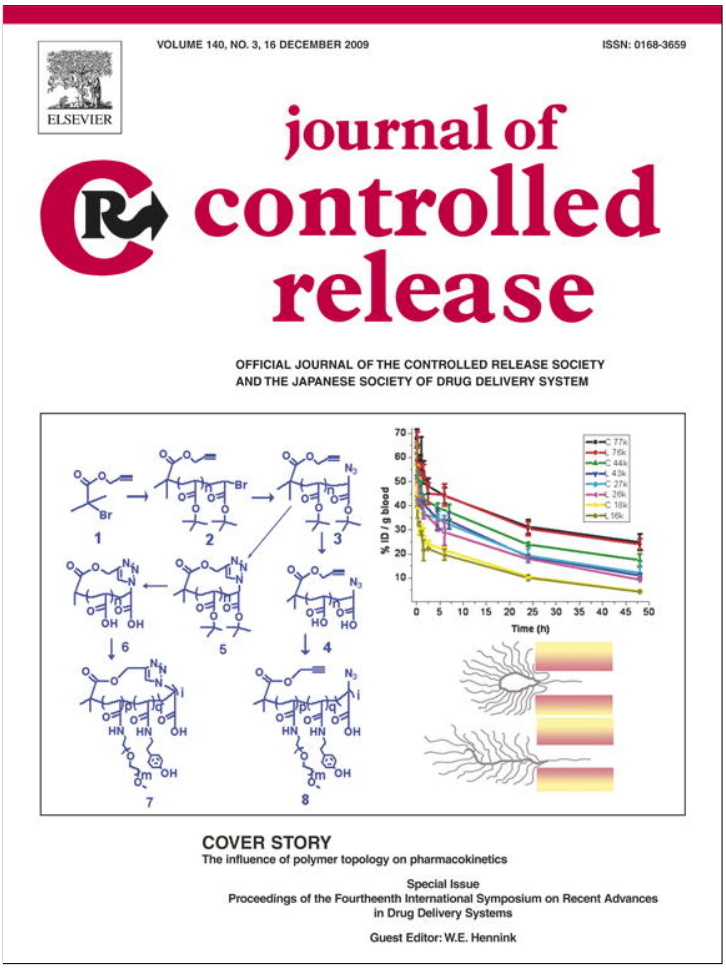

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Cover Story

The influence of polymer topology on pharmacokinetics

Water-soluble polymers have been used widely for delivery of chemotherapeutic drugs. Drug molecules can be covalently attached to the polymer chains. The drug–polymer conjugates are known to target solid tumors passively by the enhanced permeation and retention (EPR) effect. Thus, longer blood circulation as a result of reduced renal clearance is expected to increase the tumor targeting. Elimination of the polymers in the kidney occurs due to filtration through biological nanopores with a hydrodynamic diameter comparable to the polymer. Linear polymers are expected to pass through nanopores in the kidneys more easily than star polymers. This is because linear chains can reptate through nanopores, whereas star polymers are excluded by the multiple arms if the polymer diameter is larger than the nanopore diameter. Consequently, the shape and flexibility of the polymer (i.e., *polymer topology*) have a significant impact on the pharmacokinetics, as well as on accumulation at the tumor site. It seems obvious, then, that cyclic comb polymers would have a longer circulation time and higher accumulation in tumors than comparable linear comb polymers when their molecular weights were above the threshold for elimination in the kidneys. This hypothesis was tested in an article in this issue [1].

Dr. Bo Chen in Professors Szoka and Frechet's research team examined the effect of polymer topology on the blood circulation times by synthesizing four pairs of similar molecular weight cyclic and linear polyacrylic acid polymers grafted with poly(ethylene glycol) (23, 32, 65, and 114 kDa) with low polydispersities using ATRP and "click" chemistry. They studied the pharmacokinetics and tissue distribution of cyclic and linear polymers radiolabled with ^{125}I by intravenous injection in normal and C26 adenocarcinoma tumored BALB/c mice. Cyclic polymers above the renal threshold of 30 kDa had a significantly longer circulation time (between 10 and 33% longer) and a greater area under curve as compared with the comparable linear polymers. This resulted in a greater tumor accumulation of the cyclic polymer than the linear polymer counterpart.

The highly elegant, systematic study explicated the importance of polymer topology on blood circulation and subsequent accumulation at the tumor site. The water-soluble, cyclic comb polymers join a growing list of polymer topologies that show greatly extended circulation times compared to their linear counterparts. It is exciting to confirm that the polymer topology has such a significant effect on blood circulation, and this provides an invaluable information on designing alternative polymer architectures for more effective applications as drug carriers.

Reference

[1] B. Chen, K. Jerger, J.M. Fréchet, F.C. Szoka, The influence of polymer topology on pharmacokinetics: differences between cyclic and linear PEGylated poly(acrylic acid) comb polymers, J. Control. Release 140 (2009) 203–209.

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