[OE1-2] [2004-10-22 15:15 - 15:30 / Room 205]

Improved Antisense Delivery System to Reduce IL-4 Level for the Treatment of Asthma In Vitro and In Vivo

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Purpose. The interleukin-4 (IL-4) is essential for T_H2-mediated inflammation observed in allergic asthma. To block the production of IL-4 for the treatment of asthma, antisense oligonucleotides (ASO) targeting IL-4 were designed, and polyethylenimine (PEI) was used to enhance the delivery of IL-4 antisense. In this study, the optimal condition of IL-4 ASO delivery system was developed in vitro and in vivo. Methods. Antisense oligonucleotides were designed to inhibit the translation initiation region of murine IL-4 mRNA (+4 to +25). In vitro transfection efficiencies of various IL-4 ASO/PEI complexes were measured using flow cytometry and ELISA. XTT assay was performed to evaluate the cytotoxicity. The size and morphology of the complex were visualized using atomic force microscopy (AFM). After BALB/c mice were sensitized to ovalbumin, the IL-4 level in bronchoalveolar lavage (BAL) fluid were analyzed using ELISA. Results. The uptake efficiency of the complex at NP ratio of 10 was 14.5-fold higher than that of naked ASO. IL-4 level was reduced to 29.4% by ASO/PEI complex at that ratio, and the cytotoxicity was low. Thus, the complex at NP ratio of 10 was most effective condition. In AFM images, the complexes were dispersed homogeneously, and the size was about 98 nm. ASO/PEI complex was more effective than naked ATS in vivo. Conclusions. In this study, effective gene delivery system for the treatment of asthma was developed by improving the delivery of IL-4 ASO with PEI. Therefore, the results of this study provide the possibility of gene therapy in allergic asthma.

[OE1-3] [2004-10-22 15:30 - 15:45 / Room 205]

Cationic solid lipid nanoparticles for in vivo gene delivery based on the dermal application

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Purpose : To develop the gene delivery system for the dermal use, a cationic solid lipid nanoparticles (SLNs) were prepared. Methods : Cationic SLNs were formulated with 3b-N-(N',N'-dimethylaminoethane)-carbamoyl cholesterol (DC-Chol) or 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP), tricaprin as a solid core and

other co-surfactants. We evaluated the physical characteristics and transfection efficiencies of DNA/SLN complexes in non-small cell lung carcinoma cells (H1299). The DOTAP-SLN formulation was tested for in vivo transfection efficiency and its retention time within the organs by applying the DNA/SLN complexes on hair-removed dorsal skin of mice non-invasively. Results : The SLNs have small sizes and positive zeta potential values. Gene trasnfection efficiency of the DOTAP-SLN reached maximum and appeared comparable to Lipofectin^{R} at 1: 14 (the ratio of lipid to DNA). The DOTAP-SLN formaulation was capable of penetrating the intact skin of mice when topically and transdermally applied. Conclusion : A cationic SLN/DNA complex system may be applied potentially for dermal gene delivery.

[OE1-4] [2004-10-22 15:45 - 16:00 / Room 205]

Synthesis of Peptides of L-Aspartic Acid Derivatives by Solid Phase Peptide Synthesis Methodology

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The polyene macrolide amphotericin B (AmB) is the most effective antibiotic for the treatment of systemic and visceral fungal infections in humans. The main advantages of this drug are: broad antifungal spectrum, fungicidal activity, and high activity against multidrug resistant strains. AmB binds to ergosterol, the sterol of fungal membranes, and destroys them. Unfortunately, its usefulness is limited by its pronounced side effects both immediate (chills, fever, nausea, headache) and delayed with dose-limiting nephrotoxicity, in particular. It is a matter of interest to design new formulations/admixtures that, like the recently commercialized AmB alternatives, can provide a better ratio between activity and toxicity compared with that of classically used formulation, Fungizone (AmB-deoxycholate [AmB-Doc]). Our present study involves the synthesis of deca-L- aspartic acid derivatives and their uses as admixture with AmB in an attempt to reduce the toxicity associated with AmB application for fungal diseases.We have used Solid Phase Peptide Synthesis (SPPS) Chemistry to synthesize our desired peptides. The intended carboxyl terminal amino acid is anchored to a solid support and the next N-protected amino acid is coupled to the first one. After the coupling step, the block is removed from the primary amino group and the coupling reaction is repeated with the next amino acid. The process continues until the peptide is completed. Then, the molecule is cleaved from the solid support and groups protecting amino acid side chains are removed. We report herein the preparation of peptide derivatives of aspartic acid with some beta-carboxyl groups blocked as aryl alkyl esters. Their applications along with amphotericin B is in progress and the results will be reported later.