Development of a novel systemic gene delivery system for cancer therapy with a tumor-specific cleavable PEG-lipid

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Gene therapy is considered as promising therapeutics for acquired and inherited diseases. For successful cancer gene therapy via i.v. administration by using a non-viaral gene vector, it is essential to optimize the stability of carriers in the systemic circulation and the cellular association after the accumulation of the carrier in tumor tissue. However, a dilemma exists regarding the use of poly(ethylene glycol) (PEG), which is useful for conferring stability in the systemic circulation, but is undesirable for the cellular uptake and the following processes.

We report the development of a PEG-peptide-lipid ternary conjugate (PPD). In this strategy, the PEG is removed from the carriers via cleavage by a matrix metalloproteinase (MMP), which is specifically expressed in tumor tissues. An *in vitro* study revealed that the PPD-modified gene carrier (Multifunctional Envelope-type Nano Device: MEND) exhibited pDNA expression activity that was dependent on the MMP expression level in the host cells. *In vivo* studies further revealed that the PPD was potent in stabilizing MEND in the systemic circulation and facilitating tumor accumulation. Moreover, the i.v. administration of PPD or PEG/PPD dually-modified MEND resulted in the stimulation of pDNA expression in tumor tissue, as compared with a conventional PEG-modified MEND. Thus, MEND modified with PPD is a promising device, which has the potential to make *in vivo* cancer gene therapy achievable.