SPECIAL ISSUE: Biomaterial Foundations of Therapeutic Delivery

Preface on “Biomaterial Foundations of Therapeutic Delivery”

Driven by the enormous clinical need, drug delivery systems (DDS) have become a prime research focus in the field of biomaterials. They offer opportunities for developing new therapeutic approaches to prevent and treat debilitating and life-threatening diseases. Smart biomaterials, whether synthetic or naturally-derived, combined with unique designs for the DDS will help to overcome some of the critical challenges related to clinical applications. This Special Issue on “*Biomaterial Foundations of Therapeutic Delivery*” presents a collection of manuscripts on most recent advances in DDS, emphasizing the development of novel biomaterials for drug formulation, encapsulation and transport, as well as delivery of diagnostic agents and phototherapy applications.

With the unprecedented progress in biomedical nanotechnology and nanomaterials over the past few decades, nanoparticles (NPs) based DDS have taken the front stage in clinical applications. Among these, magnetic NPs are attracting increasing attention as smart systems owing to their responsiveness to external magnetic fields. Liu *et al.* review the basic physicochemical and magnetic properties of desirable magnetic DDS that fulfill the requirements for specific clinical applications and discuss the surface modifications and functionalization issues that arise when designing elaborate magnetic NPs with improved targeting efficacy and reduced toxicity. The ability to modify the surface of magnetic NPs at will, as well as the possibility of combining them with functionally-dictinct biomaterials open the way for a multitude of therapeutic and diagnostic applications.

Hydrogels constitute a group of physically and/or chemically network of polymeric materials, which can hold a large amount of water in their three-dimensional structure due to their hydrophilic moieties. In a long line of investigations, they have been explored for various biomedical applications including drug/cell carriers, tissue engineering, and biosensors. Zhang *et al.* review recent advancements in the use of hydrogels in phototherapeutic applications in anticancer and antibacterial fields, two diseases

with significant burden on human health. By focusing on nano- and macro-gels, recent advances in the use of hydrogels as the basis of photodynamic and photothermal therapies are summarized. Combinations of distinct photo-initiated therapies with each other and other modalities, such as chemotherapy, have been presented to overcome the limitations of individual approaches.

NPs can be enriched at tumor sites and improve the efficacy of many chemotherapy drugs with the well-known enhanced permeability and retention (EPR) effect. As a new generation of NPs, cell membrane-coated ‘biomimetic’ NPs combine the complex biological functions of natural membranes and the physicochemical properties of synthetic nanomaterials for a more effective drug delivery. Chai *et al.* briefly review the recent advances on cell membrane-coated NPs for tumor-targeted drug delivery *via* the prolonging systemic circulation lifetime and the active targeting effect. Such particles could act as ‘carriers’ of chemotherapeutic drugs as well as active tumor-trophic targeting agents, greatly facilitating the fight against cancer. The biomimetic particles could also help to overcome specific barriers in the body with the careful choice of biomimetic coating, which could significantly expand their utility beyond cancer.

The CRISPR-Cas system, especially the type II CRISPR-Cas9 system from *Streptococcus pyogenes*, has rapidly emerged as an effective tool to edit mammalian genomes. The development of Cas9 derivatives further expanded the toolbox of CRISPR-Cas9 based genome editing. However, the therapeutic translation of CRISPR-Cas9 system *in vivo* is severely impeded by the absence of delivery vehicles that can transport a complex set of reagents without using unpredictable viruses. Sun and Gu survey recent advances in the development of non-viral delivery systems for CRISPR-Cas9, and discuss challenges and future directions in this emerging field.

Gene therapy targeted to vascular cells represents a promising approach for prevention and treatment of pathological conditions such as intimal hyperplasia, and

in-stent and post-angioplasty restenosis. The concerns related to clinical use of viruses to deliver genetic material can be overcome with effective non-viral delivery systems. Towards this goal, Pezzoli *et al.* present the synthesis of a library of 24 branched polyethylenimine (bPEI) derivatives modified with hydrophobic moieties aiming to identify delivery agents with superior transfection efficiency and low cytotoxicity on primary vascular cells. It is possible to identify sub-sets of polymers that appear to function optimally, providing drug delivery leads that can be further modified for improved function and can be explored in animal models.

While recent emphasis on NP-based DDS have attracted significant attention, applications of their predecessors, namely microparticles (MPs), still retains great potential. Ma *et al.* report on the development of porous calcite microspheres as multifunctional biomaterials for dental treatments. The porous calcite microspheres are featured by highly uniform spherical morphology and large open pores. The MPs can not only inhibit demineralization efficiently based on an antibacterial protein (immunoglobulin Y) delivery strategy, but can also enhance remineralization of damaged teeth as a fast-reacting biomaterial. With the possibility of delivering a range of antimicrobial drugs and peptides, the potential applications of the reported MPs could be multifaceted.

The development of uniquely performing DDS could heavily rely on exploitation of new fabrication techniques. Li *et al.* present a particular microfluidics technique for the generation of structured MPs with improved functions. Composite core-shell MPs formed from the microfluidic double emulsion templates are attempted for sustained delivery of synergistic hydrophilic and hydrophobic drugs. The size and component of the MPs can be conveniently and precisely adjusted by manipulating the flow solutions during microfluidic emulsification. Similarly, in a clever approach to fabrication, Chen *et al.* demonstrate an albumin nanoreactor templated synthesis of theranostic Gd₂O₃/CuS hybrid nanodots for multimodal imaging guided photothermal tumor ablation. The albumin nanoreactor provides a facile and general strategy to synthesize multifunctional NPs for cancer theranostics. Functional imaging and therapeutic effects were readily

obtained in animal models, allowing one to prepare a range of NPs from different protein cores and inorganic materials.

The covalent attachment of ‘protein-repellent’ polymers to therapeutic proteins is a widely used method for extending *in vivo* half-lives of administered proteins. Wang *et al.* report on the synthesis of a polyethylenglycol (PEG)-like polymer conjugate of interferon-alpha (IFN- α) with tunable molecular weights. Unlike previous approaches where the polymer is haphazardly attached on protein side-chains, the authors focus on specific C-terminus modification of the proteins. Detailed studies were reported on the effect of polymer molecular weight on the physicochemical properties and antitumor efficacy of the conjugated protein. Their findings offer a new viewpoint on the molecular size rationale for designing the next-generation protein-polymer conjugates to benefit patients by reducing administration frequency and adverse reactions, and improving therapeutic efficacy.

The range of biomaterials formulated as DDS and presented in this issue is diverse. It confirms the plethora of choices emerged when one wants to formulate functional DDS and provides flexibility in the R&D approach to be pursued for an intended goal. One, however, needs to undertake systemic review of the performance of DDS in established preclinical systems and animal models before clinical testing. This slow and deliberate process will determine successful translation of DDS for clinical application. From the initial emphasis on ‘therapeutic’ delivery with DDS, the field has evolved to include diagnostic delivery as well as other specialized applications such as detoxification. This Special Issue provides ample leads for these important endeavors.

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