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editorial

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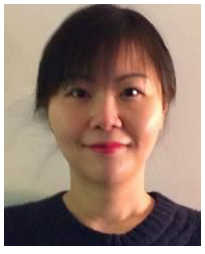

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Therapeutic nanomaterials for cancer therapy and tissue regeneration

Therapeutic nanomaterials ranging in size from 1 to 100 nm possess similarity to hierarchical structures of human tissues at nanoscales, affording them a superior capability in advancing traditional therapies by improving the accuracy of diagnosis, effectiveness of drug delivery, therapeutics and tissue regeneration. As drug carriers, therapeutic nanomaterials, such as nanoparticles, can improve drug loading efficiency with enlarged surface-area/volume ratio, conjugate or encapsulate water-insoluble drugs, promote drug stability, enhance blood circulating time, target to the disease site and on-demand release after fabrication with stimuli-responsive functional groups and reduce systemic adverse effects on other tissues or organs.

Diseases such as cancer and tissue/organ failure are amongst the leading causes of mortality worldwide and their incidence is still increasing because of the growing and aging global population. Hence, there is an increasing demand for advanced therapeutics affording precise diagnosis, improved therapeutic efficacy and tissue regeneration. Advances in the field of nanotechnology have revolutionized traditional therapies by improving accuracy of diagnosis, and effectiveness of drug delivery, therapeutics and tissue regeneration, due to the size similarity of nanomaterials (1–100 nm) to hierarchical structures of human tissues at the nanoscale. For instance, various organic or inorganic nanoparticles have been engineered to prolong their systemic circulation half-life after systemic administration, diffuse from blood into tumor with enhanced blood vessel permeability, selectively bind to tumor cells, visualize their locations and tumor boundary and release antitumor drugs for improved cancer therapy. Likewise, nanofibrous scaffolds that mimic the native fibrous structure of the extracellular matrix (ECM) have been intensively applied for tissue regeneration. With their enlarged surface-area/volume ratio, nanofibrous scaffolds can provide more accommodation for cell attachment and other cellular activities, realize efficient bioactive molecular loading and easily incorporate functional components (*e.g.*, graphene and carbon nanotubes) to provide biochemical and biophysical cues for enhanced tissue regeneration.

This special issue of the Drug Discovery Today focuses on recent advances in the development of therapeutic nanomaterials and covers a diversity of research areas involving the fabrication and application of different nanomaterials (nanoparticles and

http://dx.doi.org/10.1016/j.drudis.2017.08.002

nanofibers), reflecting the latest progress and future perspectives in cancer diagnosis, drug delivery and tissue regeneration. We believe that the research work presented in this special issue would be interesting and informative to the readers.

Cancer diagnosis and therapy based on therapeutic nanomaterials

The development of cancer (malignant tumor) involves sustained chronic proliferation of cancer cells, which (in the case of solid tumors) leads to the formation of hypervasculature and defective vascular architecture. Such architecture enables nanomaterials (mainly nanoparticles) to diffuse easily from blood vessels and accumulate within and around the tumor, which is defined as the enhanced permeability and retention (EPR) effect. However, different tumors or the same tumor at different locations have different vascular porosity and pore size. Therefore, an image-guided diagnostic approach is necessary for the evaluation of EPR effect to assess the accumulation efficiency of the designed nanoparticle-drugs at the target tumor.

Various imaging modalities have been used for cancer detection, such as magnetic resonance imaging (MRI), positron emission tomography (PET), computed tomography (CT), ultrasound and single-photon emission computed tomography (SPECT). Nevertheless, these techniques suffer from limited spatial resolution and contrast to allow precise visualization of the cancer location and boundary. In addition, these techniques are not really appropriate for real-time imaging during surgery, leading to a high risk in incomplete dissection of a tumor. Fluorescence imaging as a manoeuvrable non-ionizing platform has superior resolution and sensitivity to visualize small tumor nodes in a real-time manner. Currently, fluorescent dyes such as indocyanine green (ICG), methylene blue (MB) and 5-ALA-induced PpIX have been used clinically for tumor imaging. However, they usually have short tumor retention times (typically only a few minutes), which limits their application in surgical settings. By comparison, nanoparticle-based fluorescent probes with larger size are more likely to accumulate at the tumors for a longer duration. Yet, without any surface modifications, these nanoparticles are lack specificity and can be trapped by surrounding tissues, leading to a low tumor/background ratio (TBR). Decorating the surface of nanoparticles with a targeting ligand (*e.g.*, proteins, peptides, nucleic acids, and small molecules) can enhance TBR in a certain degree. However, it is still challenging to target ligand-conjugated nanoparticles to achieve an adequate TBR for visualizing a cancer's boundary, because of the potential uptake by normal tissue. With the gaining of cancers' hallmarks in terms of self-sufficiency in growth signals, insensitivity to antigrowth signals, limitless replicative potential, evasion of apoptosis, sustained angiogenesis, and metastasis, activatable nanoparticle-based fluorescence probes that only respond to tumor-specific targets (*e.g.*, low pH and overexpressed enzymes) can be designed to enhance further the TBR for advanced tumor diagnosis and imaging.

One concern when using conventional fluorescent dyes for tumor imaging is their poor stability. Because of the inherent hydrophobic properties of most conventional fluorescent dyes, they are more likely to form aggregates, resulting in a significant decrease in fluorescence signal, *i.e.*, aggregation-caused quenching (ACQ). Recently, a new class of organic luminogens, aggregation-induced emission fluorogens (AIEgens), have been developed that are able to overcome the drawback of ACQ associated with conventional fluorescent dyes. AIEgen-based nanoprobes have unique advantages, including high brightness in an aggregated state, high stability and low cytotoxicity, rendering AIEgens broadly applicable in biomarker detection, cell imaging and tracking. Furthermore, many AIEgens have been engineered as a theranostic platform for cancer diagnosis and therapy, due to their ability to be simultaneously able to generate fluorescence signal and reactive oxygen species (ROS) under the same laser excitation. Compared with conventional hydrophobic photosensitizers (PSs) that suffer from significantly decreased generation of ROS in aggregation state, AIEgen-based PSs can still maintain their high quantum yield of ROS, even when they are encapsulated in a polymeric matrix at a high concentration. Another concern for fluorescent probes is the limited tissue penetration depth and inability to provide anatomical information. To solve these issues, the combination of fluorescent probes with superparamagnetic iron oxide (SPIO) nanoparticles in a single formulation could facilitate advanced cancer theranostics with integration of anatomical information. Besides directly targeting to cancer cells, nanoparticles have also been designed to target to immune cells (*e.g.*, dendritic cells, B cells and T cells) for improved targeted cancer immunotherapy.

Drug delivery and tissue regeneration based on therapeutic nanomaterials

Nanoparticles have been widely applied as drug/gene delivery vehicles, due to their ability to realize enhanced drug loading efficiency with large surface-area/volume ratio, conjugation or encapsulation of water-insoluble drugs, promoted drug stability, enhanced blood circulating time, targeted delivery and on-demand release after fabrication with stimuli-responsive functional groups and reduced systemic adverse effects on other tissues or organs. For instance, the biocompatible FDA-approved polymers of polylactic acid (PLA) and poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles have been intensively used for growth factor loading and delivery to promote neovascularization and tissue regeneration. Alternatively, cationic polymers such as polyethylenimine (PEI), poly(L-lysine) (PLL), poly(amido-amine) (PAMAM) and chitosan have been used to package DNA *via* electrostatic interaction and the formed nanocomplexes can protect the genes from extracellular digestion and prolong their circulation time for efficient delivery into target cells. Additionally, nanoparticle-based drug delivery vehicles, such as calcium phosphate nanoparticles, gold nanoparticles and nanodiamonds have demonstrated unique advantages in treating bone diseases through stimulating mineralization or promoting bone cell activity.

Although various nanoparticle-based drug/gene delivery vehicles have been developed, their therapeutic efficiency has not always been realized, mainly due to the issues of drug/gene dissociation from the vehicle and off-targeting. Moreover, after intravenous injection, these vehicles encounter a complicated *in vivo* microenvironment, which makes it challenging to realize specific delivery or transfection. Local drug/gene delivery using scaffolds that can continuously deliver therapeutic agents at the target site can solve the above mentioned issues. Of the various scaffolds, nanofibrous scaffolds have been widely used for tissue

regeneration because of their close imitation of the natural ECM, thus supporting cell adhesion, proliferation, migration and differentiation. Furthermore, with high surface-area/volume ratio, nanofibrous scaffolds have been explored as local delivery carriers for bioactive proteins and genes, enabling the use of lower drug doses with subsequently decreased adverse side effects. Cationic polymers such as PEI, PLL and chitosan have been fabricated into nanofibrous scaffolds for local gene delivery. However, the gene transfection efficiency of the cationic polymeric scaffolds is usually in direct proportion to their concentration, while high concentration of cationic polymeric scaffolds may cause toxicity to cells and surrounding tissues. In addition, these cationic scaffolds suffer from limited control over retention and delivery of genes. To address these issues, responsive polymeric nanoparticles that can respond to pH, glutathione or intracellular enzymes for enhanced gene intracellular delivery have been embedded within nanofibrous scaffolds to permit advanced local gene delivery. As a versatile approach, encapsulation of drug-loaded responsive nanoparticles into nanofibers can successfully manipulate local environment to control cell functions for improved disease therapy and tissue regeneration.

The Guest Editors would like to thank Dr. Stephen Carney, the Editor-in-Chief of Drug Discovery Today, for support and recommendations, the reviewers for their time and valuable advice to the authors, and all the authors for their contributions. This special issue includes a collection of latest research ongoing in the field of therapeutic nanomaterials for cancer diagnosis and therapy, as well as tissue regeneration. We hope that this special issue will offer the reader an overview of the most recent advances and open the opportunities in the field.

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