

## TARGETED NANOSIZED SYSTEMS FOR NUCLEIC ACIDS DELIVERY: THE ROLE OF FOLATE LIPOCONJUGATES

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The efficient delivery of therapeutic nucleic acids (NA) into target cells is one of the requirements for successful development of non-viral NA delivery systems. Many of mammalian tumors (i.e. ovarian carcinoma, prostate, colon, breast, lung, and kidney cancers as well as brain metastasis) over-express folate receptors (FR) on their cellular membranes. Folic acid (FA) is the main component for nucleotides biosynthesis, and hence for the cells activity and growth. The use of FA as a targeting ligand provides important advantages by contrast with other low-molecular ligands, such as the higher cell-specificity and the rapid penetration into tumor cells.

The decoration of surface of non-viral NA delivery systems with FA may mediate the folate-linked endocytosis and provide an efficient transfer of therapeutic NA into tumor cells. We have prepared a number of FA-equipped lipoconjugates differed with length of the spacer between hydrophobic domain and FA and investigated the influence of this structure unit on the NA delivery.

Liposomes composed of spermine-based polycationic amphiphile, DOPE and synthesized FA-lipoconjugates provided the delivery of FITC-labeled oligonucleotide and plasmid DNA into KB-3-1 and HEK 293 cells. It was found that the transfection efficiency of folate-conjugated liposomes was higher than one of non-targeted liposomes. The influence of liposomes to NA ratio in complexes also was investigated and the best results were indicated for low N/P +/- ratios 1/1 and 1/2. Further augmentation of +/- ratio led to the loosing of targeting potential of folate-containing liposomes.

Structure-activity screening studies showed that FA-lipoconjugate with long polyethyleneglycol spacer group exhibited the highest transfection activity among all lipoconjugates tested.

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