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Editorial
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Innovative Polymers for Controlled Release Applications

The concept of personalized medicine and healthcare has spurred enormous research and development of molecular diagnosis and therapy for various diseases. It has been found that many symptoms including cancers are related to one or more DNA, RNA, or protein mutations, which vary from patient to patient. Better understanding of the molecular basis of diseases has led to novel treatment modalities that selectively target the mutations. It should be noted, however, that despite significant progress in personalized medicine, few of these findings have or can be directly translated to the clinical setting as these novel treatment modalities (e.g., therapeutic DNA, siRNA, or miRNA) often show fast degradation and excretion in vivo, poor uptake by target cells, and cumbersome intracellular trafficking. It becomes clear that personalized medicine further critically relies on advancement of clinically viable delivery systems that are able to efficiently load and transport bioactives to target cells. Biomedical polymers including natural and synthetic polymers (including dextran, hyaluronic acid, chitosan, albumin, transferrin, antibody, poly(ethylene glycol), polyesters, polycarbonates, and polypeptides) are undoubtedly the best materials apart from liposomes suited for fabricating targeted nanosystems.[1−3] It should further be noted that, with targeted delivery systems, precision therapy might also be achieved with commonly used nonselective chemical drugs such as docetaxel, doxorubicin hydrochloride, cisplatin, and mertansine.[4,5] Several clinically used nanomedicines like Abraxane, Kadcyla (T-DM1), and Genexol-PM (Cynviloq, IG-001) are based on polymeric carriers.[6] Many more polymeric nanodrugs are currently under different phases of clinical trials for treating various human malignancies.[7] These nanoformulations are reported to afford reduced adverse effects and improved therapeutic indexes for toxic drugs, though most often resulting in only moderate improvement in therapeutic efficacy. In the case of gene therapy, polymer-based nonviral systems have demonstrated clearly better safety and reproducibility than viruses. The inferior therapeutic effect in vivo, nevertheless, restrains them from clinical applications. To this end, significant effort has recently been directed to the development of innovative polymer carriers that are able to selectively home to target cells and respond to one or more stimuli including acidic pH, reduction, enzyme, magnetic field, and light for drug and gene delivery.[8,9] In addition to therapy, polymeric nanoparticles also provide a promising technology platform for targeted and early diagnosis of various medical problems.[10]

Different from personalized medicine, another big clinical need is long-term controlled releasing depots or matrices that are capable of locally releasing small chemical drugs, proteins, or even live cells over an extended period of time ranging from days to years. Notably, several drug and protein releasing systems based on poly(lactic-*co*-glycolic acid) (PLGA) microparticles are widely used in clinical settings.[11] It is noticed, however, that these PLGA microparticular systems expose several problems such as acid accumulation and nonideal drug release behavior (with the occurrence of burst or lagged release). Biodegradable polymeric porous scaffolds and hydrogels are the main extracellular matrices (ECMs) for tissue engineering and regeneration. For functional human tissues and organs to be generated, it is of critical importance to develop biomimetic ECMs that have similar physiochemical, biological, as well as mechanical properties to their natural counterparts. Accordingly, the design and development of innovative polymers and hydrogels to create multifunctional ECMs that support cell adhesion, growth, and migration, attract stem cells, and/or slowly release growth factors has been an important theme in the field of tissue engineering and regeneration.[12−14]

The Fourth Symposium on Innovative Polymers for Controlled Delivery (SIPCD 2016) held in September 23−26 in Suzhou, China was dedicated to discussing the cutting-edge development and challenges of innovative polymers for controlled release purposes, which broadly include controlled drug and gene release, diagnostic imaging, and tissue engineering and regeneration. In SIPCD 2016, 12 Rising Stars (<40 years old) were selected for 7 min oral presentation and 8 out of 340 posters for the *Biomacromolecules* Poster Awards. This virtual issue (http://pubs.acs.org/page/bomaf6/vi/innovative-polymers) contains 10 invited papers from the Rising Stars and *Biomacromolecules* Poster Awardees, which nicely reflect the research trends of biomedical polymers and controlled release fields.

Bingyang Shi et al. have given a comprehensive review on challenges in DNA delivery and recent advances in multifunctional polymeric DNA delivery systems.[15] The interactions of DNA vectors with protein corona, working principles, and challenges of polymeric DNA delivery systems, design concepts for DNA carriers, and advances in multifunctional polycation-based nonviral systems were discussed. Lichen Yin et al. reported that light-degradable and cross-linked 600 Da polyethylenimine (PEI) had a low cytotoxicity and could effectively condense DNA to nanosized particles while quickly releasing DNA upon UV irradiation.[16] The DNA polyplexes coated with hyaluronic acid exhibited enhanced serum stability, active targeting ability to CD44 overexpressing cancer cells, and 1−2 orders of magnitude higher transfection efficiencies in serum as compared to those of the 25 kDa PEI control. Huayu Tian et al. reported that pH-responsive detachable PEG shielding of PEI/DNA polyplexes had good colloidal stability and pH-dependent transfection in vitro.[17] The in vivo studies showed that detachable PEG-modified PEI/DNA polyplexes gave enhanced accumulation and gene expression in the tumor as compared to those of the unmodified PEI/DNA counterparts.

Yang Shi et al. discussed factors influencing tumor penetration as well as strategies to potentiate tumor penetration of nanomedicines.[18] Approaches like size switchable nanomedicines, penetration-promoting ligands (e.g., iRGD), intratumoral drug release, and pharmacological modulations of tumor microenvironment and vasculature seemed interesting to

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Biomacromolecules 2017, 18, 3652−3653

enhance the tumor penetration of nanomedicines. Xin Huang et al. reported that sodium alginate-loaded glutathione-responsive proteinosomes caused widespread death of HepG2 and NIH 3T3 cells due to triggered cytoplasmic release and aggregation of hydrogels.[19] This in situ gelation inside the cancer cells provides a potent, drug-free approach for cancer therapy. Hao Wang et al. reported that an intracellular structural change process of pH-responsive nanoparticles based on RGD-dextran/purpurin 18-phenylboronic acid conjugates in human cervical cancer HeLa cells could be conveniently monitored by ratiometric photoacoustic tomography.[20] Xian Jun Loh et al. reported that a host−guest inclusion complex significantly boosted aggregation-induced emission (AIE) of tetraphenylethene-conjugated poly(ethylene glycol) due to enhanced restricted intermolecular rotations in the α-cyclodextrin cavities.[21] This AIE active pseudorotaxane luminogen was found to be noncytotoxic and interesting for functional bioimaging applications.

Baolin Guo et al. designed an elastic and conductive poly(ethylene glycol)-*co*-poly(glycerol sebacate)-*graft*-aniline pentamer copolymer for skeletal muscle tissue engineering and regeneration.[22] The resulting conductive and flexible films were shown to greatly promote C2C12 myoblast cell proliferation and myogenic differentiation. Xuesi Chen et al. reported that cell-adhesive injectable polypeptide hydrogels based on 4-arm-poly(ethylene glycol)-*block*-poly(L-glutamic acid)-*graft*-tyramine/cRGD promoted NIH 3T3 cell adhesion and proliferation.[23] Guosong Chen et al. studied the influence of benzyl protecting groups in solution properties and self-assembly of glycopolymer-containing block copolymers.[24]

There is no doubt that polymeric materials play an important role in controlled release applications. The development of innovative polymers for drug and gene delivery, diagnostic imaging, and tissue engineering and regeneration is anticipated to make a major impact on future pharmaceutics, biomedical engineering, and healthcare. The Fifth Symposium on Innovative Polymers for Controlled Delivery (SIPCD 2018, http://www.sipcd.com) to be held in September 14−17, 2018 in Suzhou, China will continue to provide a top platform for the communities of biomedical polymers and controlled release.

Zhiyuan Zhong*

Biomedical Polymers Laboratory, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou, 215123, P. R. China

AUTHOR INFORMATION

Corresponding Author

*E-mail: zyzhong@suda.edu.cn.

ORCID

Zhiyuan Zhong: 0000-0003-4175-4741

Notes

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