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Biofilms/Implant associated infections

S02-01

Local drug delivery from transcatheter heart valves for the prevention of implant infection– chitosan as adhesion promoter for polymer/drug coating

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Infective endocarditis after transcatheter aortic valve implantation (TAVI) constitutes a serious complication of this rapidly growing therapeutic approach for the minimally invasive treatment of aortic stenosis in elderly patients, with a potential incidence of about 3 % [1]. Infective endocarditis may arise at an early stage, as well as in the further course after implantation. In particular early stage infections could be addressed by preventive or responsive implant-based local drug delivery. However, coating of TAVI materials, such as xenogenic pericardium, is highly challenging. In this context, the application of chitosan may be a promising approach for the modification of implant surface characteristics in the context of polymer/drug coating.

In the present study, chitosan dip coating as a technological approach for establishing a continuous polymer/drug coating layer with high stability in aqueous media is described. Different parameter sets and their implications for the resulting coating properties are considered. For inhibition of *S. aureus*, the drug incorporation of *N*-acetylcysteine, as well as a combination of rifampicin and minocycline in a biodegradable polylactide carrier are investigated. Depending on the incorporated drug and their concentration, a drug release in the range of 24 hours up to several weeks can be observed. Both drug concepts are highly capable of inhibiting different bacterial strains, such as *S. aureus*.

First results indicate that chitosan may be useful as a promoting coating layer in combination with drug-incorporated polylactide for the inhibition of TAVI-associated infective endocarditis.

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S02-02

Development of a biomimetic physical/chemical implant functionalization

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Biofilm-induced implant-associated infections still pose severe problems in modern implantology. The attached microbial communities are surrounded by a self-produced extracellular matrix and exhibit distinct gene expression profiles. They are able to escape the host immune defense and antibiotic therapy, which makes their treatment difficult. Therefore, new implant materials are required, which inhibit biofilm formation without the use of antibacterial agents. The biomimetic "slippery liquid-infused porous surfaces" (SLIPS) principle exhibits great potential for this purpose. To transfer this principle to the common implant material titanium, physical material structuring by ultra-short pulsed laser ablation was combined with chemical lubricant immobilization by specifically matching wetting characteristics. Different structure/lubricant combinations were analyzed for water contact angles and lubricant stability at different shear forces. Additionally, biofilm attachment was characterized for *Streptococcus oralis* monospecies and oral multispecies biofilms under static and fluid flow conditions. Analyzing the physical/chemical functionalized titanium's underlying mechanism could exclude a toxic effect of the surfaces' components. Furthermore, reduced bacterial initial adhesion due to reduced adhesion forces could be detected. The strongest water-repellency and biofilm reducing effect could be observed when combining a bioinspired lotus leaf-like structure with a perfluoropolyether lubricant of medium viscosity. This physical/chemical titanium functionalization may serve as a basis towards the development of an infection-resistant implant surface.

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S02-03

Bimetallic nanoparticles with tunable antimicrobial activity and osteo-promotive effects on human mesenchymal stem cells

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Introduction

The inhibition of initial bacterial colonization by supportive antimicrobial agents such as silver (Ag) is an efficient way to avoid implant-related infections. Using Ag nanoparticles (NP), a rapid and time-limited Ag ion release can be achieved at reduced total Ag amount. Furthermore, the combination of Ag with other metals is a promising approach to obtain materials with tunable properties. Platinum (Pt) was already reported to reduce bone loss by inhibition of osteoclastogenesis [Nomura 2011].

We have synthesized bimetallic AgPt NP and analyzed their antimicrobial activity and the osteo-promotive effect on human mesenchymal stem cells (hMSC) depending on the metal composition.

Methods

Bimetallic PVP-coated NP with different Ag and Pt content as well as pure Ag and pure Pt NP (5-10 nm) were synthesized by reducing $AgNO_3$ and H_2PtCl_6 with $NaBH_4$ or citrate/tannic acid. The antimicrobial activity against *S.aureus* and *E.coli* was analyzed by determination of MIC and MBC. HMSC viability and osteogenic differentiation were analyzed by Calcein-AM and Alizarin Red S staining. A Scratch assay was applied to examine the hMSC migration upon NP exposure by life cell imaging.

Results and Discussion

In contrast to pure Pt NP, AgPt and pure Ag NP showed significant antimicrobial activity against *S.aureus* and *E.coli* as well as impacts on hMSC viability, depending on NP concentration and the individual Ag content. Long term exposure of hMSC with Pt-containing NP (at least 50% Pt) induced the formation of cell nodules and enhanced hMSC calcification during osteogenic differentiation. The Pt-related effects decreased with increasing Ag content and vice versa, yielding NP with the combinatorial properties of Ag and Pt.

We demonstrated bimetallic AgPt NP with antimicrobial activity as well as an osteo-promotive effect on hMSC. Our results suggest that NP with tunable properties can be obtained by controlling the metal composition for directed biological responses.

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S02-04

Thin, degradable coatings promote osteointegration and prevent infections

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Thin, degradable and simultaneously osteoconductive coatings with the addition of bactericidal metals may shorten the amount of time to establish secondary stability in the bone after implantation of prosthesis. It also prevents bacterial colonization and the formation of biofilms. The goal is to produce thin layers containing copper via high-velocity suspension flame sprayingmethod.

The cylindrical test specimens were implanted bilaterally into the femoral condyles with the standardized drill hole method. The experiment took place over the course of 2, 4, 6, 12 and 24 weeks, respectively. The group size amounted to 12 animals per trial period. For the trial period of 24 weeks, 24 animals were needed, including a group with unaltered materials. Four different materials with a layer thickness of 20 µm were tested, namely GB14, Bioglass, HA and ß-TCP. Additionally, the coatings contained copper, which is known for its bactericidal effects. The implant fixation was analysed with push-out-tests by determining the shearing strength. Histological and image analysis was combined to assess the quantitative and time-dependent degradation of the material layers as well as document the progression and quality of osteointegration.

In the histological and histomorphometric analyses, the coatings showed a good integration and a high percentage of implant surface covered by bone. The addition of copper showed no significant effects. The thickness of the layering negatively impacted osteointegration. The dynamics of the bone healing process differed depending on the material. Coatings with bioglass caused a mineralisational dysfunction at the contact area with the bone and also showed the least shearing strength throughout the trial period. These studies support the evidence that implants coated with degradable materials improve the early stability of prostheses. The addition of bacteriocidal metals also prevents bacterial infection.

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S02-05

Superparamagnetic silica core-shell nanoparticles for the implant-directed magnetic drug targeting

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After the implantation of endoprostheses or osteosynthesis devices, implant-associated infections are one of the major challenges in the orthopedic surgery. Magnetic nanoporous silica nanoparticles (MNPSNPs) are promising candidates as drug carriers for the selective treatment of these infections. In combination with an external applied magnetic field and magnetizable implants, it is possible to accumulate the MNPSNPs and thus pharmaceuticals in selective areas of the organism.[1] In this implant-directed magnetic drug targeting (ID-MDT) the particles consists of superparamagnetic Fe3O4 cores which are encapsulated in a nanoporous silica shell with prominent biocompatibility, high specific surface area, large pore volume and adjustable pore sizes for drug delivery.[2] For *in vitro* and *in vivo* bioimaging the shell can be functionalized with organic fluorophores like fluorescein isothiocyanate (FITC) or rhodamine B isothiocyanate (RITC).[3] In addition to it, the covalent grafting of polyethylene glycol (PEG) on the outer surface of the core-shell nanoparticles is a further functionalization.[4] This PEGylation is a versatile method to improve the general biocompatibility and biodistribution based on a lower decomposition rate and thus a higher blood circulation time. A further aspect for ID-MDT is the loading and delivery of drugs from the MNPSNPs. Especially for the treatment of acute infections, an initial burst release with a fast delivery of the pharmaceutical within the first few hours can be advantageous.

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S02-06

Do blockstructures improve the copolymers properties compared to their statistical analogues?

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Worldwide, over one million dental implants are placed per year. However, up to 4.2% of the patients suffer from postoperative infections [[1]]. The mouth"s humidity, temperature and food remnants favor bacterial growth that often results in a biofilm formation. The biofilm entails severe consequences up to the failure of the implant. One approach to avoid this are copolymeric coatings containing an antimicrobial moiety like a NR4+-group [1] and a phosphonate group to attach to implant [2].

Statistical copolymers **3** containing the monomers BMADUA (**1**) and DMMEP (**2**) were prepared via free radical polymerization in THF by Waßmann [[2]]. The diblock copolymers **5** were synthesized via *reversible addition-fragmentation chain transfer* in DMF.

Figure 1: Synthesis of **3** and **5**.

All polymers were synthesized with different monomer ratios, *spin-coated* onto titanium and characterized by ellipsometry and wettability measurements. Additional XPS results prove the structure of the surface coating. Antimicrobial tests are existent for **3** and show good results against *S. aureus* [2]. Comparing similar BMADUA contents, the wettability decreases by approx. 10° and the layer thickness increases by approx. 10 nm for statistical copolymers. It seems that different polymer architectures have an influence in physicochemical properties for the described copolymer system.

Derived from these results the antimicrobial properties might also change positively for block copolymers. Necessary measurements will be performed in the future.

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Figure 1