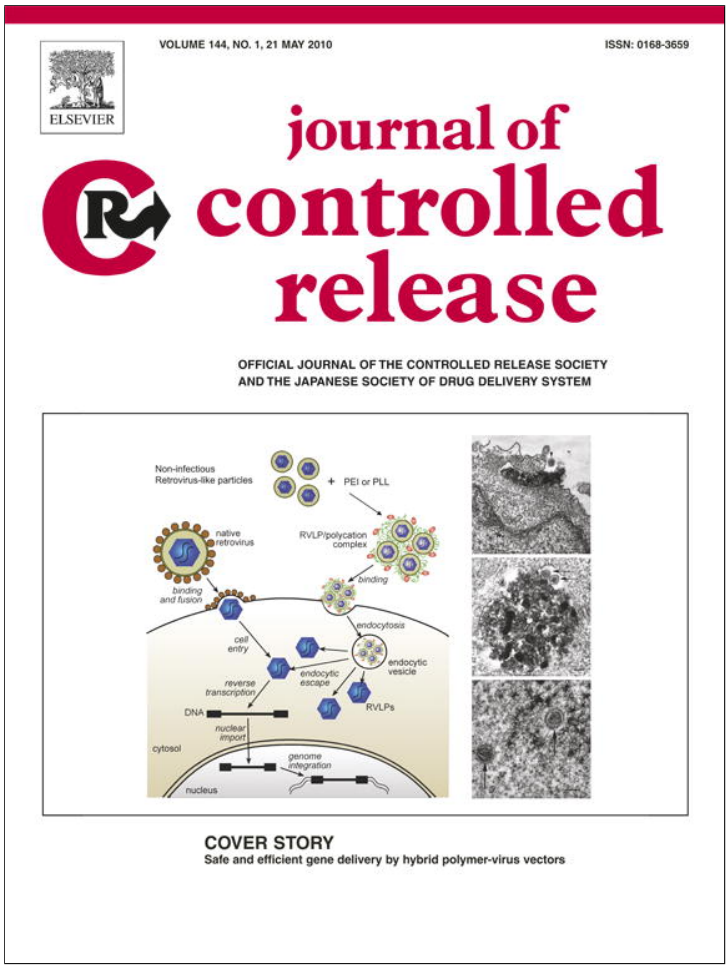

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Cover Story

Safe and efficient gene delivery by hybrid polymer–virus vectors

Each issue of the Journal of Controlled Release (JCR) presents the Gene Delivery section to highlight all papers dealing with various aspect of gene delivery. In this issue, the Gene Delivery section has 7 articles, and one of them deserves our special attention. Gene therapy was first used clinically 20 years ago to treat the lack of production of adenosine deaminase. Since then, the progress has been extremely slow. The success of gene therapy largely depends on the use of effective, and yet safe, vectors that deliver a specific gene to the target site. The idea of gene therapy is simple in theory, but it is very difficult in practice mainly because of the lack of such vectors. Initially, the viral vectors seemed to be the ideal vehicles for gene delivery, and indeed, at least two thirds of approved, ongoing, or completed clinical trials worldwide have employed adenoviruses, retroviruses, vaccinia viruses, poxviruses, adeno-associated viruses, or herpes simplex viruses [1]. The strong preference for viral vectors among clinical researchers is due largely to their undeniable advantage in gene delivery efficiency, and a majority of the first gene therapy protocols to reach the clinic will most likely employ them. But their triumph comes at a cost, most notably in safety. While viruses have been evolving mechanisms for more efficient delivery of nucleic acids to mammalian cells, mammals have also been evolving immune systems for keeping the viruses out. When the two clash, the consequences can be far different from intended, and sometimes can be fatal.

While the high transfection efficiency of the gene delivery vectors is critical for the success of gene therapy, it has to be accompanied by safety. For this reason, many researchers have turned their attention to developing nonviral vectors that, ideally, would exhibit enhanced safety. To date, however, they are far less efficient than viruses. Nonviral vectors based on polymers or lipids will require significant improvement in materials design to catch up to and surpass viral vectors in clinical significance. Recombinant viruses and synthetic vectors are likely to continue to battle for dominance on the road to clinical implementation of human gene therapy. In reality, however, a compromise between the two distinct approaches may provide more practical solution. It has been rather rare to combine viral components and nonviral materials to make effective vectors, but such hybrid approach may be the key to the successful gene therapy. For example, the surface of viral particles may be modified with polymers or lipids in order to reduce immunogenicity and/or allow for cell-type retargeting [2–4]. By combining viral and synthetic materials, it may be possible to alleviate some of the disadvantages of each individual class of vector while retaining of their respective advantages. Such hybrids are a relatively new class of material that show much promise but have been minimally investigated.

The paper by Professor Pack and his group in this issue represents a new step in the development of hybrid gene delivery vectors [5]. Unlike other hybrid vectors, these systems are based on a retroviral-like particle from Moloney murine leukemia virus (M-VLP) or human immunodeficiency virus (H-VLP) electrostatically complexed with cationic polymers, polylysine and polyethylenimine. Also unique to the work of Professor Pack and his co-workers, the viral portion of the hybrid vectors comprises only a portion of the native virus. M-VLP consist of the viral genome, capsid proteins and enzymes along with a lipid bilayer membrane obtained from the producer cell, but lack the viral envelope protein that is crucial for infectivity. Thus, these vectors are designed such that the viral portion, on its own, is non-infective, and the synthetic part recapitulates the function of the missing viral components. This is the first report of a hybrid vector in which the synthetic component plays an essential rather than supplementary role. The authors have demonstrated that these hybrid vectors are capable of relatively efficient gene delivery, retain important functions of the viral component including the capacity to integrate with the host genome and to infect non-dividing cells, and circumvent some disadvantages inherent to the native viruses, such as the notorious fragility of retroviruses to physical forces often encountered in production and purification protocols.

While the results are highly promising, it is still too early to predict whether hybrid vectors can achieve the combination of efficiency, safety and robustness that would be needed to reach clinical applications. Nevertheless, the article by Professor Pack and his colleagues in this issue clearly demonstrates that the field has just begun to tap the potential of hybrid gene delivery vectors. Furthermore, whether or not they are ultimately successful in their own right, exploration of hybrid vectors provide a new model that will teach a great deal about the design and assembly of safe and efficient gene delivery systems. Overall, the hybrid vector designed by Professor Pack presents the first step toward the right direction in the pursuit of the highly efficient, and at the same time safe, gene delivery vectors.

References

[1] Gene Therapy Clinical Trials Worldwide, <http://www.wiley.co.uk/genetherapy/clinical/>, accessed March 29, 2010.
[2] G.K. Lee, N. Maheshri, B. Kaspar, D.V. Schaffer, PEG conjugation moderately protects adeno-associated viral vectors against antibody neutralization, Biotechnol. Bioeng. 92 (2005) 24–34.
[3] R.C. Carlisle, R. Benjamin, S.S. Briggs, S. Sumner-Jones, J. McIntosh, D. Gill, S. Hyde, A. Nathwani, V. Subr, K. Ulbrich, L.W. Seymour, K.D. Fisher, Coating of adeno-associated virus with reactive polymers can ablate virus tropsim, enable retargeting and provide resistance to neutralising antisera, J. Gene Med. 10 (2008) 400–411.
[4] D.E. Fein, M.P. Limberis, S.F. Maloney, J.M. Heath, J.M. Wilson, S.L. Diamond, Cationic lipid formulations alter the in vivo tropism of AAV2/9 vector in lung, Molec. Ther. 17 (2009) 2078–2087.
[5] J.D. Ramsey, H.N. Vu, D.W. Pack, A top down approach for construction of hybrid polymer–virus gene delivery vectors, J. Control. Release 144 (2010) 39–45.

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