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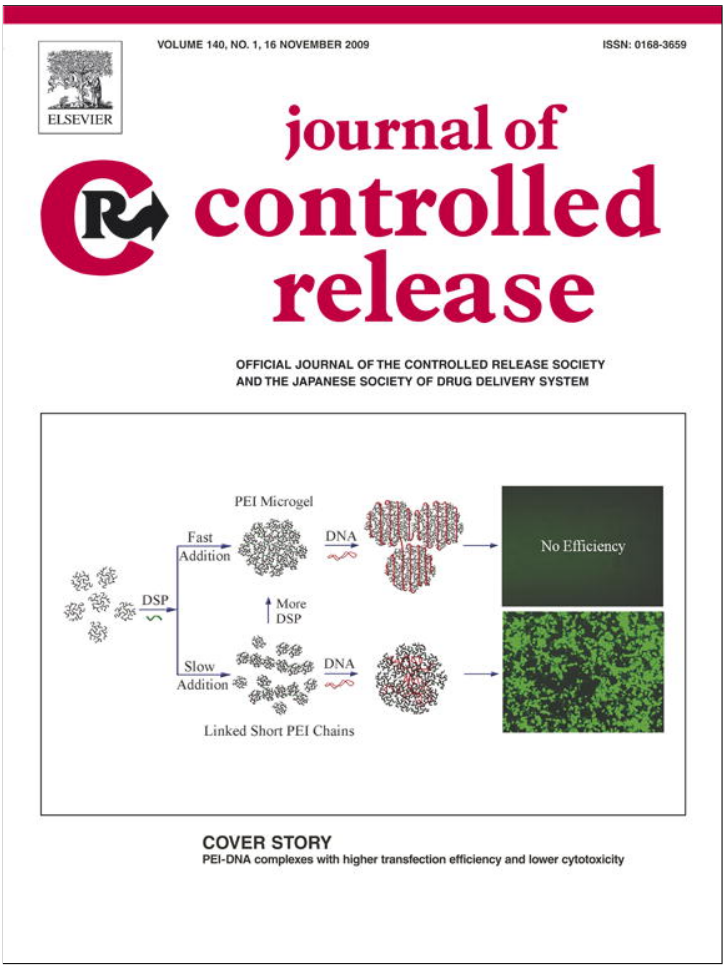

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Cover Story

PEI–DNA complexes with higher transfection efficiency and lower cytotoxicity

Since its introduction in 1995, cationic polyethyleneimine (PEI) has become one of the most efficient non-viral gene-transfection agents. The commercially available branched PEI (25,000 g/mol) has been widely used as a "gold standard" for evaluation of transfection efficiency of other newly developed polymer- or surfactant-based gene carriers. PEI, however, has a catch-22 problem: i.e., the increase in transfection efficiency is accompanied by the increase in cytotoxicity. It is well known that both efficiency and cytotoxicity increase with its chain length. Such a problem has to be resolved for clinical application of PEI, as well as other non-viral vectors. One approach to overcome this problem has been coupling short PEI chains into a longer one using biodegradable linkers. This particular approach makes sense, but the results have been inconsistent. One of the reasons is that previous studies did not pay sufficient attention to characterization of the linked polymer chains, such as their molar mass and subsequent structure of the PEI–DNA complex.

The study by Deng et al. published in this issue [1] deals with understanding of the effects of PEI chain length and polyplex structure on the transfection efficiency. The authors obtained PEI of a controlled chain length (or molecular weight) by improving a few experimental conditions. First, they noticed that complete removal of carbon dioxide made PEI dissolvable in pure DMSO, and the absence of water in the reaction solution prevented undesirable side reaction, i.e., water-induced hydrolysis of dithiobis(succinimidyl propionate) (DSP). DSP is a linking agent which has been shown to boost intracellular release of its cargo from polyplexes [2]. Second, they developed a laser light scattering (LLS) device for in-situ monitoring of the linking reaction. This device allowed them to stop the reaction at the right time to control the molecular weight of the linked PEI. Armed with such well-defined PEI chains, Deng et al. were able to correlate the chain length and polyplex structure to the gene-transfection efficiency and cytotoxicity in a more quantitative way. They found that over-coupling resulted in the formation of large clusters or microgels which were not effective. On the other hand, coupling of several short PEI chains (2000 g/mol) to form slightly larger chains (7000–8000 g/mol) increased the gene-transfection efficiency by three orders of magnitude. PEI with lower molecular weight (7000–8000 g/mol) was 10 times more effective and much less cytotoxic than the PEI gold standard (25,000 g/mol) and Lipofectoramine-2000. The study by Deng et al. presents important information on optimization of PEI as an effective transfection vector with minimal cytotoxicity by carefully controlling the chain length, and thus the structure of the polyplex. Other studies have also shown that the cytotoxicity of PEI can be reduced substantially, for example by ketalization of the primary amines of PEI [3]. While more studies using other polymers or transfection vectors need to be done before generalizing these findings, they collectively suggest that it will be only a matter of time before non-viral vectors with high transfection efficiency and no cytotoxicity can be developed for clinical applications.

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