Polymer Chemistry

ROYAL SOCIETY OF CHEMISTRY

EDITORIAL

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Cite this: *Polym. Chem.*, 2025, **16**, 1894

DOI: 10.1039/d5py90026c

rsc.li/polymers

Published on 03 April 2025. Downloaded on 1/25/2026 3:49:27 PM.

Introduction to polymers for gene delivery

Sébastien Perrier, *[a] Youqing Shen, *[b] Zhuxian Zhou, *[b] Todd Emrick *[c] and Marxa L. Figueiredo *[d]

This themed collection of articles highlights innovations and the latest advances in polymer-based gene delivery systems. This collection emphasizes the profound impact of polymer chemistry on the functional properties of polymer as non-viral delivery systems, towards significantly increasing their therapeutic potential by improving safety, efficiency, and specificity. The featured articles include a diverse spectrum of advances in a wide range of therapeutic applications, including genome editing, cancer therapy, and tissue regeneration.

The innovations presented in the manuscripts are grouped into key thematic areas central to advancing the field of non-viral gene delivery, seen for example in the striking advances resulting from CRISPR/Cas9-based gene editing systems. A comprehensive review by Gameiro, *et al.* (**https://doi.org/10.1039/D4PY00298A**) discusses the most recent developments in lipid–polymer hybrid nanoparticle (NP) delivery systems, with a focus on combining the stability and bioavailability of lipids with the functional versatility of polymers. These hybrid systems show promise in overcoming current challenges in gene delivery, such as effective cellular uptake, tissue-specific targeting, and delivery to difficult-to-transfect primary cells. These technologies may significantly enhance genome editing efficacy, offering safer, nonviral alternatives to existing methods. Complementing this, the study presented by Huang, *et al.* (**https://doi.org/10.1039/D3BM01981K**) demonstrates an innovative approach to CRISPR/Cas9 gene editing by utilizing ionic liquid-conjugated polymers (IL-CPs) as efficient delivery systems. The IL-CPs, particularly those integrated with fluorinated monomers, exhibit high plasmid encapsulation capacity, achieving over 90% delivery efficiency across various cell types without serum interference. *In vitro* and *in vivo* experiments demonstrate that PBF-IL-CPs are effective in delivering CRISPR/Cas9 components, such as Cas9/PLK1 plasmids, to cells. These NPs facilitate intracellular delivery and successful genome editing, leading to significant tumor suppression, offering a promising solution for the challenges associated with CRISPR/Cas9 gene delivery, and improving both safety and efficiency.

The theme of using polymer design and functionalization to improve nucleic acid delivery is highlighted in the review by Porello, *et al.* (**https://doi.org/10.1039/D4PY00234B**) that examines how the integration of non-cationic building blocks into cationic polymers enhances nucleic acid delivery systems. The authors outline how these modifications could improve key characteristics of gene delivery vectors, such as targeting behavior, cellular uptake, endosomal escape, and transfection efficiency, while reducing toxicity. The strategic design of these non-cationic elements may yield more efficient and safer delivery systems to address longstanding challenges in nucleic acid-based therapeutics. The review by Li, *et al.* (**https://doi.org/10.1039/D4PY00124A**) covers many of the cutting-edge, recently developed polymeric vectors for gene delivery, focusing on rational design strategies that enhance efficacy and safety features of these systems. This work highlights key innovations in polymer chemistry that address toxicity, cellular uptake, and endosomal escape, all common roadblocks to optimally performing gene delivery vectors in clinical applications. Also examined are novel polymer designs that combine functionality with biocompatibility, aiming to optimize the delivery of nucleic acids for therapeutic purposes. Notably, several research articles follow this conceptual theme, with the work of Zhang, *et al.* (**https://doi.org/10.1039/D4PY00610K**) focusing on novel polyester-based gene delivery vectors. This study introduces a new strategy for synthesizing block copolymers through ring-opening polymerization, specifically using valerolactones with alkyl sulfide chains and propargyl valerolactone, further functionalized with [12]aneN_3. The resulting copoly-

[a]*Department of Polymer Chemistry, University of Warwick, Gibbet Hill Road, Coventry, CV4 7AL, UK. E-mail: S.Perrier@warwick.ac.uk*
[b]*College of Chemical and Biological Engineering, Zhejiang University, 866 Yuhangtang Road, Hangzhou, Zhejiang, 310058, China. E-mail: shenyq@zju.edu.cn, zhouzx@zju.edu.cn*
[c]*Polymer Science and Engineering Department, University of Massachusetts, Conte Center for Polymer Research, 120 Governors Drive, Amherst, MA 01003, USA. E-mail: tsemrick@mail.pse.umass.edu*
[d]*College of Veterinary Medicine, Purdue University, 625 Harrison Street, West Lafayette, IN 47907, USA. E-mail: mlfiguei@purdue.edu*

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mers, particularly TMN-3 with a 10-carbon alkyl sulfide chain, demonstrate significantly improved DNA binding and gene transfection efficiency, surpassing traditional polyethyleneimine (PEI) vectors. TMN-3 shows enhanced cellular uptake, lysosomal escape, and nuclear entry relative to PEI. Additionally, TMN-3-DOPE/pDNA polyplexes exhibit anticancer activity, suggesting that these functionalized polyesters have strong potential as non-viral gene vectors for tumor treatment. On a similar topic, the article by Kusmus, *et al.* (**https://doi.org/10.1039/D4LP00011K**) explores the synthesis and functionalization of nanogels for gene delivery. The nanogels, made from glycidyl methacrylate, are post-polymerized with sulfonium groups through ring-opening reactions with diethyl sulfide. This affords water-soluble, cationic nanogels with a zeta potential of +40 mV. The sulfonium-functionalized nanogels are tested for their ability to deliver pDNA to cells, showing promising synthesis and tunable functionalization, though their nucleic acid delivery efficiency was initially poor. This research introduces the potential of sulfonium nanogels as versatile gene delivery vectors, with further optimization promising improved performance. Finally, Nutting, *et al.* (**https://doi.org/10.1039/D4PY01135J**) contribute to the theme of polymer design and functionalization for enhancing interactions with biological targets. In this study, they investigate the impact of molar mass in poly(2-oxazoline)-based glycopolymers on lectin binding, enhancing targeting through multivalent lectin–carbohydrate interactions. By manipulating molar mass and functionalizing with glucose moieties, they improved the specificity and efficiency of polymer-based delivery systems. These advances highlight the importance of polymer design and functionalization in optimizing gene delivery systems, improving the efficacy and safety of non-viral gene therapies.

The theme of messenger RNA (mRNA) delivery and cancer treatment described by Bayraktutan, *et al.* (**https://doi.org/10.1039/D4PY00064A**) reports on a novel triblock copolymer of polysarcosine (pSar) connected to poly(β-amino ester)s (PBAEs), which are known for their potential in delivering mRNA vaccines and therapeutics. pSar enhances stability and reduces toxicity relative to traditional polyethylene glycol (PEG)-modified systems, while also improving the delivery of self-amplifying mRNA. Interestingly, the study finds that polyplexes formed with different ratios of pSar in the PBAE backbone show effective RNA encapsulation and small particle sizes (sub-200 nm), with higher transfection efficiency in cells and excellent penetration in 3D human colorectal cancer organoids, indicating high potential for RNA-based gene delivery to treat cancer. Another paper in this theme is the review by Wan, *et al.* (**https://doi.org/10.1039/D4PY00206G**), which explores the design of polymer-based delivery systems for mRNA cancer therapeutics. These systems are critical for overcoming the delivery challenges of mRNA-based treatments, such as vaccines and protein replacement therapies, by enhancing encapsulation, stability, tissue targeting, and endosomal escape. The work highlights the importance of polymer-based systems in enabling cancer-selective delivery and intracellular mRNA release, focusing on strategies for improving antitumor therapeutic efficacy through customization and functionalization of polymer structures.

On the theme of targeted and tissue-specific delivery, the article by Misaizu, *et al.* (**https://doi.org/10.1039/D4BM00510D**) explores a zwitterionic polymer, carboxyalkyl poly(1-vinylimidazole) (CA-PVIm), for pDNA delivery to skeletal muscle. The polymer exhibits a biocompatible structure, with imidazolium cations and carboxylate anions, and forms a polyion complex with pDNA, preserving its higher-order structure and promoting widespread gene expression in skeletal muscle following localized delivery. The approach is promising for treating muscle diseases by improving pDNA diffusion and transfection efficiency *in vivo*. The report by Ting, *et al.* (**https://doi.org/10.1039/D4PY00196F**) describes programmable polymer nanoparticles for lung-specific delivery that leverages predictive design and data-driven workflows. The authors demonstrate significant enhancement in lung specificity for pDNA delivery *in vivo*. This work illustrates the potential of multi-monomeric polyelectrolytes to improve the precision of gene delivery, showing that molecular design can directly influence therapeutic outcomes, in this case, in the context of lung-related disease.

Regarding polymer conformation in polymersome membranes, and its impacts on gene delivery mechanisms, the work from Effenberg and Gaitzcsh (**https://doi.org/10.1039/D4SM00239C**) reviews polymersomes formed from amphiphilic block-copolymers, where the hydrophilic blocks are loosely assembled toward the solvent and the hydrophobic blocks are packed inside the membrane. The conformation of the hydrophobic blocks can vary between stretched and coiled, as influenced by factors like block length and side-chain bulkiness. Longer hydrophobic blocks tend to have a coiled conformation, while bulkier side chains or polymers with less conformational freedom, adopt a more stretched conformation. This meta-study provides insights into the physical chemistry of block copolymer membranes and their structural properties. In addition, the work by Giaouzi and Pispas (**https://doi.org/10.1039/D4PY00144C**) details the synthesis and properties of temperature- and pH-responsive triblock terpolymers consisting of poly(diethylene glycol methyl ether methacrylate) (PDEGMA), poly(2-(dimethylamino)ethyl methacrylate) (PDMAEMA), and poly(lauryl methacrylate) (PLMA), synthesized *via* RAFT polymerization. The study examines quaternization (methylation) of PDMAEMA blocks, which enhances solubility and introduces permanent positive charges and temperature-responsiveness. The self-assembly of these triblock terpolymers in aqueous media results in micelles with a hydrophobic PLMA core and responsive PDEGMA and PDMAEMA coronas. These micelles undergo structural changes in response to variations in temperature and pH, and form micelleplexes with DNA, with their size and surface charge influenced by the composition of the terpolymer blocks, the N/P ratio, and temperature changes.

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Turning to electrochemical techniques for conjugating and controlling the release of antisense oligonucleotides for gene therapy applications, Oleszko-Torbus, *et al.* (**https://doi.org/10.1039/D3PY01313H**), described DNA complexation properties of copolymers prepared from oxazoline monomers. The researchers focus on modifying these copolymers to introduce amino groups at various positions, aiming to enhance DNA condensation into polyplexes. The study demonstrates that the position of amino groups significantly affects the ability of the copolymers to form stable DNA complexes. Specifically, copolymers with primary amino groups hinder DNA binding, while those with secondary amines, whether in the main chain or as pendant groups, form smaller and more stable complexes. Biological testing indicates that copolymers with secondary amines are non-toxic and capable of transfecting cells. These findings indicate the importance of the amino group's placement in polymer design for DNA delivery and suggest that 2-oxazoline copolymers, especially with secondary amines, could be effective tools for nucleic acid delivery in therapeutic contexts. Another report along this theme focuses on delivering antisense oligonucleotides as drugs. This work by Beikzadeh, *et al.* (**https://doi.org/10.1039/D3LP00047H**) describes a system developed for the electrochemical conjugation and controlled release of connexin43 antisense (AS) oligonucleotides for wound healing applications. The system utilizes a conducting terpolymer (P(EDOT-*co*-EDOTSAc-*co*-EDOTEG)), coated onto porous substrates such as carbon cloth and electrospun fibers. Interestingly, the terpolymer contained EDOTSAc, a group capable of undergoing reversible oxidation/reduction cycles, which enables electrochemical conjugation and controlled release at moderate potentials (+1.0 V for conjugation, −0.8 V for release). The system demonstrates quick conjugation (1 min) and release (5 min) of a model thiol, and successful conjugation/release of the *connexin43* AS oligonucleotide. This advanced drug delivery system may prove useful for promoting wound healing *via* electrochemical control over the release of therapeutic agents.

In conclusion, this topical collection of articles highlights numerous key advances in polymer-based gene delivery systems, from CRISPR/Cas9, to mRNA, to cancer therapies and responsive polymer systems. The manuscripts assembled here collectively demonstrate how polymers address key challenges in efficiency, specificity, and safety. As the field progresses, interdisciplinary collaboration, particularly from *in vitro* to preclinical stages, will be essential for translating these innovations into widespread clinical use. Continued optimization of polymer structure and functionality promises to unlock the full potential of these non-viral systems for successful therapeutic utilization.

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