102d Formulation of the Anti-Inflammatory Cationic Lipid Dexamethasone-Spermine with Adenovirus for Targeted Gene Delivery to the Lung Airway Epithelia

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We formulated adenovirus (AdV) vectors with cationic steroid liposomes containing dexamethasone-spermine (DS)/Dioleoylphosphatidylethanolamine (DOPE) in an effort to overcome the lack of apically expressed AdV vector receptors on airway epithelial cells and to reduce the inflammation associated with AdV vector exposure. An AdV vector (1 to 2.5 x 10^{11} genome copies) expressing human placental alkaline phosphatase (AlkP) or β-galactosidase (LacZ) was delivered alone or complexed with DS/DOPE, DC-Chol/DOPE, or dexamethasone to C57Bl/6 mice via intranasal instillation. Formulation of the AdV vector with DS/DOPE and DC-Chol/DOPE resulted in transgene expression targeted only to the airway epithelial cells with minimal expression in alveolar cells, while AdV alone caused high alveolar transduction. The DS/DOPE and dexamethasone formulations greatly reduced cellular infiltrates compared to AdV vector alone, while formulation with DC-Chol/DOPE did not. IFN-γ was significantly elevated at day 7 in mice receiving only the AdV vector compared to the AdV vector formulated with DS/DOPE, DC-Chol/DOPE, or dexamethasone. Furthermore, staining for CD8 positive cells at days 1 and 7 post-instillation revealed significantly less CD8+ cells in the DS/DOPE formulated group compared to AdV alone. Lipid formulation of adeno-associated virus (AAV) vector expressing LacZ also produced airway epithelial targeting similar to the AdV vector. Viral vectors can be formulated with DS/DOPE to improve targeting to the airway epithelium in vivo and to attenuate vector-induced inflammation through the pharmacological activity of DS.