisch zu variieren und für spezifische therapeutische Fragestellungen anzupassen. Dabei bieten die lokalisierte Bereitstellung und funktionelle Stabilisierung von Wachstumsfaktoren besondere Möglichkeiten. 2015 war es davon ausgehend im Transregio-Sonderforschungsbereich 67 möglich, durch Abstufung der Sulfatierungsmuster von Glykosaminoglykan-Hydrogelen die Differenzierung von dermalen Fibroblasten gezielt zu stimulieren (Acta Biomaterialia 25, 2015, 65-75) sowie die Applikation von angiogenesefördernden Wachstumsfaktoren zu optimieren und damit die dermale Wundheilung im Tiermodell signifikant zu verbessern (Journal of Controlled Release 220, 2015, 79-88). Makroporöse Cryogel-Partikel, die durch Gelierung der Gel-Prekursoren in wässrigen Medien unter Anwesenheit von Eiskristallen erhalten werden, erwiesen sich als geeignet um eine schonendere Transplantationsmethode für neuronale Zellen zu etablieren (Small 11, 2015, 5047-5053), was wertvolle neue Möglichkeiten für die Therapie des Morbus Parkinson eröffnet, insbesondere wenn künftig auch die dopaminerge Stimulation von Zellen durch biomolekulare Funktionalisierung der Gel-Matrices einbezogen wird (Biomaterials 67, 2015, 205-213).
Neben der Nutzung in therapeutischen Ansätzen des Tissue Engineering konnten Biohybrid-Hydrogele auch vorteilhaft zur Entwicklung von antikoagulanten und antimikrobiellen Beschichtungen von blutkontaktierenden Medizinprodukten (Biomaterials 56, 2015, 198-205) und von dreidimensionalen Kokulturen humaner Primärzellen als realistischerer *in vitro* Tumormodelle herangezogen werden. Die Aussagekraft eines in dieser Weise etablierten *in vitro* Modells der Vaskularisierung von dreidimensionalen, aus Brustkrebszellen gebildeten Strukturen wurde anhand des Vergleichs mit klinischen Daten zur Wirksamkeit von Medikamenten eindrucksvoll belegt (Biomaterials, 2015, 53:609-20).
Polymer-basierte Konzepte kamen auch bei der Integration dendritischer Kern-Schale-Architekturen in Knochenzementen zur verzögerten Freisetzung des Proteasominhibitors Bortezomib für die Abtötung von Krebszellen des multiplen Myeloms zum Einsatz (Macromol. Biosci., 2015). Die besten Ergebnisse lieferten hier neuartige Kern-Doppelschale-Architekturen mit einem dendritischen Polyethylenimin-Kern und einer Zucker- und Polypeptid-Schale (Polymer, in print, 2016).
Effektive exogene Steuerung von Stamm- und Vorläuferzellen *in vitro* ist eine zentrale Herausforderung aktueller biotechnologischer Forschung. Mit 2015 am IPF erhaltenen Ergebnissen konnten die Möglichkeiten der physikalischen Kontrolle von Stammzellen des Knochenmarkraums weitergehend belegt werden. In Kooperation mit Partnern am CRTD, am BIOTEC und am Universitätsklinikum der TU Dresden wurden Blutstammzellen unter den Bedingungen definierter räumlicher Einschränkung (Biomaterials 53, 2015, 709-715) und im Kontakt mit nach dem Prinzip des Macromolecular Crowding erhaltenen dezellularisierten Extrazellulärmatrices (Biomaterials, 2015, 73:60-9) kultiviert sowie hinsichtlich ihrer adhäsiven Wechselwirkungen quantitativ untersucht (Scientific Reports 5, 2015, article nr.: 15680). In Zusammenarbeit mit Partnern am MPIKG Potsdam konnte die Bedeutung der Verfügbarkeit von Matrixproteinen und des Differenzierungsstatus der Zellen für das dreidimensionale Wachstum von mesenchymalen Stromazellen in Mikrokanälen gezeigt werden (Biomaterials 60, 2015, 121-129).
B CUBE, das BMBF-Innovationszentrum für Molekulare Bioingenieurswissenschaft an der TU Dresden, und das Max-Bergmann-Zentrum für Biomaterialien organisierten im September 2015 gemeinsam das internationale Symposium Engineering Life 'Synthetic Biology meets Bioinspired Materials'.
Mit Laura Bray, die den Lush Prize für die Vermeidung von Tierversuchen erhielt (www.lushprize.org/2015-prize-winners), und Benjamin Newland, der mit dem Barkhausen Young Scientist Award ausgezeichnet wurde (www.mfd-dresden.de/veranstaltungen/barkhausen-award/aktuell), wurden 2015 Nachwuchswissenschaftler des ST2 für ihre herausragenden wissenschaftlichen Leistungen mit Preisen geehrt.

Biologie-inspirierte Grenzflächen- und Materialgestaltung

Heparin desulfation modulates VEGF release and angiogenesis in diabetic wounds

Uwe Freudenberg, Andrea Zieris,
Mikhail V. Tsurkan, Manfred F. Maitz,
Passant Atallah, Carsten Werner

While vascular endothelial growth factor (VEGF) has been shown to be one of the key players in wound healing by promoting angiogenesis current clinical applications of this growth factor to the wound environment are poorly controlled and not sustainable. Hydrogels based of sulfated glycosaminoglycans (GAG) allow for the effective administration of growth factors via biomimetic electrostatic interactions. Accordingly, mechanically adjusttable biohybrid hydrogels with tunable sulfation pattern were synthesized following a rational design concept utilizing star-shaped poly(ethylene glycol) and selectively desulfated heparin derivates (1). Materials with variable sulfation pattern were tested with respect to VEGF-165 (VEGF) binding and release, their anticoagulant activity and for supportive effects on migration and tube formation of human umbilical vein endothelial cells (HUVECs) in vitro and on the wound healing in genetically diabetic (db/db) mice (see Fig. 1 and (2)).
The results demonstrate that the release of VEGF from the hydrogels is modulated in dependence on the GAG sulfation pattern. In vitro studies showed a pronounced pro-angiogenic response of HUVECs as obvious from enhanced cell migration and tubular formation in dependence of the VEGF amounts released from desulfated heparin hydrogels. Furthermore, desulfated heparin hydrogels with superior low anticoagulant activity were transplanted in db/db mice to investigate the effect of the modulation of VEGF release from the matrices. Hydrogels made of low sulfate content (11% of the initial heparin) were found to be superior in efficacy of VEGF administration, low anticoagulant activity and promotion of angiogenesis in vivo (see Fig. 1).

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Co-operation:
Dr. K. Chwalek, Havard University, USA
Dr. K. R. Levental, University of Texas
Prof. S. A. Eming, Universitätsklinikum Köln

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Keywords
hydrogel
heparin
angiogenesis
wound healing

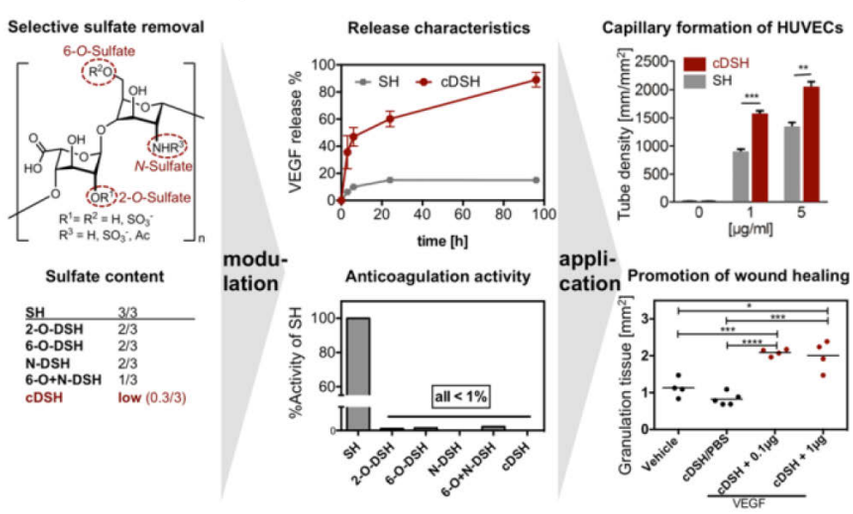


Fig. 1:
StarPEG-heparin hydrogels with variable sulfation pattern.
Left: Selectively desulfated heparin used as building block for biohybrid StarPEG-heparin hydrogels.
Middle-Modulation (top): Cumulative VEGF release from heparin (SH) and completely desulfated heparin (cDSH) hydrogels expressed as % percent of immobilization.
(bottom): Anticoagulant activity of desulfated heparin derivatives compared to standard heparin.
Right-Application (top): Quantification of the tube length of HUVECs on collagen I/starPEG-heparin gel sandwich after 3 days culture.
(bottom): StarPEG-heparin hydrogels promote wound angiogenesisi in diabetic mice. Morphometric quantification of granulation tissue after 10 days.

Biologie-inspirierte Grenzflächen- und Materialgestaltung

Keywords
cryogel
microcarrier
cell delivery
brain

Tackling cell transplantation anoikis: An injectable, shape memory cryogel microcarrier platform material for stem cell and neuronal cell growth

Ben Newland, Petra B. Welzel, Heike Newland, Claudia Renneberg, Petr Kolar, Mikhail Tsurkan, Uwe Freudenberg, Carsten Werner

For some neurodegenerative disorders, particularly those such as Parkinson's disease which have a relatively selective loss of a specific cell type (dopaminergic neurons) from a relatively focal region, cell therapies offer a possible means of replacing or protecting the dying neurons. Unfortunately only 5-10% of the dopaminergic neurons survive the transplantation process and anoikis (Greek meaning: without a home i.e. the process by which cells die through lack of attachment), has been proposed as a major factor contributing to cell death post-transplantation in the CNS [1].
The aim of this study was to use a recently developed biohybrid hydrogel material consisting of star-shaped poly(ethylene glycol) (starPEG) and heparin that already has proven biocompatibility in the brain [2] to construct macroporous cryogel microcarriers [3] for cell adherence/growth. We hypothesized that by using a combination of an emulsion technique with cryogelation, micron scale cryogel particles (microcarriers) could be produced which can bind growth factors, and allow cell growth in the interconnected macropores to protect them during injection through a small bore needle.

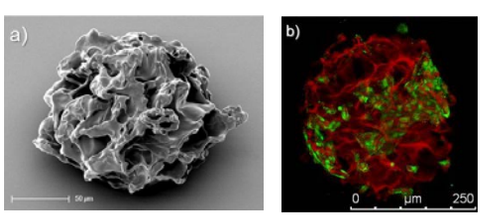
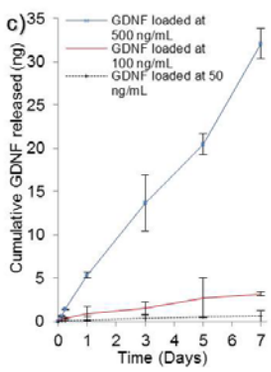


Fig. 1:
showing a scanning electron microscope image (a) of a dry microcarrier allowing visualization of the highly porous structure. The labelled heparin allows confocal microscopy analysis (b) of swollen microcarriers (red) loaded with rat mesenchymal stem cells (green). The growth factor GDNF can be released from the microcarriers over a period of seven days which may further improve cell survival post transplantation into the brain.

Cryogel microcarriers were synthesized via EDC/sulfo-NHS mediated crosslinking of amino terminated starPEG and Alexa 647 labeled heparin whilst being frozen and stirred in a water-in-oil emulsion (Fig. 1a). These spherical and highly porous microcarriers could be loaded with stem cells (Fig. 1b) and also growth factors such as nerve growth factor (NGF) and glial cell line-derived neurotrophic factor (GDNF). Since these growth factors have extensively been shown to be neuroprotective, we analyzed the release of them into media as this could provide a protective environment for transplanted neurons. GDNF was released steadily over a period of 1 week (Fig. 1c) and could be varied depending on the loading concentration used.



The microcarriers were injectable through a 30 gauge needle without loss of cell viability and are now being prepared for transplantation studies into the Sprague Dawley rat brain.

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Prof. A. Rosser, Cardiff University, Brain Repair Group, United Kingdom

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Biologie-inspirierte Grenzflächen- und Materialgestaltung

Multilayer hydrogel coatings to combine hemocompatibility and antiseptic activity

Marion Fischer, Manfred Maitz,
Carsten Werner

The functionalization of blood-contacting biomaterials with antimicrobial compounds is done to address the persisting problem of device-related infections, but often is associated with a considerable loss of hemocompatibility. We here report on silver-loaded hydrogel coatings with combined antiseptic and anticoagulant properties to be used as coatings for medical devices with intensive blood contact [1]. We designed hydrogel film coatings of four-armed poly(ethylene glycol) cross-linked to heparin, supplemented with silver nanoparticles and grafted onto thermoplastic polyurethane bulk materials (TPU) (Fig. 1A). The hydrogels additionally were designed as multilayer gel constructs with a silver-free shielding top layer [1] or they were equipped with thrombin-cleavable peptide linkers that enable feedback controlled heparin release [2]. Besides the antiseptic silver-loaded hydrogels, we included test materials of distinct antiseptic capacities with passive (polystyrene) and non-fouling characteristics (native hydrogel). For simultaneous analysis of material-related hemocompatible and antiseptic properties, surface coatings were exposed to defined concentrations of Escherichia coli (E.coli) and Staphylococcus epidermidis (S.epidermidis) strains and subsequently incubated with fresh human whole blood. Bacterial presence, coagulation and platelet activation (prothrombin fragment F1+2, platelet factor PF4) and inflammation parameters (complement fragment C5a, granulocyte activation marker CD11b) were evaluated upon incubation. Silver-containing hydrogels achieved a long term antiseptic efficacy depending on the dose of silver loading as determined by inhibition zone assay against both bacterial strains [1]. The exposition of surfaces to bacterial solutions revealed significantly reduced bacterial adhesion for all hydrogel samples, with even none bacteria adherent on silver-loaded hydrogels (Figure 1B). While a significantly elevated granulocyte activation and plasmatic coagulation was found on polystyrene along with the increased bacterial adhesion, this was not observed on hydrogel coatings (Fig. 1C). The silver-derived prothrombotic effect of silver-loaded hydrogels pre-seeded with E.coli was avoided due to the response characteristics of the cleavable hydrogels leading to adjusted release of the anticoagulant heparin.
The combination of antiseptic modification together with anticoagulant response systems was proven suitable for indwelling blood-contacting surface coatings. The explored silver-loaded starPEG-heparin concept can be used in a variety of applications that require the long-term release of bioactives to be combined with optimal hemocompatibility. The presented hydrogel platform enables the development of advanced concepts using either feedback-controlled heparin release or multilayer constructs for device coatings guaranteeing a safe clinical performance.

Co-operation:
R. Konradi, BASF SE, Advanced Materials and Systems Research, Germany

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Keywords
antibacterial
hemocompatiblity
hydrogel
silver
drug-release

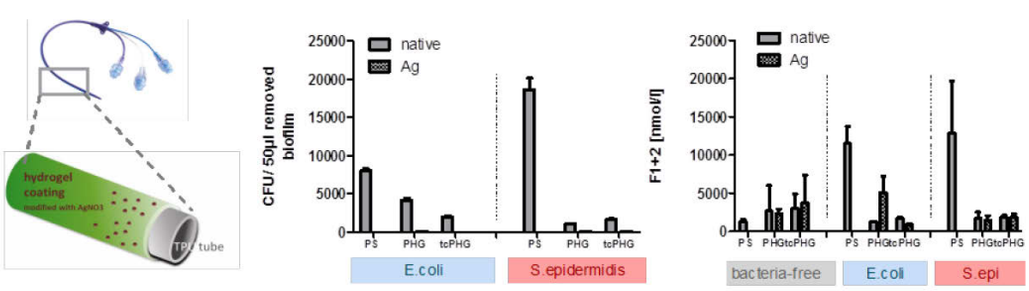

Fig. 1:
Left: Scheme of hydrogel coatings on TPU-based catheter tubes
Middle: Colony formin unit (CFU) counts of E. coli and S.epidermidis determined through plate outs of biofilms removed from the pre-seeded surfaces after blood incubation. Samples include non-cleavable hydrogels (PHG) and thrombin-cleavable hydrogels (tcPHG) loaded with silver (Ag) or silver-free (native), and the reference polystyrene (PS).
Right: Fragment F1+2 measured by ELISA analysis after surface whole blood incubation of bacteria-free and pre-seeded hydrogel coatings with and without silver, and reference polystyrene.

Biologie-inspirierte Grenzflächen- und Materialgestaltung

Keywords
smart polymer
core shell microgel
acetyl CoA synthetase
enzyme adsorption
acetyl CoA synthesis

Microgel based membrane reactor for biosynthesis of acetyl Coenzyme A

Nidhi C. Dubey, Bijay P. Tripathi, Martin Müller, Manfred Stamm, Leonid Ionov

Polyketides are natural products with complex chemical structures and immense pharmaceutical potential that are synthesized via secondary metabolic pathways. The in-vitro synthesis of these molecules requires high supply of building blocks such as acetyl Coenzyme A (CoA), etc. Acetyl CoA synthetase (Acs) is one of the enzyme that catalyze acetyl CoA synthesis, and the enzyme is essentially employed for continuous supply of the acetyl CoA for the production of these metabolites [1,2]. Owing to the expensive nature of the enzymes, it is important to immobilize enzymes to improve the process economics by enabling multiple uses of catalyst and improving overall productivity and robustness. The polymer-based particles of nano and submicron size have become attractive material for their role in the life sciences [3].

To achieve reusable and a more robust entity of the enzyme, we carried out the immobilization of Acs on poly(N-isopropylacrylamide-poly(ethyleneimine) (PNIPAm-PEI) microgels via adsorption[4]. Cationic PNIPAm-PEI microgel was synthesized by one-step graft co-polymerization of NIPAm from PEI. Adsorption studies of Acs on microgel indicated high binding of enzyme. The immobilized enzyme showed improved biocatalytic efficiency over free enzymes, beside this, the reaction parameters and circular dichroism (CD) spectroscopy studies indicated no significant changes in enzyme structure after immobilization. This thoroughly characterized enzyme bioconjugate was further immobilized on ultrathin membrane to assess the same reaction in flow through condition. Bioconjugate was covalently immobilized on a thin layer of already prepared microgel support upon polyethylene terephthalate (PET) track etched membrane. The prepared membrane was used in a dead end filtration device to monitor the bioconversion efficiency and operational stability of cross-linked bioconjugate. The bioconversion efficiency (i.e. the amount of product (acetyl CoA) formed from definite amount of substrate); from Fig. 1 it can be observed that the membrane reactor performance was linear and consistent with respect to the control samples (conjugate in batch and free enzyme).

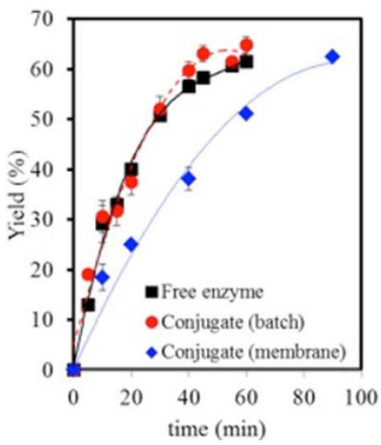

Fig. 1:
Acetyl CoA formation is given as percent yield with respect to time by free Acs (■) and conjugate (●) in batch condition and conjugate on the membrane (◆) at 25 °C.

The membrane reactor showed consistent operational stability and maintained >70% of initial activity after 7 consecutive operation cycles (Fig. 2). The better and consistent performance of enzyme reactor can be attributed to the stabilizing effect of PEI shell of microgel on enzyme and also the membrane, which maintain the total enzyme concentration on the surface. These results suggest that the prepared membrane serve as a platform for acetyl CoA synthesis with enhanced activity and can be explored for other precursor biomolecule production.

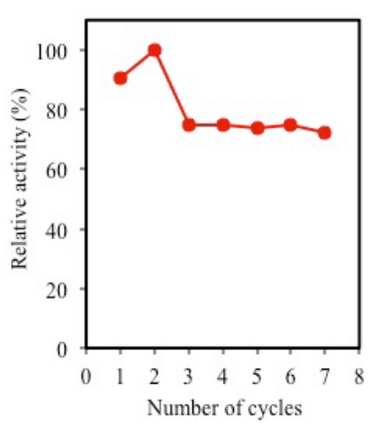

Fig. 2:
Operational stability of bioconjugate membrane at 25 °C

Biologie-inspirierte Grenzflächen- und Materialgestaltung

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Leibniz-Institut für Neue Materialien,
Leibniz-Institut für Analytische Wissenschaften

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Hemocompatibility of silk nanoparticles tested under static and flow conditions

Manfred F. Maitz, Manuela Herklotz, Claudia Sperling, Carsten Werner

Keywords
nanoparticles
inflammation
silk
coagulation
complement system

Nanoparticles are frequently administered into the blood stream for diagnostic or therapeutic purposes. These nanosized particles with diameter below 100 to 200 nm have different properties than the corresponding bulk materials: Their big surface area leads to intense interaction with the biological environment and high amount of protein adsorption. As a consequence of the small radius and high curvature, the conformation of adsorbed proteins is affected, and protein-protein-interactions of surface adsorbed proteins can be directly influenced by the high curvature. Depending on the size, the interaction of the nanoparticles with blood proteins varies, leading to either pro- or anti-coagulant properties.
As nanoparticles frequently have a tendency to aggregate from nanosize to microsized clusters, this process may alter their interaction with the blood cascade systems and ultimately their hemocompatibility. This effect is typically ignored when testing nanoparticles.
Silk proteins have a long tradition as a medical suture material and emerged as scaffold materials for tissue engineering [1-2]. Due to the possibility of nanoparticle formation, the material also enters nanomedicine as a drug delivery system.
In this work, we incubated silk nanoparticles and reference silica particles, both of about 100 nm at a concentration of 250 µg/ml in human whole blood for two hours. The incubation was performed either under quasi-static conditions in reaction tubes or under flow conditions in a Chandler loop set-up, as sketched in Fig. 1.

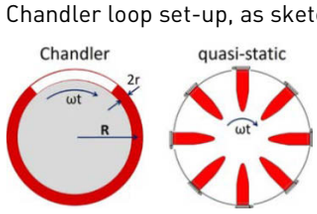

Fig.1:
Scheme of Chandler loop and quasi-static blood incubation

In the Chandler loop, gravity induces a flow in a rotating tube without the need of additional pumps. This shear condition keeps the nanoparticles better suspended than the quasi-static incubation, which only avoids sedimentation.

Biologie-inspirierte Grenzflächen- und Materialgestaltung

After the incubation, hemocompatibility parameters were determined. Coagulation activation, measured as prothrombin F1+2 fragment, was generally low for the silk nanoparticles when compared to silica. Both types of nanoparticles tended to induce stronger coagulation during the static incubation than under dynamic chandler loop incubation (Fig. 2A). The silk nanoparticles induced very high activation of the inflammatory complement system (C5a) under static condition, but not under flow condition, where particles are better dispersed (Fig. 2B). PEGylation of the silk nanoparticles did not sufficiently suppress aggregation and complement activation (Fig. 3).

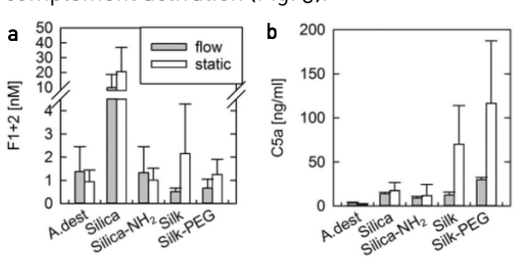

Fig. 2:
a: Prothrombin F1+2 fragment as marker of coagulation activation;
b: complement fragment C5a as marker of complement activation after incubation of nanoparticles with whole blood either under static condition or under flow conditions in a Chandler-Loop set-up.

Coagulation and complement activation both are processes, which involve the formation of multiprotein complexes on a surface. The high curvature of the surface of nanoparticles disturbs the assembly of these complexes, whereas the assembly is undisturbed at the larger aggregates. This concept it supported by reported observations, where polystyrene nanoparticles above 20 nm are more coagulant than smaller particles [3-5]. In this study, the difference between the static incubation with aggregate formation and the flow condition was more prominent for complement than for coagulation activation. This difference may be attributed to the bigger dimension of the complement activation complex compared to the complex of the coagulation contact phase.
In conclusion, hemocompatibility evaluation of nanoparticles has to include several different aspects. To address this need we compared the quasi static with the physiological flow incubation and demonstrate that the resulting differences in aggregation may cause higher activation of enzyme cascade systems under quasi-static conditions.

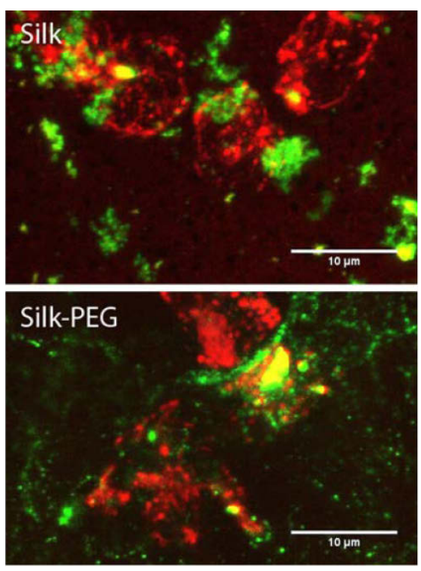

Fig. 3:
Fluorescent microphotographs of nanoparticles (aggregates, green) and leukocytes (lysosomes labeled in red)

Co-operation:
F. Philipp Seib, University of Strathclyde, Strathclyde Institute of Pharmacy and Biomedical Sciences, Glasgow, UK

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Biologie-inspirierte Grenzflächen- und Materialgestaltung

Interaction between adhesive polyelectrolyte complex particles and hard tissue related cells

David Vehlow, Birgit Urban, Bernhard Torger, Martin Müller

This work aims at the development of an adhesive nanoscaled carrier system for bone therapeutic drugs usable for the functionalization and improvement of bone substituting materials (BSM). We have chosen biocompatible polyelectrolyte (PEL) complex (PEC) nanoparticles (NP) [1] fabricated by mixing polycation and polyanion solutions loaded by relevant therapeutics such as bisphosphonates and bone related growth factors and attached to BSM and model substrates. Herein we address the cytocompatibility of such PEC NP films towards bone cells like human mesenchymal stromal cells (hMSC) relevant for osteoblasts and human peripheral blood monocytes (hPBMC) relevant for osteoclasts.

hMSC

In the Fig. 1 surface concentration profiles of the metabolic activity of hMSC cultured above casted PEC NP films of two compositions are shown.

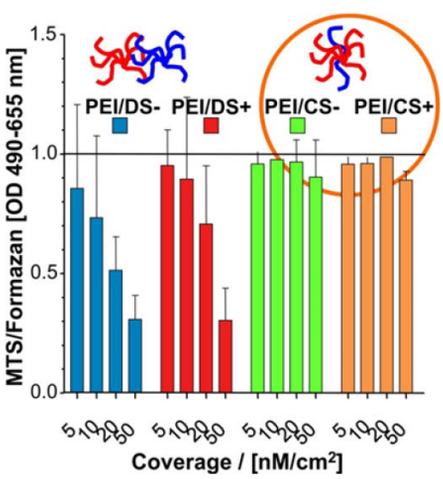

Fig. 1:
Relative metabolic activity of hMSC cultured onto immobilized PEI/CS and PEI/DS (PEC-0.9, PEC-1.1, control: Tissue culture polystyrene). Detailed conditions and parameters can be found therein [2].

While poly(ethyleneimine)/dextransulfate (PEI/DS) results in a strong dependence of metabolic activity on concentration, PEI/cellulosesulfate (PEI/CS) results in no such dependence suggesting better cytocompatibility. We suggest, that toxicologically suspected branched PEI is better masked by linear CS than by branched DS due to steric reasons [4]. Surprisingly, net charge sign (PEC-0.9: positive, PEC-1.1: negative) did not influence metabolic activity of hMSC. Both Fluorescence [2] and TOF-SIMS [3] imaging at hMSC onto FITC labelled PEC-NP coatings suggest internalisation of single PEC NP (green) as it is shown in Fig. 2.

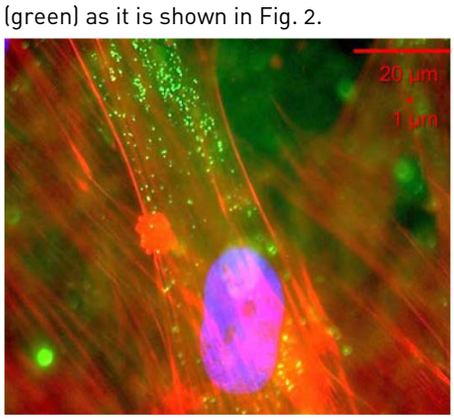

Fig. 2:
Fluorescence imaging of hMSC cultured above coatings of FITC labelled PEC NP (PEI/CS-0.9) [2].

hPBMC

First studies at osteoclast related hPBMC onto mineralised bone matrix showed, that the osteoclastogenesis inhibitor zoledronate (ZOL) bound at PEC NP (ZOL/PEC) resulted in higher reduction of hPBMC viability and differentiation in comparison to pure ZOL [4]. This was observed for pure ZOL and ZOL/PEC given in the cell volume phase as well as attached directly to mineralized bone matrix (Fig. 3).

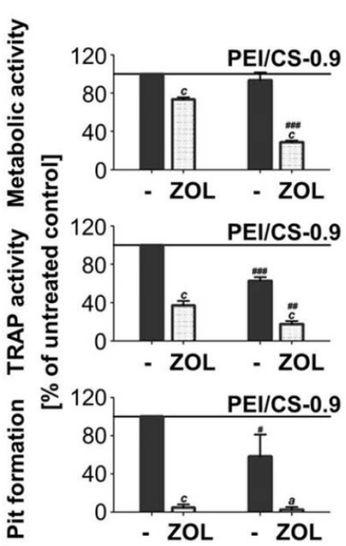

Fig. 3:
Metabolic activity, differentiation and pit formation (bone resorption) of hPBMC cultured above mineralized bone matrix in the presence and absence of pure ZOL and ZOL/PEC. Detailed conditions and parameters can be found therein [4].

Keywords
bone substituting material
polymer nanoparticle
polyelectrolyte complex
cytocompatibility
drug delivery

Biologie-inspirierte Grenzflächen- und Materialgestaltung

Keywords
macromolecular crowding
extracellular matrix
haematopoietic stem and progenitor cells

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Extracellular matrix deposition of bone marrow stroma enhanced by macromolecular crowding

Marina Prewitz, Aline Stißel, 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.

After we have investigated the complexity of the extracellular matrix (ECM) generated by MSC in vitro, we have shown their potential to serve as *in vivo*-like matrix scaffolds for BM stem cell maintenance [1]. To further maximize the potential of *in vitro* generated matrix scaffolds we applied macromolecular crowding (MMC), the supplementation of synthetic or naturally occurring molecules resulting in excluded volume effects (EVE). The concept of MMC has been demonstrated to provide valuable options for recapitulating the physiological environment of cells. MSC-derived ECM was produced upon supplementation of standard culture medium with three different macromolecules of various size (10 - 500 kDa). Matrix secretion, ECM morphology and composition were compared for matrices obtained from crowded and non-crowded MSC cultures. In the context of generating functional stem cell niches, the ECM scaffolds generated under MMC were tested for their supportive effect to maintain and expand human hematopoietic stem and progenitor cells (HSPC). MMC in combination with metabolic stimulation of MSC was found to result in tissue-specific, highly organized ECM capable of retaining glycosaminoglycans and growth factors to effectively build *in vitro* microenvironments that support HSPC expansion [2].

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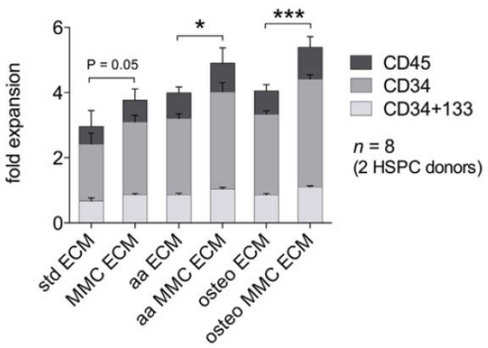

Fig. 1:
Expansion of HSPC is presented as fold expansion from starting cell number. Total cells (CD45), late stem cell progenitors (CD34 positive), and early stem cell progenitors (CD34 + CD133). Under MMC conditions all ECM scaffolds more effectively supported HSPC expansion. Metabolic stimulation by ascorbic acid (aa), or osteogenic supplements (osteo) caused higher levels of HSPC expansion, compared to standard culture medium.

Sponsor:
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Co-operation:
Prof. M. Bornhäuser, Technische Universität Dresden, Universitätsklinikum, Medizinische Klinik I
S. Vogler, Technische Universität Dresden, Center for Regenerative Therapies Dresden

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Anisotropic liquid microcapsules from biomimetic self-folding polymer films

Leonid Ionov, Svetlana Zakharchenko

Keyords
self-folding
polymer bilayer
encapsulcation

The anisotropic or elongated capsules are of a special interest, since the shape anisotropy gives them a number of advantages. For example, anisotropic capsules are particularly attractive for energy storage, design of self-healing materials. Anisotropy of delivery carriers is also a very desirable feature for pulmonary drug delivery since elongated carriers possess the same aerodynamic diameter as an equivalent spherical carrier, allowing at the same time for delivery of a larger amount of cargo.
One possible approach for the encapsulation is based on the use of self-folding films. Self-folding films are thin bilayers, which fold spontaneously in response to external stimuli in order to release internal stress or external force. The behavior of self-folding films is very similar to actuation in plants, where non-homogenous swelling results in complex movements such as twisting, bending or folding. Such folding results in a transformation of 2D shapes into 3D objects, wherein the shape of the final object depends on many factors including the shape of the initial layout, the composition and the thickness of the film and the presence of hinges.
We demonstrated a novel approach for the fabrication of anisotropic capsules with liquid content using biomimetic self-folding thermosresponsive polymer films. The behavior of self-folding films is very similar to actuation in plants, where non-homogenous swelling results in complex movements such as twisting, bending or folding .This approach allows the design of anisotropic liquid capsules with rod-like and dumbbell-like morphologies. We found that these capsules are able to assemble into different complex structures, such as nematic-like one and 3D network depending on their morphology.

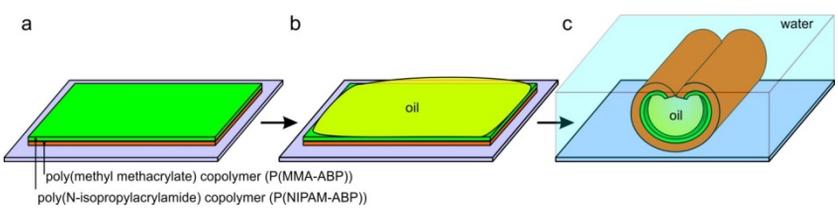

Fig. 1:
Scheme of the encapsulation of oily liquid into self-rolled polymer tubes in aqueous media:
a) as prepared bilayer,
b) bilayer with deposited oil,
c) rolled bilayer tube with oil inside.

Biologie-inspirierte Grenzflächen- und Materialgestaltung

Keywords
porous hollow fibres
biopolymers
tissue engineering

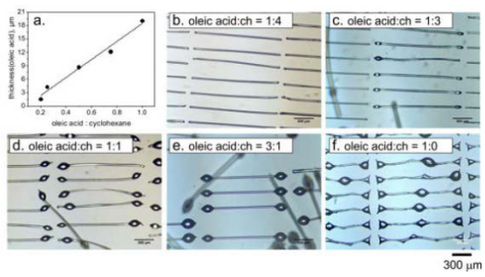

Fig. 2:
Tubular self-rolled capsules with encapsulated oleic acid: (a) Thickness of the film of oleic acid on the surface of patterned bilayer depending on the volume ratio of oleic acid and cyclohexane;
(b-f) Optical microscopy images of capsules with oleic acid obtained by rolling of polymer bilayer with different thickness of oleic acid, which is determined by ratio between oleic acid and cyclohexane (ch).

Sponsor:
Deutsche Forschungsgemeinschaft, IO68/1-3

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Abbaubare poröse Hohlfasern auf Basis eines CaCO3 Biopolymerkomposites

Claudia Hinüber, Harald Brünig, Roland Vogel

Wesentliche Fortschritte konnten in den letzten Jahren im Bereich des Tissue Engineering zum Aufbau funktioneller Strukturen unter Verwendung biomimetischer drei-dimensionaler Scaffolds erreicht werden. Stimulierte Zelladhäsion, Proliferation und die Bildung extrazellulärer Matrix konnten an einer Vielzahl von Scaffoldvarianten eindrucksvoll demonstriert werden, dennoch zeigen sich häufig starke Einschränkungen im Langzeitverhalten aufgrund schlechter Nährstoffversorgung und fehlender Vaskularisierung über den Querschnitt des künstlichen offenporigen Konstrukts, die schließlich zum Zelltod und zum Absterben des Gewebes führen. Eine Strategie die Permeabilität und die Nährstoffversorgung signifikant zu verbessern besteht in der Verwendung von mikroporösen Hohlstrukturen bzw. Hohlfasern [1].
Ein aktuelles Forschungsziel im Bereich Verbundwerkstoffe/ Schmelzspinntechnologie umfasst daher die Entwicklung von porösen hohlfaserbasierten Textilverbundstoffen/ textilen Scaffolds für die Anwendung im Bereich der Knochenregeneration bzw. des Bandapparates.
Die Herstellung von permeablen Hohlstrukturen aus PHB im Bereich des Neuro-Tissue Engineering als auch mikroporöse schmelzgesponnene Hohlfasern auf der Basis von PP für technische Anwendungen, wie z.B. für Füllungen, als selektiv permeable Membranen oder zur Hämodialyse, konnten bereits erfolgreich demonstriert werden [1,2]. Letzteres beruht auf einem konventionellen Schmelzspinnprozess eines typischen Spinnpolymers und darin integrierten ausgefällten Calciumcarbonat Mikropartikeln und der anschließenden longitudinalen Verstreckung der Faser, welche zur Rissinitiierung am Partikel führt sowie dem darauf folgenden selektivem Herauslösen der Mikropartikel, welches schließlich Mikroporen in zwei Größenordnungen generiert (Abb. 1a).
Die gegenwärtigen Arbeiten beruhen auf der Übertragung dieser Methode auf ein Biopolymer bzw. eine Biopolymerkombination mit Hinblick auf biomedizinische Anwendungen.

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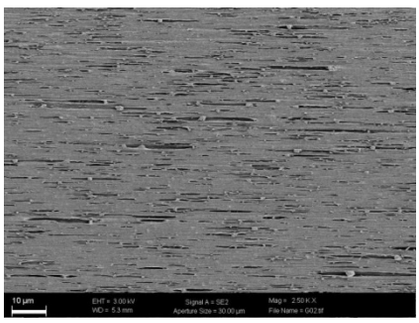
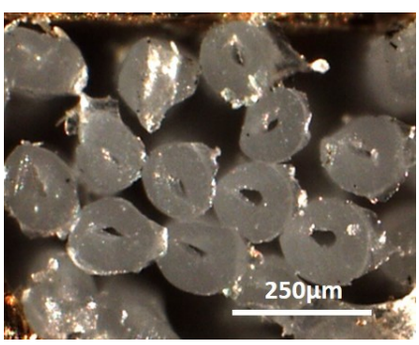
a)



b)



c)

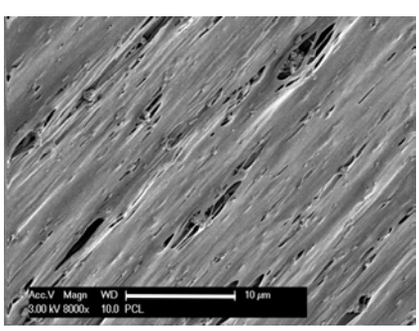


Abb. 1:
a) Poröse PP Hohlfaseroberfläche mit Poren im Bereich von 0,045 -120 µm und 0,1-99 nm,
b) Hohlfaserquerschnitt von PCL Fasern,
c) poröse Oberfläche der PCL Hohlfaser

Die Herausforderung ein schwer spinnbares, thermolabiles Polymer wie PLA oder PCL, zu Hohlfasern zu verarbeiten wird hierbei mit Hilfe eines Minidoppelschnecken-Extruders und unter Verwendung einer speziellen Düsengeometrie bewältigt. Dieser Aufbau ermöglicht die rasche Verarbeitung im Labormaßstab, ohne auf die Extrusionswirkung zur Einbringung von PCC zu verzichten. In exemplarischen Versuchen konnte anhand gefertigter poröser Hohlfasern (Porosität 25 %) aus PCL und Calciumcarbonatpartikeln die Übertragbarkeit der Methode prinzipiell gezeigt werden (Abb. 1 b, c). Ziel der fortlaufenden Untersuchungen ist die Einstellung einer für den kontinuierlichen Nährstoff- und Metabolitenaustausch als auch zur möglichen Vaskularisierung geeignete die Faserwand durchdringende Porosität, die als topografischer Schlüsselreiz ein dreidimensionales textiles Scaffold grundlegend aufwerten kann sowie die Charakterisierung dieser Fasern hinsichtlich ihrer textiler Verarbeitungsmöglichkeiten und mechanischer Stabilität. Fasern dieser Art könnten bei schwer regenerierbaren Bereichen, z. B. beim Knochenübergang im Bandersatz, zur deutlichen Beschleunigung der Scaffoldintegration und damit zu verbesserter Therapie des Defektes führen.

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