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IN FOCUS: NANOMEDICINE - EDITORIAL

Nanomedicine *In Focus*: Opportunities and Challenges Ahead

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Nanomedicine has emerged during the past decades to promise extraordinary breakthroughs in a wide range of diagnostic and therapeutic endeavours. Understanding and controlling the interfacial interactions of nanomaterials with biological entities such as soluble and insoluble proteins, biological membranes, and genetic materials are of paramount importance towards their successful implementation in medical applications. This special 'Nanomedicine' *In Focus* issue of Biointer*phases* illustrates the way exquisite control of the unique physicochemical properties of nanoscaled materials and advanced understanding of their bio-interfacial activity are rapidly translating into medically relevant applications as diverse as regenerative medicine, molecular imaging, molecular diagnosis, and targeted therapy.

One review article included in this special edition focuses on stimuli responsive polymers and their application in nanomedicine. The review by Palivan and coworkers describes in particular the different types of stimuli responsive materials and how their integration in biomedical devices bears some exciting promises towards advances in fields as diverse as drug delivery, biodiagnostics, cell culture and tissue engineering, or biosensing [Stimuli-responsive polymers and their applications in nanomedicine]. Along with this exciting review, an innovative application of light responsive materials is presented by Boyd, Hanley and collaborators (Fong et al.) [Alkylation of spiropyran moiety provides reversible photo-control over nanostructured soft materials for drug delivery]. In this work, photochromic spiropyran moieties are used to achieve reversible photo-control over nanostructured liquid crystalline systems, opening new horizons for on-demand light-triggered drug delivery. A critical requirement towards the integration of polymeric biomaterials in the medical field is the understanding of their structure–activity relationship in contact with biological materials. Polymeric surfaces that resist non-specific adsorption of proteins, bacteria, and higher organisms are of particularly high interest in diverse applications ranging from drug delivery to diagnostic devices and biomedical implants. A study from Pidhatika and co-workers demonstrates that coatings made of poly(2-methyl-2-oxazoline), a graft copolymer with excellent non-fouling properties, are significantly more stable than poly(ethylene glycol) ones [Comparative stability studies of poly(2-methyl-2-oxazoline) and poly(ethylene glycol) brush coatings]. Such thin films maintained their protein-repellent properties even under aggressive conditions, and appear therefore as a promising alternative to PEG in biomedical applications.

In a second review article in the special edition, Nisbet and Williams provide an overview of nanostructured supramolecular biomaterials that can be constructed by non-covalent self-assembly of peptides [Self assembled peptides: characterisation and in vivo response]. The article focuses in particular on the structures and forces underpinning the formation of self-assembling scaffolds useful for regenerative medicine applications. Such systems have been widely explored in recent years to overcome the

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limitation of engineered scaffolds, which often fail to appropriately recreate tissue analogues due to the intrinsic complexity and hierarchical nature of biological tissue. An exciting feature of peptide-based self-assembled scaffolds is their compatibility with in vivo applications, as they can be directly injected into diseased tissue to recruit native cells, provide the required biological cues, and ultimately promote regeneration. On the other range of the fabrication spectrum, Brown et al. present an interesting innovative approach to the fabrication of flexible tubular structures designed for tissue engineering applications [Design and fabrication of tubular scaffolds via direct writing in a melt electrospinning mode]. By using non-conductive polymer melts instead of polymer solutions, and using a finite element model as a predictive design tool, the authors demonstrate that the path and collection of electrospun fibers becomes predictable, which results in cell-compatible scaffolds with controllable mechanical properties and patterns on the micron-scale.

Functional nanoparticles have become the poster child of nanoscience in medicine, and diagnostic and therapeutic nano-sized agents have already entered the clinical world, with many more to come in the near future. Improved control over nanoparticle synthesis is rapidly providing the biomedical community with an ever-increasing number of diagnostic and therapeutic materials with very potent activities. Three research articles illustrate the therapeutic and diagnostic potential of colloidal nanomaterials. In a manuscript from the group of Tanja Weil, the design and characterization of albumin-based micelles is reported towards the development of robust nanocarriers of the cytotoxic drug doxorubicin. An in vitro cytotoxicity five-times higher than that of the free drug was observed, suggesting the potential of such nanocarriers against cancer [Nano-sized albumin-copolymer micelles for efficient doxorubicin delivery]. Along with the potential to improve the delivery of cytotoxic drugs, nanocarriers are being actively advanced towards the development of safe and efficient strategies to control gene expression and induce therapeutic responses against a range of diseases. In an article by Pei Li's group, the ability of amphiphilic core–shell nanoparticle to deliver gene in various mammalian cell lines is demonstrated [Polyethylenimine-based amphiphilic core–shell nanoparticles: study of gene delivery and intracellular trafficking]. The well-defined branched polyethylenimine shell facilitated the formation of plasmid DNA complexes, making these core–shell carriers a potential alternative to viral vectors. The diagnostic potential of rationally designed nanoprobes is exemplified by a contribution from Yukio Nagasaki's group [Nano-sized albumin-copolymer micelles for efficient doxorubicin delivery]. This article describes the preparation of a hydroxylamine-containing nanoparticle which emits an intense electron spin resonance (ESR)-signal upon enzymatic oxidization and in a pH-sensitive fashion, which could in turn enable ESR imaging of inflammation in vivo. Despite these remarkable progresses, the required understanding of the interactions between colloidal nanomaterials and biological entities such as cells, tissues and proteins remains limited; future progress in understanding the mechanistic aspects of nanoparticle performance in vitro and in vivo will be decisive for successful translation to applications.

The biointerfacial properties of functional nanomaterials are of critical importance in this regard, and mostly dictate their fate in biological systems. A number of articles in the Nanomedicine special edition cover the very critical issue of nanoparticles and cell interactions, and demonstrate how advanced biointerfaces can be used to control cellular interactions. A study by Guangjun Nie's group reports that gold nanoparticles, although non-toxic, induce significant change of gene expression, in this case up-regulation of heme oxygenase-1, in a cell-specific manner, which draws attention to the importance of intracellular molecular mechanisms when deciphering the biological effects of nanomaterials in cellular models [Deciphering an underlying mechanism of differential cellular effects of nanoparticles: an example of bach-1 dependent induction of ho-1 expression by gold nanorod]. Viruses, nature's ultimate nanocarriers, have evolved to be extremely efficient delivery vehicles for genetic materials. Understanding the interactions between viruses and cells is therefore of tremendous importance, not only to help fighting viral diseases but also to assist scientists in developing better nanomedicines. A manuscript from Nam-Joon Cho's group reviews the recent developments in the field of cell membrane mimics and their uses to unravel the mechanisms of viral membrane disruption [Model membrane platforms for biomedicine: case study on antiviral drug development]. Further illustrating the importance of controlling cell membranes and nanoparticles interactions, a manuscript from Stellacci and coworkers reports that both ligand arrangement and composition on gold nanoparticles play a crucial role in their cellular internalization [Dynamic cellular uptake of mixed-monolayer protected nanoparticles]. Using mixed self-assembled monolayers of thiolated organic molecules, which spontaneously phase separately into stripe-like domains, this study provides interesting clues about how to overcome energy-mediated cellular membrane transport processes. A feature of the special edition describes a novel approach to controlling interactions between liposomes and myoblast cells. The manuscript from Brigitte Stadler's group uses poly(dopamine) (PDA), a eumelanin-like material deposited via the "self"-oxidative polymerization of dopamine, to coat liposomes and control their interaction with cells [Myoblast cell interaction with polydopamine coated liposomes]. In order

to increase the biological specificity of nanocarriers such as liposomes, molecular targeting approaches are being actively sought. This topic is addressed in the special edition by a study from Alain Brisson's group, which describes an innovative platform to prepare antibody-presenting liposomes [Development of a platform of antibody-presenting liposomes]. Molecular targeting of liposomes is of very high interest in molecular imaging and drug delivery, and the proposed platform, based on the fusion of protein between Annexin-A5 and the IgG binding ZZ repeat derived from *Staphylococcus aureus* protein A, is an interesting alternative to conventional covalent coupling strategies. Such molecularly targeted approaches have been advanced towards increased specificity to the target cells and tissues, and thereby reduced systemic side effects while improving diagnostics/therapeutics.

The lack of specificity of nanocarriers remains a significant obstacle toward their clinical implementation, and progresses have been slow in this area since the visionary warning thirty years ago of Gregoriadis, who stated in the Lancet that "there is little use for a carrier that although highly selective in vitro, ends up in phagocytic cells or cannot reach its destination in vivo" [1]. Innovative targeting approaches combined with improved mechanistic understanding, such as the one presented here, are steps in the right direction towards fulfilling the tremendous potential of nanomedicines.

Finally, two contributions by Bert Müller's group cover the development and application of advanced characterization techniques to the field of nanomedicine: (a) interrogation of structural details at the macro- to nanoscale of human teeth by spatially resolved synchrotron radiation-based small-angle X-ray scattering, shedding light on the important, complex architecture of collagen and anisotropic calcium phosphate crystallites of this hard composite tissue; and (b) preparation of disposable, polymeric microcantilevers by micro-injection molding and their validation in DNA hybridization experiments, which may contribute in the future to the development of more efficient medical diagnostics.

The Nanomedicine special edition covers a remarkable range of important topics and provides exciting insights into the very dynamic and fast growing nanomedicine field. Nanomedicine is approaching the age of technological maturity, and fundamental and applied research such as that presented here will likely contribute not only to the development of the knowledge and understanding required to foster novel medical technologies, but also stimulate new ideas and concepts.

Reference

1. Gregoriadis G (1981) Lancet 2:241–246