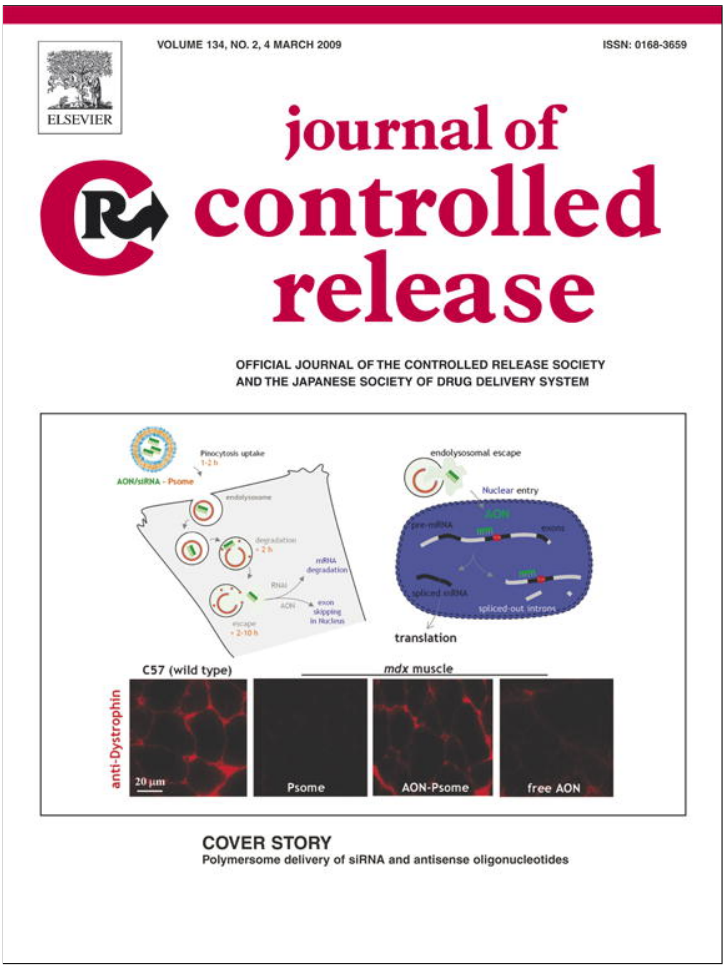

COVER STORY
Polymersome delivery of siRNA and antisense oligonucleotides

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Cover Story

Non-ionic polymersomes for delivery of oligonucleotides

The revolution in molecular biology during the last half-century was based largely on engineering of DNA and RNA at the bench. *In vivo* delivery of nucleic acids, both small and large, however, turns out to be a major challenge. The pros and cons of viral and non-viral delivery systems have been discussed extensively [1]. Non-viral approaches to delivery can in principle avoid some of the immunogenicity and complications of otherwise efficient viral delivery. For this reason, extensive research efforts have been focused on non-viral delivery systems. Most of the current non-viral delivery systems are based on polycations which are necessary for condensing polyanionic nucleic acids to maximize packaging efficiency into nano-carriers. The polycation-based approach, while effective, runs the risk of exposing positive charge, which generally limits dispersion *in vivo*. Small interfering RNA (siRNA) is 20–23 nucleotides in length and antisense oligonucleotides (AON) are similar in size. Since both siRNA and AON are much smaller than plasmid DNA, condensation is not physically needed to fit these oligonucleotides within a nano-carrier. An aqueous compartment such as the lumen of a vesicle should be sufficient. In an article in this issue, Professor Dennis Discher and his group show that non-ionic polymersomes can indeed encapsulate sufficient oligonucleotide to exert effects both *in vitro* and *in vivo* [2].

Polymer vesicles, or polymersomes, have emerged over the last decade from the convergence of work on block copolymers and lipid-based vesicles. Water-soluble poly(ethylene glycol) (PEG) is often attached to both types of vesicles to prolong systemic circulation. Block copolymers can be made amphiphilic by essentially attaching PEG to any number of choices for hydrophobic polymer chains, including degradable and biocompatible polyesters. When the molecular weight ratio of the hydrophilic PEG and hydrophobic polyester is made similar to that of a lipid, stable but degradable polymer vesicles can be made by various methods. Professor Discher's research team solubilized their block copolymers in DMSO together with siRNA or AON, and then dialyzed into physiological saline to generate non-ionic polymersomes with the oligonucleotides entrapped. Delivery of siRNA into the cytosol of cultured cancer cells occurred following uptake and endolysosomal escape, with evidence of efficient knockdown of the constitutive protein lamin, which is a common target for proof of principle studies. Delivery of AON by polymersomes was also examined in muscle cells, with exon-skipping of dystrophin being the intended target. Both *in vitro* and *in vivo* studies showed fluorescent-AON localized in the cell nucleus. In addition, the mice expressed significantly increased levels of dystrophin along most of the muscle membrane after polymersome delivery of the exon-specific AON. Although further characterization is needed before translating this approach to clinical applications, design of more such controlled release polymersome systems should create new opportunities for gene-directed, oligonucleotide delivery in many disease contexts. The absence of cationic groups in antisense-polymersomes together with initial tests of efficacy suggests broader utility of these non-viral carriers.

References

[1] S.-D. Li, L. Hwang, Non-viral is superior to viral gene delivery, J. Control. Release 123 (2007) 181–183.
[2] Y. Kim, M. Tewari, D. Pajerowski, S. Cai, S. Sen, W. Jason, S. Sirsi, G. Lutz, D.E. Discher, Polymersome delivery of siRNA and antisense oligonucleotides, J. Control. Release 134 (2009), doi:10.1016/j.jconrel.2008.10.020.

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