Guest Editorial

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Polymer Therapeutics—From Bench to Bedside

This special issue of the Israel Journal of Chemistry on "Polymer Therapeutics as Novel Nanomedicines" focuses on the rationale and methodology of polymer synthesis, the current status of the resulting polymers in drug delivery, and the potential applications of these polymers for the development of new systems. The concept of a drug delivery system based on synthetic polymers was first proposed by Helmut Ringsdorf in 1975,[1] and used later to describe polymeric drugs, polymer–drug conjugates, polymer–protein conjugates, and polymeric micelles in which the drug is covalently bound to the polymeric backbone[2,3] (see Cover). These polymeric conjugates, also termed "polymer therapeutics", which have already been successfully transferred to the clinic, include synthetic polymers such as poly(ethylene glycol) (PEG),[4,5], *N*-(2-hydroxypropyl) methacrylamide (HPMA) copolymers,[6] poly(vinylpyrrolidone) (PVP),[7] poly(ethyleneimine) (PEI),[8,9] linear polyamidoamines and DIVEMA, poly(amino acids) including poly(L-lysine)[10] and poly(glutamic acid) (PGA),[11] poly(malic acid), and poly(aspartamides), as well as natural polymers, including dextran (α-1,6 polyglucose) and dextrin (α-1,4 polyglucose), hyaluronic acid, and chitosans.[12,13] The conjugation of anticancer drugs with biocompatible polymers offers many advantages over small molecular therapeutics, such as improved solubility and bioavailability, increased passive accumulation of the drug at the tumor site by the enhanced permeability and retention (EPR) effect,[14] active accumulation of the drug at the tumor site by targeting moieties, reduced systemic toxicity and immunogenicity of both the drug and the targeting moiety, and enhanced therapeutic efficacy.[13] Currently, a number of polymer–drug conjugates are available for cancer treatment, and more are in the pipeline for clinical studies.[15,16]

The first major success of a polymer–drug conjugate was based on the conjugation of PEG with an active entity (i.e., polypeptide), known by the term "PEGylation", designed to increase protein solubility and stability, and to reduce protein immunogenicity. Moreover, by preventing rapid renal clearance of small proteins and receptor-mediated protein uptake by cells of the reticuloendothelial system, PEGylation was proved to extend the plasma half-life. In this special issue **Pasut and Veronese** present the various methodologies for PEG modification of small-molecular-weight drugs, such as doxorubicin, epirubicin, psoralen, and chelating agent of radionuclides, as well as proteins.[17] **Caliceti and his coworkers** follow up on this theme by describing a few grafting-to and growing-from PEGylation techniques for the preparation of therapeutically effective protein bioconjugates.[18] These PEG conjugates increase passive accumulation of the proteins at the tumor site due to the increased permeability of tumor blood vessels, in direct correlation with the molecular weight of the conjugate. In a related article, **Vachutinsky and Kataoka** describe the physicochemical properties associated with the biological activity of PEG-based polyplexes, and approaches undertaken to promote gene delivery for in vivo applications.[19] This review article also discusses several key factors in the construction of PEG–polycation vectors, and highlights various structural modifications that affect the behavior of the resulting gene delivery systems.

Ringsdorf's model of the mid-1970s, of a targeted polymer–drug conjugate, was based on five key components: macromolecular polymeric backbone, drug, spacer, targeting group, and a solubilizing agent. At the same time, Jindrich (Henry) Kopecek, Karel Ulbrich, and their coworkers at the Institute of Macromolecular Chemistry, Czechoslovak Academy of Sciences, Prague, and Ruth Duncan at Keele University (UK) had designed a new polymer carrier named HPMA copolymer, with which a drug was conjugated by pendant tetrapeptide linkages that were degradable by the lysosomal enzyme, cathepsin B.[20–22]. A large number of HPMA copolymer-based anticancer agents have been evaluated at the preclinical level, carrying not only the standard chemotherapeutic drugs but also the heat shock protein inhibitor geldanamycin and the anti-angiogenic agent TNP-470. Two review articles in this collection address the efforts undertaken to improve the efficacy of anticancer therapy using HPMA-based polymer–drug conjugates bearing drug molecules and targeting ligands covalently bound to a single polymeric backbone that, in turn, can be targeted to the tumor. **Satchi-Fainaro and her coworkers** review the development of multifunctional drug delivery strategies using polymer therapeutics to target both the tumor and its supporting vasculature using different polymeric carriers (HPMA copolymers, PEG, PGA, PG dendrimers). Drugs, targeting moieties, and detection molecules were conjugated to these polymers via several polymerization techniques[23] for cancer therapy and diagnostics, a combined function named "Theranostics". The use of novel polymer therapeutics represents an alternative preventive therapy for patients with high risk of outbreak of metastases or for those with dormant lesions. **David** summarizes some of the work done on actively-targeted HPMA copolymers for selective delivery of drugs to tumor tissues via carbohydrate–endogenous-lectin inter-

actions.[24] Polymer conjugates for targeting the asialoglycoprotein receptor (ASGP-R), galectins (galectin-1, galectin-3), selectins (E-selectin, P-selectin), mannose receptors (ManR, mannose-binding protein (MBP)), and hyaluronic acid receptors (CD44, receptor for hyaluronan-mediated motility (RHAMM)) are described. These novel HPMA copolymer–carbohydrate conjugates hold promise as clinically relevant drug delivery systems for cancer therapy.

Recently, biodegradable macromolecular MRI contrast agents based on polydisulfide-Gd(III) chelates have been developed. **Lu and Wu** show in their contribution that these biodegradable macromolecular agents offer superior contrast enhancement in the vasculature and in tumor tissues.[25] The polydisulfide biodegradable macromolecular contrast agents are readily degraded in vivo into small molecular chelates that can be rapidly excreted from the body via renal filtration, resulting in minimal long-term tissue accumulation, which has consistently been one of the problems with small molecular MRI contrast agents.

In the 1970s and 1980s, biodegradable polymers of poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and poly(lactic-co-glycolic acid) (PLGA) were adopted by drug delivery researchers to create "sustained release" macro/microscopic biodegradable depot systems.[26] Robert Langer's lab produced a family of polyanhydrides that have seen clinical success when loaded with drugs and implanted as macroscopic, disc-shaped depot systems for treatment of brain tumors (glioblastomas).[27] **Pawar, Kharat, and Domb** describe fatty acid-based pasty injectable polyesters and poly(ester-anhydrides), biodegradable polymers suitable for the localized delivery of anticancer agents.[28] Hydrophobic fat-based polymers that turn into a gel when injected into tissue have been used for the extended release of paclitaxel, cisplatin, and other anticancer agents. After gelation, the polymer releases the drug in a controlled manner with no burst release, and thus can potentially be used as a drug carrier for regional or systemic drug delivery.

The uniqueness of this special issue on polymer therapeutics is that it highlights a "taste" of several paramount examples from laboratories active in the fields of preclinical design, synthesis, and both in vitro and in vivo characterization of polymeric conjugates. Their achievements are described from the reviewers' personal perspectives. Overall, the many examples covered in these articles delineate the long pathway along which rationally-designed polymer therapeutics have progressed all the way from the research lab to the clinic.

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