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Biofunctionalization of Scaffold Material with Nano-Scaled Diamond Particles Physisorbed with Angiogenic Factors Enhances Vessel Growth after Implantation

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Biofunctionalized scaffold facilitates complete healing of large defects [1,2]. Biological constraints are induction and ingrowth of vessels. Angiogenic growth factors such as vascular endothelial growth factor or angiopoietin-1 can be bound to nano-scaled diamond particles. Corresponding bioactivities need to be examined after biofunctionalization. We therefore determined the physisorptive capacity of distinctly manufactured, differently sized nDP and the corresponding activities of bound factors. The diamond particles were previously tested for their biocompatibility on cultivated human mesenchymal stem cells (MSC) and distribution in living systems using the developing chicken as a model organism. The properties of biofunctionalized nDPs were investigated as well on MSC and on the developing chicken embryo chorio-allantoic membrane (CAM) (Figure 1). Eventually porous bone substitution material was tested for biocompatibility using 3D MSC cultivation techniques. The material was also coated with nDP to generate an interface that allows biofactor physisorption. Angiopoietin-1 was applied shortly before scaffold implantation into an osseous defect in sheep calvaria. Biofunctionalized scaffolds exhibited significantly increased rates of angiogenesis already one month after implantation. Conclusively, nDP can be used to ease functionalization of synthetic biomaterials.

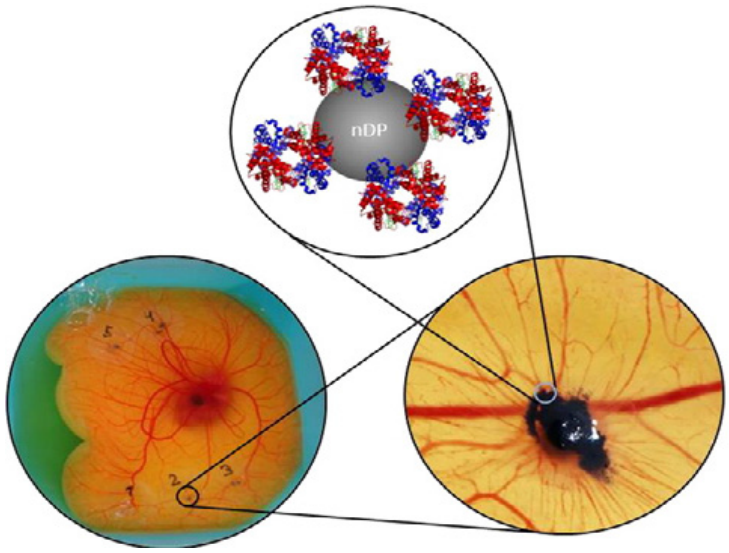

Figure 1: Graphic description of functionalized nDPs being mounted on the chicken embryo chorio-allantoic membrane to induce vascularization.

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The Interaction of Allergens with Nanoparticles Can Impact the Human Allergic Response

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Abstract

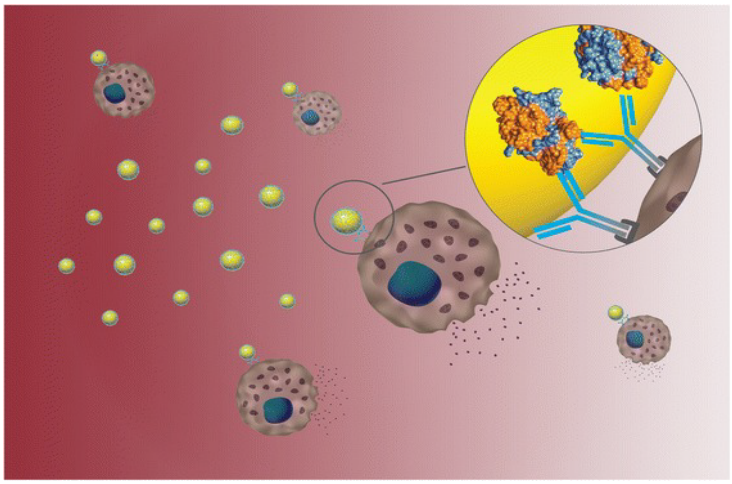
Nanoparticles interact with biomolecules as soon as they are in contact, a process which has become known as protein corona formation. In the environment, allergens may thus represent potential interaction partners for nanoparticles. Upon interaction with nanoparticles, allergens may undergo structural changes, and this may have a potential consequence on the allergenic response.

This study aimed to elucidate the interactions of gold nanoparticles, as inert model system, with a panel of seasonally and perennially occurring outdoor and indoor allergens.

Gold nanoparticles were coupled with highly purified recombinant major allergens from birch pollen (rBet v 1), timothy grass pollen (rPhl p 5), and house dust mite (rDer p 1). The gold nanoparticle-allergen conjugates were characterized by transmission electron microscopy, dynamic light scattering, zeta potential measurements, and hyperspectral imaging. In silico 3D models were constructed, based on the characterization data, to visualize the arrangement of allergens on the nanoparticle surface and evaluate potential electrostatically favored orientations.

Depending on the individual allergen and patient, modulating effects on the allergic response due to interaction with nanoparticles were determined by activation assays using human basophils derived from sensitized patients. Among the observed differences was also an enhancement of the allergic response, as found most frequently against the major house dust mite allergen and, in some patients, against the major birch pollen allergen.

In conclusion, this study showed potential modulations in the human allergic response upon contact with nanoparticles. The degree of modulation seemed to depend on the individual allergen and on the epitope specificity of the respective allergic patient.



Graphical abstract: Cross-linking of IgE receptors and degranulation of human basophils due to epitope alignment of nanoparticle-coated allergens.

Keywords: Gold nanoparticles; Recombinant allergens; Human allergic response; Basophil activation

Acknowledgment

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An Integrated Bioenergetic and Metabolomic Toolbox for Safety Evaluation of Nucleic Acid Therapeutics: The Kinetic Dimension of Cytotoxicity

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Polycations such as polyethylenimines (PEIs) and poly(lysine)s are highly efficient non-viral transfectants, but the underlying mechanisms of polycation architecture- and size-dependent cytotoxicity still poorly understood. Through an integrated analysis of polycation and polyplex trafficking at live- and single-cell levels, global proteomic fingerprinting and metabolomic profiling we show that polycation-induced cytotoxicity is dynamic, multifaceted, and occurs through different modes of cell death processes (apoptosis, necrosis, programmed necrosis and autophagy). PEIs and poly(L-lysine)s in an architecture and size-dependent manner destabilizes plasma membrane and mitochondrial membranes differently and with consequences on mitochondrial dynamics, motility, oxidative phosphorylation and energetics, glycolytic flux and redox homeostasis that ultimately modulate the switching of cell death pathways. These integrated approaches have provided a rapid approach for mechanistic understanding of multifactorial and multifaceted polycation-mediated cytotoxicity, and could form the basis for combinatorial throughput platforms for improved design and selection of safer polymeric vectors for transfection purposes. On the basis of these approaches, we have further designed libraries of PEI-based polymeric nanosystems as simple, safe and versatile vehicles for cell targeting.

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Platelet-Rich Fibrin as a Biomimetic Nanomaterial for Bone Tissue Engineering in Dentistry: Practical Tools for Successful Implantation

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Potential clinical indications of platelet-rich fibrin (PRF) in oral and maxillofacial surgery are numerous, including, for example, the improvement of soft tissue healing and bone graft protection and remodeling. Beneficial effects of PRF have been studied in various procedures such as a facial plastic surgery, periodontal surgery, sinus floor augmentation, and implant placement [1]. The production of PRF is inexpensive since it requires only a centrifuge, something which is already present in many operating theatres in general hospitals (Figure 1a). Fibrin mesh it is a flexible and strong three-dimensional structure that can capture cytokines and moving cells. Recent study has demonstrated that the PRF has a significant sustained release of key growth factors for a period of at least one week and up to 28 days. The growth factors that are released from PRF are as follows: platelet-derived growth factor (PDGF), transforming growth factor (TGF)-β1, insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF) [2]. PRF acts as a healing and interposition biomaterial. In addition, this biomaterial can be used in together with bone graft material to accelerate dental bone regeneration (Figure 1d) [3]. Direct interactions between fibrin and osseous cells during healing are insufficiently documented [4]. Also, PRF can be used as a membrane. By driving out the fluids trapped in the fibrin matrix (Figure 1b), practitioner can obtain very resistant autologous fibrin membrane (Figure 1c). The potential of the fibrin membrane was proved when used as a barrier in the process of dental bone regeneration (Figure1e, f & g) [5].

According our experience the use of PRF the following four advantages: first, the PRF membrane maintains and protects the grafted biomaterials by stabilizing the fibrin clot and PRF fragments serve as biological connectors between osteoblasts. Second, the integration of this fibrin network into the regenerative site facilitates cellular migration, particularly for endothelial cells necessary for the neo-angiogenesis, revascularization and survival of the bone graft. Third, the platelet cytokines (PDGF, TGF- β1, IGF, VEGF, EGF) are gradually released as the fibrin matrix is resorbed, thus supplying a continuous source of growth factors for wound healing to occur. Lastly, the presence of leukocytes and cytokines in the fibrin network can play a significant role in the self-regulation of inflammation within the bone grafted material.

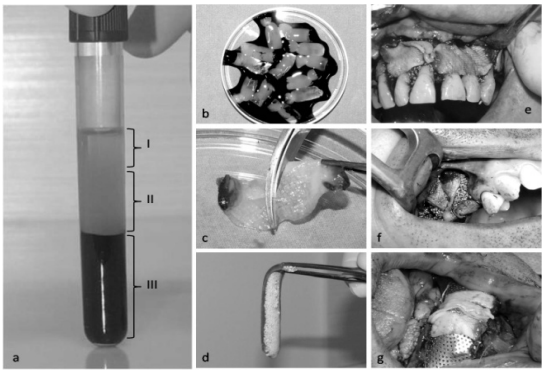

Figure 1: (a) blood centrifugation leads to formation of structured fibrin clot in the middle of the tube (II), just between the red corpuscles at the bottom(III) and a cellular plasma at the top (I); (b,c) PRF separated from red corpuscles base using a sterile tweezer and scissor just after removal of platelet poor plasma and PRF membrane prepared; (d) PRF was mixed with bone graft material; (e,f,g) PRF membrane applications.

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Cellular Action of Short Carbon Nanotubes

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Due to their exceptional physicochemical properties carbon nanotubes (CNTs) are included in a variety of industrial applications and consumer products. They might also find applications in medial diagnosis and treatment provided they are non-toxic. Toxicity of CNTs has been related to contamination with heavy metals, to the high relation of length to diameter (termed 'aspect ratio') and to the surface functionalization with carboxyl groups [1]. CNTs with shorter lengths (<2 µm) are expected to react less toxic.

In order to study whether short single-walled CNTs (SCNT) and multi-walled CNTs (MCNT) possess cytotoxic potential pristine (SCNT, MCNT) and carboxyl-functionalized CNTs (SCNTc, MCNTc) of different diameter (1-50 nm) were characterized according to purity, size and zeta potential. Cellular localization, cytotoxicity after 4h and 24h and after 4 weeks, effects on apoptosis, membrane integrity, oxidative stress and cytokine secretion were studied. Furthermore, in order to reveal changes in gene regulation whole genome expression analysis was performed. As CNTs are intended for intravenous application, endothelial cells were used for the studies.

Cells ingested small diameter (<8 nm) and large diameter (≥20 nm) CNTs to similar degree and no cytotoxicity of all CNTs at 24h was seen below 50 µg/ml [2]. At higher concentrations CNTs <8 nm acted more cytotoxic than CNTs≥20 nm and carboxylated CNTs were more cytotoxic than pristine CNTs. Protection against oxidative stress by co-exposure with N-acetyl cysteine reduced cytotoxicity markedly for large diameter pristine CNTs and only minimally for small diameter carboxylated CNTs. CNTs decreased intracellular glutathione levels to different extent and acted on cells by different mechanisms; carboxylated CNTs of small diameter caused disruption of plasma membrane integrity while the large diameter pristine CNTs induced apoptosis (Figure 1).

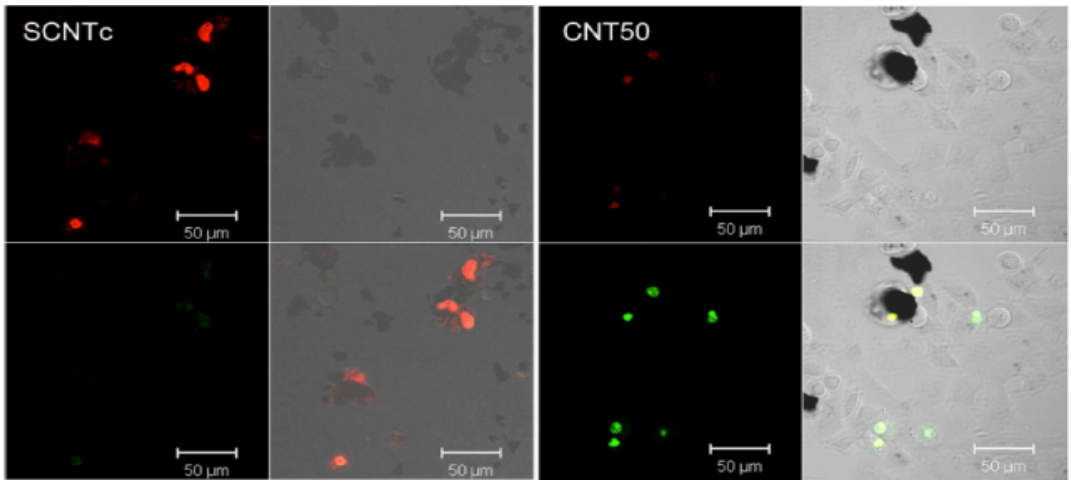

Figure 1: Induction of membrane damage (red) and apoptosis (green) by small diameter carboxylated (SCNTc) and large diameter pristine (CNT50) CNTs. Changes induced by carboxylated small diameter CNTs in cytokine secretion were more pronounced than those of large diameter pristine CNTs. The observed changes corresponded to respective changes in gene expression (Figure 2).

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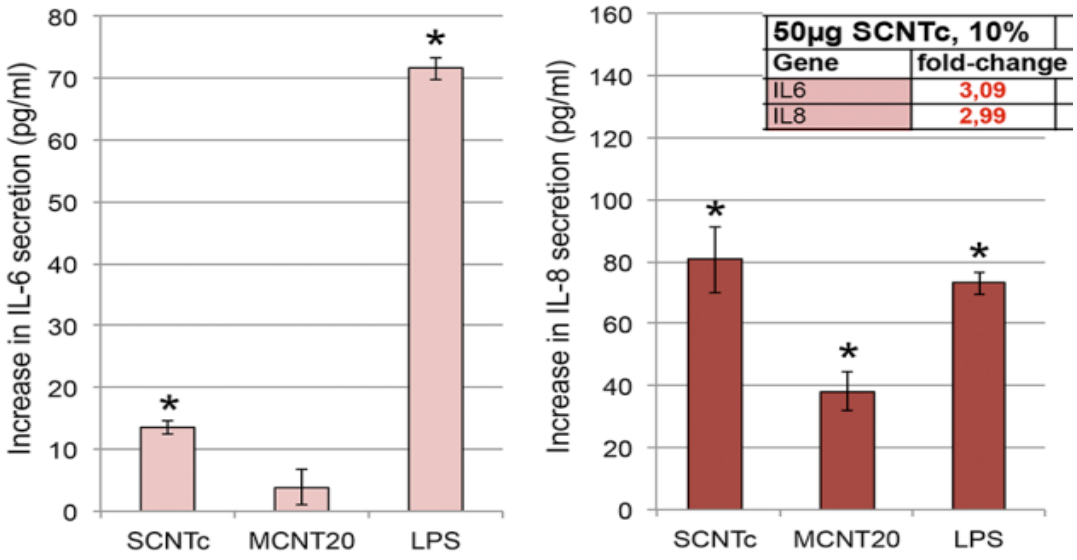

Figure 2: Increases in cytokine secretion and changes in gene expression (insert) in CNT-treated cells compared to untreated controls. Reaction to pro-inflammatory lipopolysaccharide (LPS) is shown for comparison.

After repeated exposure of cells to CNTs for 4 weeks only SCNTc impaired cell viability. Cell numbers decreased over 3 weeks and then returned to values of the untreated cells.

Our studies indicate that adverse effects caused by short CNTs were small and that cells show some adaptation upon repeated exposure.

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Analysis of Mesenchymal Stem Cell Interactions with Cross-Linked Collagen-Based Scaffolds

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Introduction

The collagen-based scaffolds have potential to imitate an extracellular bone matrix and support human mesenchymal stem cells (hMSCs) in adhesion, proliferation and osteogenic differentiation. However, the fast biodegradation rate and the low mechanical strength of the untreated collagen very often complicate *in vitro* and *in vivo* applications [1]. The stability of collagen scaffolds can be enhanced by cross-linking. Thus, the impact of various cross-linking agents (genipin [2], EDC/NHS/EtOH or EDC/NHS/PBS [3,4]) on scaffold properties were tested *in vitro*.

Methods

The structural and mechanical properties of the newly developed scaffolds were tested using pore size measurement by scanning electron microscopy and microCT, by determination of degradation rate and swelling ratio as well as compressive strength and elastic modulus. For in vitro tests cell metabolic activity (MTS, Promega, USA) of the cells cultivated in scaffolds infusions and of cells cultivated on the scaffolds, the number of cells adhered on scaffolds and fluorescence 2D/3D visualization of cell/scaffold interactions were determined. All procedures were performed after 48 h and 168 h of cell cultivation. Tissue culture treated polystyrene (PS) (TPP, CH) was used as a positive control. hMSCs were isolated from a bone marrow blood of three healthy donors.

Results

Composite scaffolds (natural collagen, poly(DL-lactide) electrospun nanofibers, calcium phosphate and sodium hyaluronate) cross-linked by EDC/NHS/EtOH, EDC/NHS/PBS or genipin were tested using different methods for their mechanical stability and proper pore size. All the methods used confirmed that scaffolds cross-linked with genipin are of outstanding properties and thus it is suitable for further biological studies. The scaffold infusions were checked for releasing of cytotoxic agents into cultivation medium. After 48 h, the metabolic activities of hMSCs cultivated in all three scaffolds infusions were comparable and higher than the PS control. After 168 h, the metabolic activities of the cells cultivated in genipin and EDC/NHS/EtOH cross-linked scaffolds infusions remained similar. However, the metabolic activity of hMSCs in EDC/NHS/PBS cross-linked scaffold infusion markedly decreased to 83 % of PS control. Metabolic activities of the cells seeded on the scaffolds was almost comparable among all three samples at 48 h and 168 h. Fluorescence visualization determined the cell ability to adhere on all the tested scaffolds. After 48 h, hMSCs on the genipin cross-linked scaffold revealed the best morphology and symmetric distribution. After 168 h, cells on all the scaffolds were similarly organized with comparable appearance. Cell penetration ability was comparable at both times. Genipin maintained constant mechanical properties in contrast to the rest of cross-linked scaffolds.

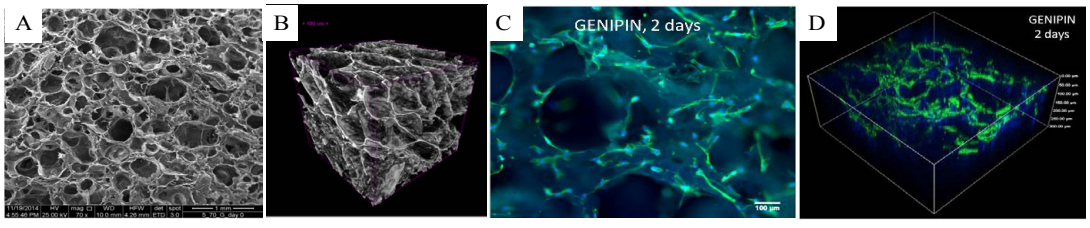

Figure 1: Collagen-based scaffold cross-linked by genipin. A) Scanning electron microscopy image, B) microCT image, C) wide-field fluorescence image of osteoblastic cells cultivated for 2 days on scaffold cross-linked by genipin, D) confocal microscopy image of osteoblastic cell penetration into scaffold cross-linked by genipin after 2 days incubation.

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Discussion and Conclusions

The entire scaffold infusions tested seemed to be non-cytotoxic; cytotoxicity is often determined by the 75% limit of the metabolic activity. However, the metabolic activities and scaffold penetration depths of cells seeded on scaffold were comparable for all three scaffolds, the quality of cell morphology, adhesion and distribution was different. The results revealed that cross-linking agents can influence cell viability, condition and scaffold behavior. In this study, the genipin assigned the best mechanical and biological features to created suitable scaffolds for hMSC application in future *in vivo* experiments and preclinical studies.

Acknowledgements

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Nanoparticulate Brain-Derived Neurotrophic Factor Improves Cognitive and Neurological Impairment in Mice with Brain Trauma

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Introduction

Traumatic brain injury (TBI) is the leading cause of mortality and disability, while the effective treatment of TBI still need to be optimized [1]. Brain-derived neurotrophic factor (BDNF) is known to protect brain tissue from injury. However, exogenous BDNF cannot itself enter the central nervous system through the blood-brain barrier (BBB) [2]. Poly(lactic-co-glycolic acid) nanoparticles (PLGA-NPs) coated with surfactant have been shown to enable the transport of drugs across BBB [3]. Thus, we hypothesized that PLGA-NPs coated by poloxamer 188 (PLGA-Pol) will serve as an effective targeted drug-delivery system delivering BDNF into the brain thus help to protect brain tissue and improve neurological and cognitive outcomes of TBI.

Methods

To design the drug, recombinant BDNF was added to PLGA-NPs (200 nm) which had been re-suspended in phosphate buffered saline (PBS) (pH 7.4). After incubation, poloxamer 188 was added to give a final dispersion and the mixture was incubated at 23°C for additional 30 min. The drug loading to the PLGA-Pol was calculated as the difference between total amount of drug in suspension and amount of unbound drug received by filtration through a membrane filter (220 nm) measured using the enzyme-linked immunosorbent assay (ELISA). TBI was induced by weight drop method [4] in 10-12-weeks-old male C57Bl/6N mice, which then were randomly divided into 6 groups (n=12). Three hours post-injury, the mice were administered intravenously (IV) 0.2 ml of the following solutions: 1st group-PBS (drug vehicle); 2nd group-solution of BDNF (5μg/per animal) in PBS; 3rd-BDNF-PLGA-NPs (uncoated); 4th-empty PLGA-NPs; 5th-BDNF + surfactant; 6th-BDNF-PLGA-Pol (coated). Sham-operated aminals received 0.2 ml IV injection of PBS. To evaluate delivery of BDNF into the brain 1 hour post-injection mice (n=6) were sacrificed and brain tissue was harvested for ELISA analysis of BDNF content. The other set of animals (n=6) were used for assessment of neurological and cognitive impairments using "Neurological Severity Score" (NSS) and passive avoidance tests. Two way ANOVA has been used to compare the different groups.

Results

About 97% of BDNF was adsorbed onto the PLGA-NPs validating good drug loading. The BDNF level in the brain was significantly higher ($p<0.001$) in mice subjected to IV injection of BDNF-PLGA-Pol in comparison with other groups. This tendency was observed in both sham-operated and animals with TBI indicating that PLGA-NPs coated with surfactant enabled transport of BDNF across the BBB. Analysis of the NSS scored revealed that one hour post-injury in group 1, the level of NSS reached 7.1 ± 0.68 demonstrating development of severe TBI. There was no difference in NSS among other groups at this time point, indicating similarity in initial TBI severity in all groups. Improvement in neurological function at day 7 was better in BDNF-PLGA-Pol group than in the rest groups ($p<0.001$). The ability of injured mice to learn the task on day 7 in 1st group was significantly decreased from 180 sec to 114.9 ± 29.2 sec showing the cognitive impairment after brain trauma. Similar findings were observed with groups 2-5. However, treatment by BDNF-PLGA-Pol significantly prolonged latency period in animals with TBI demonstrating memory improvement.

Conclusion

We have designed a new nanoparticulate BDNF coated with surfactant and the data from our study has proved that this drug-delivery system is able to transport BDNF across the BBB and also causes improvement in both cognitive and neurological deficits in mice with TBI.

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Journal of Nanomaterials & Molecular Nanotechnology

Biocompatible Drug-Antibody Conjugated Au-Znte Core-Shell Nanoparticles for Biosafety and Anti-Cancer Drug Delivery Applications

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Abstract

There is a growing demand for the development of innovative nano-drug delivery systems that can both target and improve cancer therapies more effectively than conventional chemotherapy. Initially the biosafety of these nanoparticles must be evaluated as a compulsory component in supporting drug delevopment. Cysteine capped Au-ZnTe core-shell nanoparticles have been structurally designed using a one-pot solution based route to support surface conjugation with 5-FU and human epidermal growth factor antibody to facilitate targeted drug delivery within the domain of cancer therapeutics (Figure 1A). The biosafety and biocompatibility of these nanoparticles was established on the cellular and whole-animal levels using in vitro and in vivo toxicity techniques. More specifically, the Au-ZnTe nanoparticles displayed no cytotoxicity effects against normal human colon, mammary epithelial and cancer cells of breast, prostate and colon origin. Moreover, under certain conditions the particles expressed cytokines in low concentrations and induced a cytotoxic response when exposed to human peripheral blood mononuclear cells. Additionally systemic circulation of Au-ZnTe particles displayed no adverse effects in the blood, liver and kidney functions of female Sprague Dawley rats. TEM, FTIR, Zeta potential and optical measurements were performed to confirm the surface conjugtion of 5-FU and EGF to Au-ZnTe nanoparticles. The in vitro anti-cancer therapeutic efficacy study was performed using the MTT cytotoxicity assay on breast cancer cells. The cytotoxicity studies have shown that all compo-nents in the 5-FU-EGF-Au-ZnTe nanoparticle formulation work synergistically to attack MCF7 cancer cells displaying 24.74 % increased effi-cacy than 5-FU at equivalent concentrations (Figure 1B). Futhermore receptor-ligand mediated uptake of nano-drug formulations was demonstrated using 5-FU-Au-ZnTe. Future work will involve pharmacokinetic and molecular modelling studies of the 5-FU-EGF-Au-ZnTe nanoparticle formulation to provide further insight of its cytotoxic and drug interaction properties. This study has generated valuable new knowledge that will help scientists within the field of biotechnology, nanomedicine, biochemistry and materials chemistry, to develop and optimize strategies for more efficient therapeutic application of such materials.

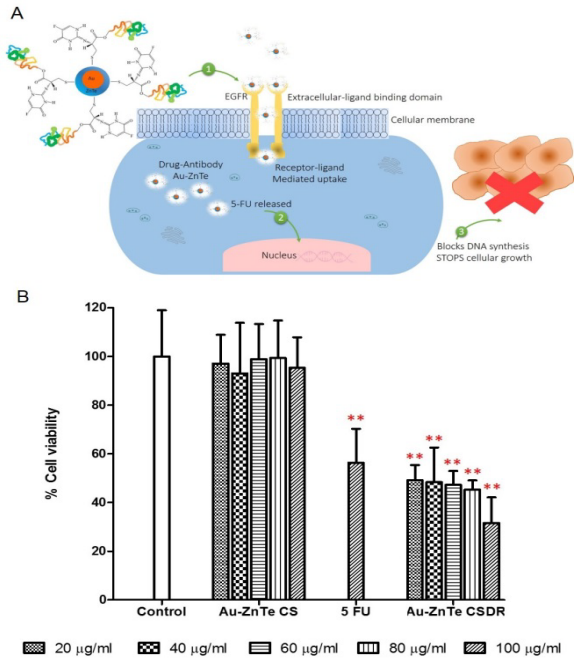

Figure 1: A. Illustrates the receptor-ligand mediated cellular uptake of 5-FU-EGF-Au-ZnTe core-shell nanoparticles for enhanced therapeutic efficacy and targeted anti-cancer drug delivery. B. Displays the comparative cytotoxicity of 5-FU and drug-antibody conjugated Au-ZnTe nanoparticles using MCF7 cancer cells.

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The Small Drug Antipyrine Impacts Polystyrene Uptake in the *Ex-Vivo* Human Placenta Perfusion Model

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The interaction between mother and unborn across the placenta is species specific hence data from animal models give limited physiological evidence. Nanoparticle kinetics at this specific biological barrier is a highly relevant topic since the unborn may also be exposed and effected by nanomaterials. The dual *ex-vivo* placenta perfusion model [1] displays the closest experimental approach to the in vivo situation during human pregnancy. Briefly, a fetal artery-vein pair that supplies a well-defined cotyledon- regarded as the functional unit of the placenta was cannulated and the flow of perfusate was established in order to simulate the fetal and maternal blood circulation in utero. Once the cotyledon was clamped into a chamber specific composed cell culture media were used in the closed configuration to evaluate maternal-placental-fetal particle distribution. Only few articles are published dealing with the interaction of nanoparticle and placenta [2]. In many published experimental placenta perfusion settings the small liposoluble drug antipyrine is used for determining the effectiveness of the perfusion since it diffuses passively from the mother across the multicellular placenta to the fetus. The aim of this study was to determine whether antipyrine used in the perfusion setting impacts the interaction of fluorescent polystyrene at the placental barrier. Polystyrene (40 µg/ml, 460 ± 4 nm) were perfused for 6h after 30min of 10 µg/ml antipyrine perfusion. In the control experiment, before adding the polystyrene, 45min of lasting antipyrine washout was carried out. Zeta potential in water of the polystyrene particles changed from -25.2 ± 6mV to -42.4 ± 5.5mV in the presence of antipyrine. Without antipyrine the mean fluorescence signal (544/590 nm) in the maternal perfusate decreased by 14.7 ± 7.8% within 6h (n=4). In the presence of antipyrine fluorescence of the perfusate dropped by 52.3 ± 10.0%, ($p<0.05$) after 6 h (n=3) which was accompanied by detection of a fluorescence signal within the placental tissue. A reference experiment revealed that the fluorescence of polystyrene in a solution of 10 µg/ml antipyrine was decreased by 9.8 ± 4.5 % compared to none antipyridine solution (6h, n=7). In none of the experiments a fluorescence signal could be observed in the fetal perfusates.

In conclusion, the safety and efficacy of nanomaterials can be influenced by minor variations in multiple parameters and need to be carefully examined in preclinical and clinical studies, particularly in context of the biodistribution and targeting to intended sites.

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Comparative Assessment of Newly Synthesized Nano TiO2 for Photocatalytic Capability and Toxicological Properties

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Understanding photocatalytic degredation and toxicity relationship between nanomaterial and pollutant interactions is critical for preventing environment and human health. The treatment of water with nanostructured TiO_2 may promise for solution to providing safe and clean water due to their photosensitivity and oxidant capacity [1]. Uptake of nanomaterials in in vivo models is also important considerations for nanotoxicology [2]. We evaluated photochemical degradation of fungicide, fluoxastrobin as a model pollutant by oxidation using 0.45% S- doped or 0.64% Mn- doped nanoTiO_2. The doped photocatalysts were synthesized using reflux and sol gel, respectively. Crystallite size and surface morphology were characterized by XRD, SEM, BET and particle size distribution. Degradation was carried out in the suspensions under UV and visible illumination in solar box. The highest degradation rates of 5 ppm fluoxastrobin with the S- doped nano TiO_2 was 98% with visible illumination due to TOC and spectrophotometric analysis. The highest degradation of fluoxastrobin with Mn- doped TiO_2 was 58%. The comparative toxic effects of the photocatalysts and photocatalytic by-products of fluoxastrobin were determined using Xenopus laevis and Danio rerio embryos for 96 h and Daphnia magna neonates for 48 h. Results showed that S- or Mn- doped TiO_2 nanoparticles did not cause significant lethality on embryos. However, D. magna neonates affected from nano materials after 48h exposure. Toxicity of Mn- doped TiO_2 was higher than S- doped TiO_2 on daphnids. Photocatalytic degradation of FLX for 15 h with Mn- doped TiO_2 significantly decreased lethality for X. laevis and D. rerio but D. magna neonates were not resistant as other species. The S- doped TiO_2 decreased lethal effect for X. laevis after 5 h photocatalysis of fluoxastrobin, but it is still significantly lethal for zebrafish embryos after 10h degradation. In conclusion, comparison of different species is critical for evaluating nanomaterials toxicity studies.

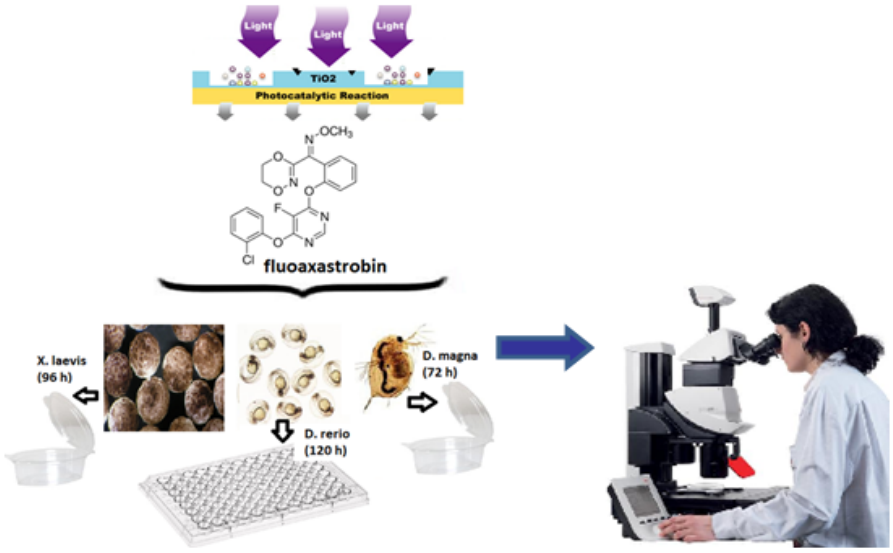

Figure 1: Study design for evaluation of toxicity of synthesized NPs on test organisms

Acknowledgement

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Nanomedicine, From Poc to Reality: The Importance of an Industrial Perspective and GMP Scale Up

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Abstract

Nanotechnology and specially its application to improvement of Human health (Nanomedicine) is expected to be one of the pillars of novel products and processes in the next future, in this case to get innovative therapies. Nano-enabled therapies , together with cell and gene therapies and personalized medicine will pave the way for a revolution in the treatment of several diseases which currently have no treatment or low efficacy ones. There is a common consensus on the potential of nanomedicine to contribute to this global improvement, but this will only be possible if all the nano medicine community is able to foster the translation of the promising results obtained at laboratory scale to real products applicable at clinical settings. This full deployment of nanomedicine must be based on the identification of the existent gaps for translation, at different levels, and on the industrialization of nanomedicines production, taking into account Good Manufacture Practices (GMP) and regulatory aspects.

From Biopraxis, the Research and Innovation Unit of the pharmaceutical Group Praxis, we have developed an intensive work to identify and propose solutions for many of those gaps. In the current moment Biopraxis holds the Chairmanship of the Nanotherapeutics Working Group in the European Technology Platform for Nanomedicine, making us a privileged stakeholder to receive inputs from the nanomedicine community and to highlight our contributions to the translation of nanomedicines.

In this communication, we aim to share all these lessons learned when trying to move nanomedicine to the next steps. To do this, we have identified and proposed solutions to the different challenges at different levels, and, due to our industrial commitment, with a special focus in GMP up scale of nanomedicines production. Main challenges are the following:

- Society: There is a need of higher acknowledgment and support for nanomedicine, avoiding a potential "nano-fobia"
- Risks: We identify risks at two main levels: safety and environment impact, and propose preventive and corrective actions
- Regulation: medicines market is a highly regulated market, and there is a need for the definition of the regulatory requirements for nanomedicines. We set the problem at three different levels: Preclinical development, clinical research and market access
- Technology implementation: There is a huge amount of technology offers, which has to be discerned by industry. An open innovation scheme is proposed as a potential solution to this challenge
- **Industrialization:** Biopraxis is specialized scaling up the manufacturing of diferent nanoformulations from milligram-scale laboratory (Figure 1) synthesis up to multigram-scale production to generate sufficient material for clinical and regulatory assays. We standardise the up-scale production of nanoparticles under GMP (Figure 2) considering the main bottleneck aspects: reproducibility, stability, and non-immunogenicity (sterility and non-pyrogenicity). At the same time, we consider critical aspects of the GMPs design such as: continuous quality control, risk assessment for manufacturing process, specifications for excipients, intermediates and finished products; rooms classification, equipment, supplies (water, heat, stirring, gases…)
- B**usiness models:** New paradigms need also innovative approaches to business models.

Nanomedicines still present some weakness on this sense, i.e. detailed cost evaluations.

As it has been shown, current landscape for nanomedicines is full of potential, but presents a series of challenges, which need to be solved, and in many cases, only the commitment and driving action of the industry can bridge this potential valley of death. At Biopraxis we are managing several projects for the development of nanomedicines, and we want to share our experiences and potential answers to contribute to nano-enabled therapies in the next future, in a context with the view from the Industry is sometimes difficult to find.

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Evaluation of Toxic and Teratogenic Effects of Core-Shell Nano TiO2 at Different Trophic Levels

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The production, number and significance of nanomaterial based products are growing, as is the gap in our knowledge is how these new materials will interact with living systems [1]. In recent years, TiO_2 nanoparticles modified with coatings for optimized remediation of contaminants in aqueous environments [2]. To determine the potential risk of the materials, we evaluated toxic and teratogenic effects of different nanoparticles (NPs) including pure TiO_2, SiO_2 and newly synthesized core-shell TiO_2-SiO_2 and SiO_2-TiO_2. Amphibian (Xenopus laevis) and fish (Danio rerio) embryos and unicellular algae (Chlamydomonas reinhardtii) and bacteria (*Escherichia coli*) were used as test organisms. Lethal effects and developmental malformations were evaluated for *D. rerio* and *X. laevis* embryos. Growth inhibition was determined for X. laevis, algae and bacteria, after acute exposure. Genotoxic effects were also tested using human lymphocyte cultures using sister chromatid exchange (SCE). Crystallite size and surface morphology were characterized by XRD, SEM, BET and dynamic light scattering. We found that none of NPs affected concentration related lethality or malformations to X. laevis and D. rerio embryos. Tested NPs did not cause growth inhibition on X. laevis embryos after 96 h. However, all tested NPs resulted in growth inhibition of algae exposed to 125 mg/L after 96 h but not in E. coli. TiO_2-SiO_2 NPs significantly inhibited growth of algae at 25 and 125 mg/L after 120 h. The SCE assay did not reveal significant genotoxic effects in in vitro assays. According to our results we suggest that tested NPs are not significantly lethal, teratogenic and genotoxic on tested organisms, but NPs may cause negative effects on other species such as algae. However, additional studies such as nanocosm models are required to determine ecosystem safety impacts of tested materials.

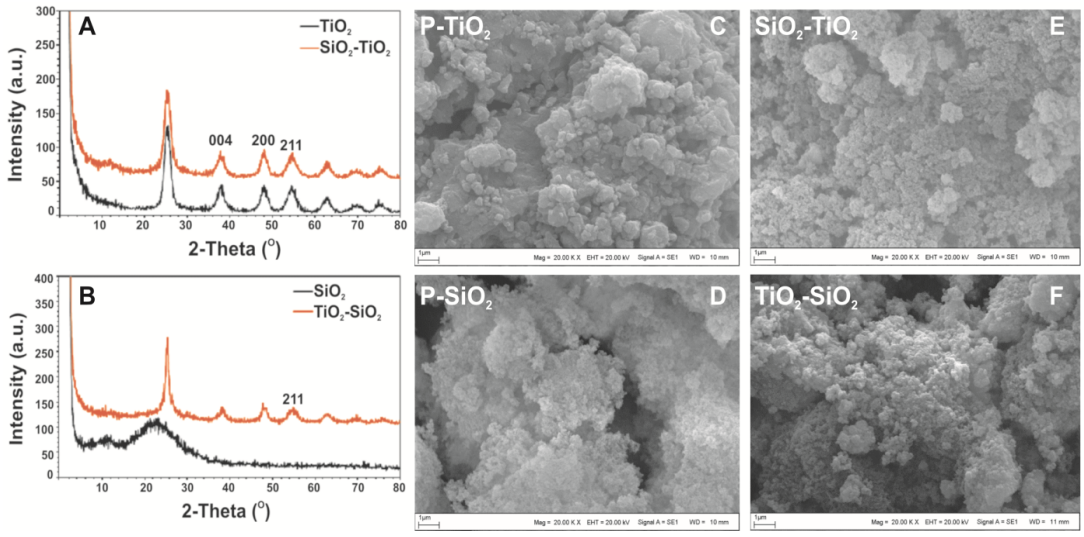

Figure 1: The XRD patterns (A-B) and SEM images (C-D for pure, E-F for coated materials) of tested NPs.

Acknowledment

This work was supported by grants from The Scientific and Technological Research Council in Turkey (TÜBITAK) (Project #113Z561).

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Spectroscopic and Calorimetric Studies of the Interactions between PAMAM G4-OH Dendrimer and 5-Fluorouracil

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Poly(amidoamine) dendrimers (PAMAM) of fourth generation (G4) with hydroxyl terminal groups (G4-OH) are tree-like regularly higly branched macromolecules that can find their use as carriers of oncologic drugs, including among others 5- fluorouracil. 5-Fluorouracil is a potent oncological drug with high toxicity. The aim of our study was to evaluate the stoichiometry of 5-fluorouracil binding with a macromolecule of PAMAM G4-OH and the equilibrium constant of such combination. Using the results of the isothermal titration calorimetry and ^{1}H NMR titration, thermodynamic parameters of binding (n, K, ΔH) were evaluated. These parameters confirm the exothermic and spontaneous character of bonding 5-fluorouracil to PAMAM G4-OH dendrimer.

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Nanofibre Scaffolds for Tissue Engineered Vascular Grafts

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Introduction

The development of shelf-ready, synthetic vascular grafts which would give equal or superior clinical long-term results than the currently used autologous internal mammary artery or saphenous veins for cardiovascular revascularization procedures has been quoted as the 'Holy Grail'. Since the introduction of Dacron over 50 years ago and ePTFE over 30 years ago, no breakthrough has been made in this field. Tissue-engineering of grafts with autologous stem cells has shown a theoretical potential, however failed commercialization due to time and cost aspects. We therefore initiated and manufactured a novel, bio-degradable, acellular, synthetic scaffold for vascular replacement and used the body as bio-reactor for in situ tissue engineering.

Materials and Methods

Fully degradable, small caliber (2 and 4mm ID), arterial poly (ε-caprolactone) (PCL) grafts were used as an interposition abdominal aortic graft and were compared to ePTFE [1]. The scaffolds were made of nano- and micro-fibres using PCL electro-spinning. Rats (n=>100) were followed up to 2-years at several time points [2]. Additionally, carotid artery replacements in the rat were performed to study different physiological flow patterns. Furthermore, pigs were used for bi-lateral carotid artery replacement for assessing biologic and species variations. At each time point, in-vivo compliance, angiography for patency and ex-vivo histological examination with morphometry were performed. Additionally, micro-CT scans were carried out for assessing the graft calcification.

Results

In the rat abdominal replacement model 100% patency was found whereas the patency of ePTFE grafts after long-term implantation was only 67% [3]. However, in the carotid artery some thrombus formation occurred and a few occlusions were found in the rat as well as the pig model (80% patency). The compliance was significantly lower than the native artery but significantly higher than ePTFE grafts. Endothelialisation was near confluent after 6-weeks in the PCL graft and much slower in ePTFE. Intimal hyperplasia was significantly lower in the PCL grafts and so was calcification. The cell ingrowth was rapid and significantly more pronounced with myofibroblasts in the PCL as compared to ePTFE. However, cell regression was noted after implantation durations, representing a life-span of a rat.

Discussion and Conclusions

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The degradable PCL grafts showed 100% patency, fast endothelialisation, good cellular infiltration, adequate compliance and low intimal hyperplasia in the rat abdominal aortic replacement model as compared to ePTFE grafts. Limited thrombogenicity was found in other anatomic positions, such as carotid arteries, in the rat and pig models probably due to biological and physiological different flow patterns, as compared to the abdominal aorta. Future studies may require heparin coating to reduce early thrombogenicity for clinical applications, but degradable nanofiber scaffolds are a promising option for shelf-ready tissue-engineered vascular grafts.

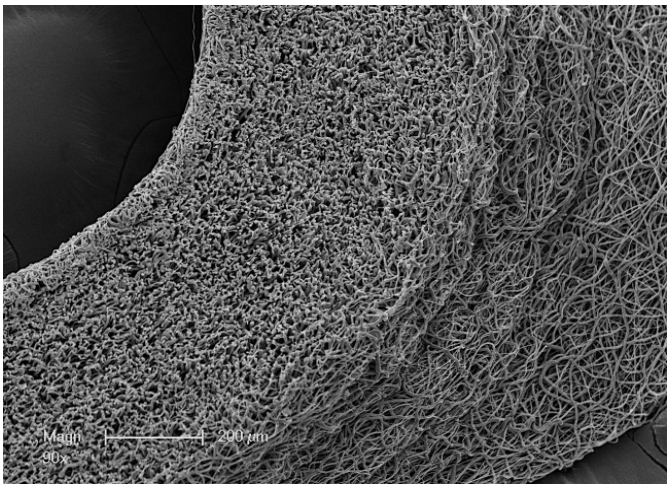

Figure 1: Figure illustrating the cut section of the PCL nano-fibre scaffold used for tissue-engineered vascular grafts.

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Nano Antibiotics: An Alternative to Combat Emergent Infectious Diseases

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Keywords: Nanoantibiotics; Silver nanoparticles; Multi-resistant bacteria; Synergia

Infectious diseases are a leading cause of death worldwide. The antibiotic-resistant organisms are an important health problem. This resistance is a global problem and a major concern in areas such as clinical, agriculture and veterinary. The pace of development of new antibiotics cannot compete with the ability of microorganisms to generate resistance; it is therefore critical to develop novel antibiotic agents. An alternative is nano-antibiotics: antimicrobial nanomaterials such as silver nanoparticles (AgNPs) and Ag-derived nanocomposites with antimicrobial properties. We study the antimicrobial effect of Ag-nanocomposites and its synergistic activity with conventional antibiotics against Gram-positive and Gram-negative bacteria, as well as some fungi, all of them causative agents of emergence diseases.

We determined antimicrobial properties of AgNPs and other Ag-based nanocomposites over bacteria and fungi. On the other hand, we determined each microorganism showed different susceptibility to different antibiotics. We found that combined treatment with AgNPs and antibiotics showed synergy. Here, we proposed a combinatorial effect of antimicrobials that drives synergy depending of their specific mechanism of action.

Despite biological differences between microorganisms, Ag-nanocomposites have significant antimicrobial properties. The inhibitory capacity of Ag-nanocomposites is independent of antibiotic susceptibility. Nano-antibiotics could be used as a first-line treatment for some infections and other related health problems. The synergistic effect could improve the effectiveness of current treatments, even allowing reuse of antibiotics that have fallen into disuse due to antibiotic-resistant microorganisms' emergence. Nano-antibiotics could have a major social and economic impact.

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Study of Redox Modulatory Response Induced by Quitosan Nanoparticles with Antioxidant Capacity in Chondrocytes

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Oxidative stress with chronic endogenous production of reactive species, play an important role in joint diseases linked to aging [1]. Antioxidants may develop significant effects in these conditions [2]. In this work the redox modulatory effect of nanoparticles prepared from Chitosan-GSH was studied using as a model in vitro primary culture of human chondrocytes taken from hyaline cartilage was evaluated.

Characterized primary chondrocytes cultures were used as experimental model. The cells exposed to H_2O_2, $CdCl_2$ and nanoparticles in a dose-response effect were analyzed. Fluorescence and confocal microscopy analysis were conducted. In order to assess the amount of reactive species, it was conducted cell rox test. The results showed that the nanoparticles modulated intracellular redox status. When we exposed the cells to high doses of nanoparticles and H_2O_2 the GSH levels showed significant differences against the control. Glutathione peroxidase activity was increased in cells exposed to nanoparticles and cadmium. Lipid peroxidation decreased when cadmium exposed cells were in contact with nanoparticles. The transcription factor Nrf2 was evaluated and the nanoparticles modified the levels of this protein. The results suggest the ability of the nanoparticles to modulating redox cell status showing different effects according the dose of nanoparticles and stressor agent used.

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Journal of Nanomaterials & Molecular Nanotechnology

Controlled Drug Delivery System for Delivery of Poor Water Soluble Drugs

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Abstract

Poor aqueous solubility of many pharmaceutical drugs and potential drug candidates is a big challenge in drug development [1]. Nanoformulation of such candidates is one of the major solutions for the delivery of such drugs [2]. We initially developed the evaporation assisted solvent-antisolvent interaction (EASAI) method. EASAI method is useful to prepared nanoparticles of poor water soluble drugs with spherical morphology and particles size below 100 nm. We successfully prepared the nanoparticles of poor water soluble drugs Carbamazepine (CBZ), Griseofulvin (GF), Fenofibrate (FF), Naproxen (NAP), Ketoprofen (KP) and Ibuprofen (IBP) [3,4]. In order to further improve the formulation to reduce dosage amount and side effects it is important to ensure controlled delivery of drugs. Among the many nano-drug carrier systems available today to address the aforementioned issue, solid lipid nanoparticles (SLNs) have gained importance owing to many advantages such as high biocompatibility, stability, non-toxicity and ability to achieve controlled release of drugs and drug targeting [5]. SLNs can be administered through all existing routes due to high biocompatibility of lipids. SLNs are usually composed of lipid, surfactant and drug is encapsulated in lipid matrix [6]. In the present work, SLNs loaded with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as Nabumetone (NBT), Ketoprofen (KP) and Ibuprofen (IBP) have been successfully prepared using different lipids and surfactants. We studied and optimized experimental parameters using a number of lipids, surfactants and NSAIDs. The effect of different experimental parameters such as lipid to surfactant ratio, volume of water, temperature, drug concentration and sonication time on the particles size of SLNs during the preparation using hot-melt sonication was studied. It was found that particles size was directly proportional to drug concentration and inversely proportional to surfactant concentration, volume of water added and temperature of water. SLNs prepared at optimized condition were characterized thoroughly by using different techniques such as dynamic light scattering (DLS), field emission scanning electron microscopy (FESEM), transmission electron microscopy (TEM), atomic force microscopy (AFM), X-ray diffraction (XRD) and differential scanning calorimetry and Fourier transform infrared spectroscopy (FTIR). We successfully prepared the SLNs of below 220 nm using different lipids and surfactants combination. The drugs KP, NBT and IBP showed 74%, 69% and 53% percentage of entrapment efficiency with drug loading of 2%, 7% and 6% respectively in SLNs of Campul GMS 50K and Gelucire 50/13. In-vitro drug release profile of drug loaded SLNs is shown that nearly 100% of drug was release in 6 h.

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Ovine Disc Regeneration by Hydrogel System in Combination with AMSC

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Introduction

Due to changed ways of life and the increasing life expectancy, the therapy of disc degeneration and its secondary diseases belongs to the most important sociomedical problems. Until today, the therapy of intervertebral disc disease is mainly based on the surgical removal of the cartilage tissue, protruding between the vertebras. Such a sequestrectomy means a permanent loss of tissue. Regenerative implants on the basis of cell transfer, can offer a promising alternative to conventional therapies. From a clinical point of view, it is assumed that a self-regenerative implant based adipose mesenchymal stem cells (AMSC), combined with an injectable scaffold material and represents a crucial improvement of the mechanical long-term stability of damaged intervertebral disc segments.

Method

The intervertebral discs of adult female sheep, 2 years of age, were mechanically damage. Subsequently, approximately 3 g of adipose tissue was taken from each sheep. From this tissue, the AMSC were recovered through outgrowing and expansion in a cell culture system, up to a number of approximately 10^7 cells. The addition of growth factors was omitted. After scar tissue has formed over the damaged annulus fibrosus, the cell differentiation was induced in combination with a collagen based hydrogel in the disc. Euthanasia was carried out after a standing time of 3,6,12 months to display the regeneration progress, as examined by CT, µCT and histologically.

Results

Approximately 6 weeks after inducing damage, a dense scar tissue over the defected site was observed. The injected mixture of cells and the hydrogel remains within the nucleus pulposus. The damage to the cells throughout the injection is minimal. At all three points throughout the study, an even distribution of cells in the nucleus tissue is present. Typical signs of degradation, characteristic of the formation of cell clusters, could not be observed. It is observed that in comparison to the negative controls, a definite decrease in disc height could be stopped through treatment. The formation of tumors could not be observed over the period of one year.

Conclusion

The application of a hydrogel AMSC may be a suitable treatment in intervertebral disc degeneration. Even if a regeneration of disc tissue cannot be proven, a progressive height loss, as a result of degeneration, could be prevented.

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Enhanced Middle Molecule Clearance with a High Cut-Off Filter

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Extracorporeal therapies are considered as an option to modulate cytokine levels in the circulation in systemic inflammatory syndromes. The technologies based on high cut-off membranes with larger pore-size and effective clearance of middle molecules is most promising. Here we show the results of in vitro experiments comparing the Ultraflux® AV 1000S haemofilter to the Ultraflux® EMiC®2 filter (both from Fresenius Medical Care, Bad Homburg, Germany) regarding cytokine elimination. In these experiments, 2 × 1000 ml human plasma was spiked with IL-6, IL-8, IL-10 and TNF-α and dialyzed with the AV 1000S filter or the EMiC®2 filter. The experiment was conducted using two Fresenius 4008 H haemodialysis machines with a plasma- and dialysate flow of 300 ml/min. Samples for clearance measurements were taken at 15, 30, 60, 120, 180 and 240 min. Sieving coefficients were determined at a filtrate flow of 10 % of the plasma flow. All experiments were carried out in triplicates and cytokines were quantified by ELISA. The results show that IL-8 is efficiently removed by both filters. Larger cytokines, such as IL-6 and TNF-α were removed only by the EMiC®2 filter with a clearance rate of 4.7 and 2.4 ml/min, respectively. For IL-10, the EMiC®2 shows much higher clearance rates than AV 1000S.

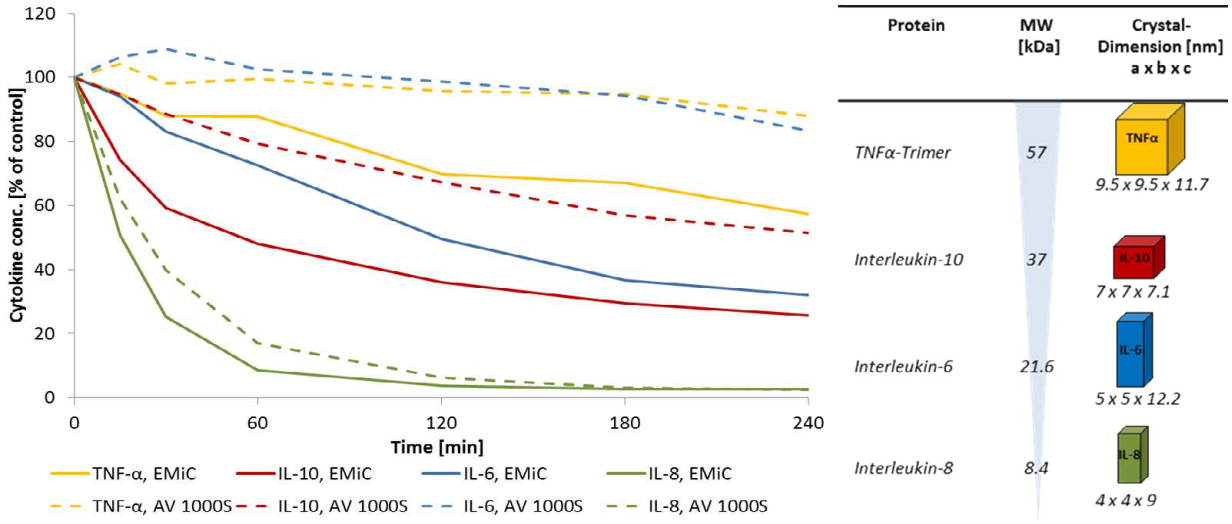

Figure 1: *In-vitro* comparison of cytokine removal between EMiC®2 and AV 1000S (left) and relative molecular mass as well as dimensions of the cytokines used in this study.

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New Materials and Methods for Nanopatterning of Proteins

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The patterned immobilization of proteins is a key-factor for cell-surface and protein-protein interaction experiments. In our project we aim for nanopatterns of anchor proteins (e.g. streptavidin) with a cell-friendly adhesion surface (e.g. fibronectin) and approach this objective by two ways. For both we prepare a stamp of a PDMS-derivate suitable for nanopatterns with a young-modulus 100 times higher than soft PDMS enabling lateral structures down to sub 10 nm [1]. We use these stamps for soft lithography and print directly onto a coated substrate, already achieving homogeneous monolayers for 200nm-width wells for selected proteins. Alternatively we imprint a residual-layer-free pattern of a water-soluble UV-resin on acryloylmorpholin-basis (UV-ACMO) [2] and incubate a protein solution onto these structures. The proteins adsorb on the exposed substrate between the ACMO, a washing step removes the ACMO and the remaining proteins finally reveal the inverse of the ACMO structure. This process promises a much better reproducibility compared to the direct printing process and is suitable for industrial scaling-up.

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Highly Sensitive Biomarker Assays for Bone Metabolism based on Metal Enhanced Fluorescence

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Serum biomarkers are an essential and emerging part of modern medical science. They are used to gather data about disease progression, to assess the risks of given population groups and to evaluate the efficacy of new therapies. As the blood of patients frequently contains only very small amounts of these biomarkers, the sensitivity of test methods must be continuously raised. Metal-enhanced fluorescence (MEF) is a promising technology to deliver such highly sensitive tests, because it allows up to a 100 fold increase of the signal/noise ratio. So far, the commercialisation of MEF for clinical tests has been unsuccessful due to the inadequate reproducibility of the required nano-metal structures and the non-availability of suitable biomarker fluorescence tests. FIANOSTICS and Sony DADC BioSciences successfully solved these problems by combining highly reproducible nano-structuring technologies (patent pending), originally developed for Blu-Ray and DVD manufacturing, with long-term experience in biomarker development.

This new MEF-platform was applied for the development of direct fluorescence immunoassays (FIA) for the biomarkers NOGGIN and ASPORIN, two molecules considered of importance for the generation of bone metastasis and for disease progression of osteoarthritis. We hereby present basic data about the MEF-platform and performance-comparison of both MEF-FIAs to conventional immunoassay technology.

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Iontophoretic Delivery of $\{Mo_{72}Fe_{30}\}$ Nanocluster

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Transdermal electrophoresis is a possible way to deliver charged nanoparticles (including so-called "nanocapsules") into the human body. It has a list of advantages in comparison with other ways. It increases the locality of impact of the drug and helps to form a "depot" in the skin.

In this context, it's important to predict a concentration profile and amount of drug delivered through the skin.

Our experiments demonstrated that polyoxomolybdate (POM) nanocluster $\{Mo_{72}Fe_{30}\}$ [1] can form associates with thiamine chloride and insulin in solutions. We studied the process of transdermal diffusion (through the rat skin) of pure $\{Mo_{72}Fe_{30}\}$ and above mentioned associates using the experimental installation described in [2]. We obtained the amounts of POM and it's associates which permeated through the skin under the influence of electric current.

Using the model of homogeneous membrane [3] we could predict the concentration profiles of POM and it's associates in the skin by numerical solution of Nernst-Planck's equation [4]. Values of diffusivity coefficient for POM and it's associates in the skin were estimated by fitting.

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Laser Sintering of Calcium Phosphate Biomaterials on Tooth Enamel

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Tooth hypersensitivity has gained attention in oral health in recent years as it is a growing problem affecting both the young and ageing population worldwide. Surveys concerning the prevalence and distribution of the disease suggest that almost 10-15% of the population suffers from tooth hypersensitivity due to mineral loss [1]. As a non living tissue, enamel cannot be self-repaired after substantial mineral loss [2] and so hypersensitivity can be treated only by exogenous means. However, a long term and effective therapy is yet to be found. Motivated by this, our aim is to develop a new treatment procedure where a thin layer of an acid resistant calcium phosphate biomaterial is sintered and densified on acid eroded enamel by irradiating with near IR femtosecond lasers [3].

For our experiments two different biomaterials were used; brushite doped with 10 mole % Fe^{3+} and hydroxyapatite (HAp) doped with 10 mole % Fe^{3+}. The addition of Fe^{3+} to the calcium phosphate matrix improves the linear photon absorption at near-IR wavelengths while at the same time enhances sintering and densification.

In the present work, experiments are carried out to establish the form of the interaction of our biomaterial with continuous wave (CW) and femtosecond (fs) lasers. To achieve this, our biomaterials were applied to acid eroded enamel surfaces, prepared using bovine incisors, in order to form thin (20-50 μm) compact layers. After forming the mineral layers, each sample was irradiated with two different lasers; one CW source emitting at 1064 nm and one fs source emitting at 1045 nm with 1 GHz repetition rate and pulse duration in the region of 100-200 fs. For all the experiments the average power of the lasers was adjusted to be 0.4 W while the exposure time of each spot was about 0.3 s.

X-Ray diffraction, Scanning Electron Microscopy (SEM), Fourier transform infrared spectroscopy (FTIR) and surface profilometry have been used to characterize the resulting surfaces. In order to verify the bonding of the formulated layer with the underlying enamel brushing trials have been conducted.

Laser irradiation was shown to cause transformation of the Fe^{3+}-doped brushite and Fe^{3+}-doped HAp samples into β-calcium pyrophosphate and calcium-iron-phosphate, respectively, with simultaneous evidence for microstructural sintering and densification. The new layer has survived brushing trials equivalent to 2 days normal tooth brushing, suggesting it has been attached and bonded with the underlying enamel (Figure 1).

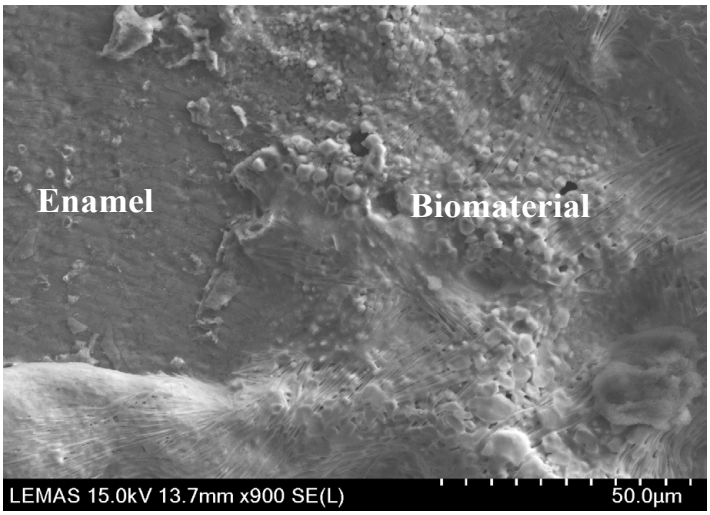

Figure 1: Densified layer of iron doped brushite on enamel surface after irradiation with a CW laser (0.4 W av. power and 0.3 s exposure time) and a subsequent brushing trial.

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We demonstrate that the laser induced mineral transformation provides a means to control the phase constitution and morphology of related surfaces on any hard tissues (bone or tooth) suggesting the importance of these results beyond treating tooth hypersensitivity. For example, such treatments could be useful for applications in bone regeneration by triggering and supporting osteogenic cell activity.

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