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Polymeric biomaterials for cancer nanotechnology

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In 2000, President Clinton announced the U.S. Government's National Nanotechnology Initiative to invest in nanotechnology research, along with many other nanotechnology initiatives in Europe and Asia around that time. As part of this initiative, the National Cancer Institute (NCI) established the NCI Alliance for Nanotechnology in Cancer to further support this growing field. One of the major classes of materials used in nano-based approaches for cancer therapy is polymers. Nano-sized systems facilitate better delivery of anti-cancer small molecule drugs to tumors by altering the biodistribution and pharmacokinetics of the free drug. For macromolecular drugs such as nucleic acid therapeutics, nano-sized systems can also mediate intracellular delivery.

Polymer micelles, nanostructures formed by the self-assembly of amphiphilic block copolymers, have been used as drug carriers to tumors. Genexol-PM, developed by Samyang Corporation, a polymeric micelle comprised of polyethylene glycol (PEG)–polylactide, carries the chemotherapeutic paclitaxel that has been approved in several countries for clinical use and in clinical trials in the U.S.[1] Polymer micelles comprised of PEG–polypeptides developed by Kataoka and coworkers are also in late phase clinical trials for delivery of cisplatin (Phase III, Nanocarrier, NC-6004), paclitaxel (Phase III, Nippon Kayaku, NK105), and doxorubicin (Phase II, Nippon Kayaku, NK911).[2] Nano-sized polymeric systems in other forms, such as polymer–drug conjugates or polymer nanoparticles, have also been intensively investigated for anticancer drug delivery.[3,4] While there are several FDA-approved PEGylated proteins, polymer drug conjugates for small molecule chemotherapy are still in the clinical pipeline. Two notable examples are the linear cyclodextrin polymer delivery system conjugated with camptothecin (Phase II, Cerulean, CRLX101)[5] and the dendrimer–docetaxel conjugate (Phase I, Starpharma, DEP™–Docetaxel).[6] Bind Biosciences is also developing a biodegradable polymer nanoparticle that encapsulates docetaxel (Phase II, BIND-014).[7]

Nucleic acid delivery vehicles have been dominated by viral vectors, but there have been a few recent examples of polymeric delivery vehicles entering clinical trials, including Calando Pharmaceuticals' targeted siRNA nanoparticles (Phase I, CALAA01).[8] Silenseed LTD recently reported their Phase I/IIa safety data on a polymeric implant for sustained release of anti-KRAS siRNA in the treatment of pancreatic cancer.[9]

Preclinical and clinical studies have in general revealed that polymeric nanocarriers, when used for chemotherapeutic drug delivery, reduce systemic toxicity and thus mitigate adverse side effects of

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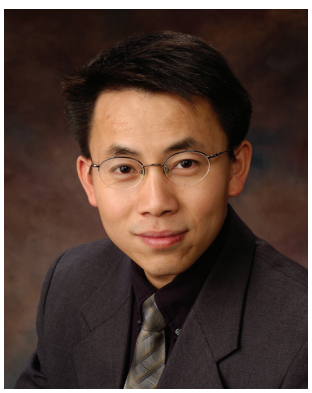

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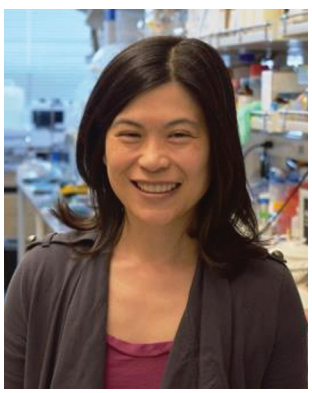

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the drug. In order to continue and even improve on the clinical progress of polymeric anticancer drug formulations, new innovations and discoveries are being made in the following areas: (i) expanding the available suite of polymeric biomaterials that can be reproducibly and controllably manufactured at a suitable scale, (ii) designing carriers with improved biodistribution to tumor sites, (iii) increasing tumor distribution and penetration of polymeric nanocarriers, and (iv) controlling efficient drug release at a desired location and with optimal kinetics.

This themed issue contains reviews and research articles in each of these areas. In addition, new advances in polymeric nanobiomaterials for both small molecule chemotherapeutics and anticancer nucleic acids are included.

First, comprehensive reviews of four classes of polymeric nanobiomaterials are presented. Seungpyo Hong and colleagues (DOI:10.1039/c4bm00351a) focus on targeted delivery using dendrimers, hyperbranched polymers with tree-like structures that can be synthesized with low polydispersity and size controlled by generation number. The review, which includes dendrimer synthesis methods and drug loading approaches, ends with hybrid materials combining dendrimers with other materials such as linear polymers or nanoparticles to address some of the limitations of traditional dendrimers. Juliana Chan and coworkers (DOI: 10.1039/c4bm00427b) discuss another type of hybrid material, lipid–polymer hybrid nanoparticles (LPNs), which typically include a polymeric core for cargo encapsulation, and are surrounded by a lipid shell. Compared to polymeric nanoparticles, LPNs have been reported to achieve higher drug loading and improved release profiles, and are being investigated for delivery of small molecules, nucleic acids, and imaging contrast agents. Next, Hua Wei and Cui-Yun Yu (DOI: 10.1039/c4bm00417e) discuss anti-cancer delivery vehicles based on cyclodextrin (CD)-functionalized polymers. Many of these formulations take advantage of the hydrophilicity of CD materials and CD's ability to form host–guest inclusion complexes with hydrophobic small molecules, a property utilized for drug incorporation and/or supramolecular assembly to form nanostructures. The aforementioned CRLX101 polymer–drug conjugate and CALAA01-targeted siRNA delivery vehicle both use cyclodextrin polymers. Supramolecular hydrogels and their broad use, including bioimaging and drug delivery, are covered by Xinyuan Zhu and colleagues (DOI: 10.1039/c4bm00448e). Finally, Wujin Sun and Zhen Gu (DOI: 10.1039/c4bm00459k) introduce a relatively new class of nanostructures prepared by DNA. DNA nanostructures are assembled by complementary base pair interactions and have recently been applied for the delivery of anticancer small-molecule and nucleic acid-based drugs. Interestingly, stimuli-responsive DNA scaffolds can even be prepared by the incorporation of small molecule-binding aptamers.

Most polymeric nanocarriers rely on the enhanced permeability and retention (EPR) effect for tumor localization. This form of "passive targeting" takes advantage of the more fenestrated tumor endothelium for preferential extravasation at tumor sites compared to most normal vasculature, and therefore also requires long circulation times so that tumor accumulation can occur. Long circulating polymeric delivery vehicles for platinum-based chemotherapeutics is reviewed by Won Jong Kim and coworkers (DOI: 10.1039/c5bm00039d). While hydrophilic PEG shields have been the gold standard for increasing the circulation time of nanoparticles, Jun Wang and coworkers (DOI: 10.1039/c4bm00430b) demonstrate in that zwitterionic polyphosphoesters can prolong drug circulation half-lives and improve tumor drug accumulation to a similar extent as PEGylation in a murine tumor model. These hydrophilic shields are necessary during circulation but can inhibit tumor penetration, drug release, and even intracellular uptake. Xuesi Chen and colleagues (DOI: 10.1039/c5bm00044k) review examples of polymeric nanocarriers with hydrophilic shells that are triggered to shed by various stimuli. Depending on the formulation, removal of the shell can improve tumor penetration or facilitate uptake due to exposure of cationic charge or targeting entities.

In addition to chemical methods that manipulate tumor localization and penetration, nanoparticle shape is now appreciated to affect biodistribution and circulation time. Hai-Quan Mao and coworkers' review (DOI: 10.1039/c5bm00006h) summarizes methods to prepare polymeric nanoparticles with shape control, and discusses how nanoparticle shape impacts circulation time, tissue distribution, and cellular uptake. Martina Stenzel and coworkers (DOI: 10.1039/c4bm00323c) further investigate tumor penetration by polymeric micelles using multicellular tumor spheroid models. One of their major findings is that transcellular transport contributes toward penetration of their polymeric micelles in spheroid cultures more than diffusion through the extracellular matrix.

Controlled drug release remains a challenge for many polymeric nanocarriers. Premature release during circulation contributes toward systemic toxicity, while inefficient release decreases drug potency. Ideally, drugs should remain protected in the drug vehicle during circulation and be triggered for rapid release after entry into the tumor environment or target cell. Rinti Banerjee and coworkers (DOI: 10.1039/c5bm00002e) review trigger responsive, anti-cancer polymeric nanocarriers, providing examples of polymer vehicles with drug release triggered by pH, redox, enzymes, temperature, ultrasound, light and magnetic fields. Chong Cheng and coworkers (DOI: 10.1039/c4bm00458b) report a brush polymer–paclitaxel conjugate with drug release occurring over the course of 10 days in both neutral and acidic buffer solutions. Two reports of new polymeric systems with redox-sensitive drug release are presented. Jianjun Cheng and coworkers (DOI: 10.1039/c4bm00452c) synthesize a PEGylated chain-shattering polymer; in reducing conditions, the PEG is released, resulting in polymer chain shattering and release of encapsulated drug within 48 hours. Zhiyuan Zhong and coworkers (DOI: 10.1039/c4bm00436a) describe a galactose-targeted, reducible poly(ester

amide) copolymer that shows targeted delivery to hepatoma cells and fast intracellular doxorubicin release in the reducing intracellular environment. Finally, Zhishen Ge and coworkers (DOI: 10.1039/c5bm00048c) develop a cyclodextrin-based nanogel loaded with doxorubicin and indocyanine green for combined photothermal therapy and chemotherapy. At high temperatures triggered by near-infrared light irradiation, inclusion complex formation is disrupted, releasing the encapsulated drug.

In addition to chemotherapeutic delivery, this issue also includes several reports on nucleic acid delivery systems. Won Jong Kim and coworkers (DOI: 10.1039/c5bm00004a) demonstrate peptide-targeted gene delivery using a PEGylated, disulfide-crosslinked polyethylenimine modified with divalent GE11 peptide, targeting the epidermal growth factor receptor (EGFR). Improved *in vivo* gene transfer to cancer cells was observed *in vivo* using the divalent GE11 peptide compared to the monovalent GE11 peptide. David Oupický and coworkers (DOI: 10.1039/c5bm00003c) develop copolymers using a CXCR4 antagonist as a monomer. The resulting polymers are used for the dual purpose of inhibiting CXCR4, a chemokine receptor expressed in cancer cells, and delivering siRNA to knockdown polo-like kinase 1 (PLK1), a mitotic regulator that is often overexpressed in cancer. Young Jik Kwon and coworkers (DOI: 10.1039/c5bm00041f) investigate the effect of mixing sequence in the formulation of polyethylenimine-based plasmid and siRNA nanoparticles.

Anticancer nucleic acids and chemotherapies can be combined in nanoparticles for cocktail drug delivery. Xintao Shuai and coworkers (DOI: 10.1039/c4bm00369a) review nanocarriers developed for combination therapy of drugs and genes. Xian-Zheng Zhang and coworkers (DOI: 10.1039/c4bm00382a) report a corona–core nanoparticle technology consisting of phenylboronic acid-modified oligoethylenimine coronas (for plasmid DNA loading) around hydrophobic cores of hyperbranched polyglycerol (for hydrophobic drug loading). They demonstrate synergistic anti-cancer effects in cultured cancer cells by dual delivery of the p53 gene with doxorubicin.

Finally, an intriguing review on drug-free macromolecular therapeutics is presented by Te-Wei Chu and Jindrich Kopecek (DOI: 10.1039/c4bm00442f). The Kopecek group has pioneered polymer-based constructs that induce cell killing by multivalent crosslinking of surface receptors such as CD20. Polymeric constructs assembled by coiled-coil peptides and also complementary oligonucleotides are summarized with discussion of *in vitro* and *in vivo* biological studies using these constructs. The specificity of action and freedom from cytotoxic drugs are major advantages of this new approach to polymeric anticancer therapies.

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