In vivo delivery of nucleic acids is a main challenge that has to be solved before gene therapeutic applications can be translated into the clinics. Preferably, the delivery should be applicable for systemic administration, because this has the potential to reach all corners of the body. More importantly, this is probably the only way of combating diseases such as cancer and metastasis. Despite intensive research over the last 20 years, only a few of the gene therapeutic vectors have been approved for the use in clinics [1]. Numerous clinical studies have revealed safety issues along with inefficacy problems.

Cell penetrating peptides (CPPs) are one class of the nucleic acid delivery vectors that have been available along with widely used liposomes and cationic polymers. The Langel group has developed CPPs that share the properties of both liposomes and cationic polymers. While all these classes of delivery vehicles are equally effective in vitro, the main challenge lies when they are tested in vivo. There are only a few studies that have specifically aimed to increase in vivo delivery efficacy of nucleic acids and even fewer that have undertaken large scale screening of libraries of compounds [2]. Despite the difficulties of in vivo studies, compounds with higher activity can only be discovered by specifically testing in vivo activity. In the current study by Freimann et al., the secondary amphipathicity of a CPP has been modified, generating an array of “NickFect” peptides [3]. The authors showed that increasing the secondary amphipathicity increased in vivo efficacy of the peptides. The resultant lead peptide NF55 showed efficient delivery of pDNA and induction of gene expression in several organs. The authors demonstrate that not only the cationic charge is important, but also other properties, such as the membrane activity play an important role in transfection.

Nevertheless, although Freimann et al. demonstrated development of a more efficient delivery vector, applications in clinics still have to wait until existing problems would be solved. First, the efficacy, although improved, needs further work. Although the vector with the pDNA is administered into the bloodstream, only some of the organs are actually transected. Within those, the lung shows by far the largest part of the signal. Obviously, this is one of the major limitations that has to be improved. Secondly, side effects may be a problem. Both the peptide NF55 and a commercial vector show elevation of liver enzymes following the treatment. Lung and/or liver toxicity has been reported for all major classes of delivery vectors: liposomes, cationic polymers and the peptides [4]. Accordingly, the question is: how should the scientists proceed? Which strategy should be used to achieve better efficacy with lower side effects?

The above questions facing efficient delivery of NickFect to the target organs apply to all delivery systems currently used, i.e., the systemic delivery systems in general. Interestingly, although Freimann et al. have found that increasing amphipathicity increases the efficacy in vivo, the in vitro data did not match the in vivo results. Thus, the initial parent vector (NF51) is an efficient in vitro transfection mediator. The optimized vector, NF55, however, shows equally similar efficacy. The situation is completely different in vivo. Here, the parent vector shows practically no activity, while the optimized vector excels. It is probable that completely different barriers play key roles or different factors determine the performance in vitro and in vivo settings. In vitro delivery efficacy seems to be a poor predictor of in vivo performance, which is not surprising at all. What we need collectively as scientists in the drug delivery field is to present the results of carefully designed studies with honest interpretation to clearly present problems and limitations of the tested methods. Only then, the field will advance to find improved delivery systems that can be translated into clinics.

References


Kinam Park
Purdue University
Departments of Biomedical Engineering and Pharmaceutics
West Lafayette, IN 47907, USA
E-mail address: kpark@purdue.edu