431d Dendrimer-Based Nanodevices for Asthma Drug Delivery: Synthesis, in-Vitro and in Vivo Studies

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Dendrimers and hyperbranched polymers possess highly branched architectures, with a large number of controllable, tailorable, ‘peripheral' functionalities. These materials have tremendous potential in targeted drug delivery. They have significant potential compared to liposomes and nanoparticles, because they can modulate the local environment through functional groups. Methyl prednisolone is a synthetic steroid that is widely used to suppress acute and chronic inflammation, especially associated with asthma. We seek to improve the ability of the inhaled drug to stay in the lung for longer times, enhance targeting to the lung, in order to prevent side effects and improve drug performance.

We report a synthesis method to obtain methylprednisolone (MP)-polyamidoamine dendrimer (PAMAM G4-OH) conjugate with a relatively high payload. Glucocorticoid MP was covalently conjugated to PAMAM-G4-OH dendrimer by incorporating glutaric acid (GA) as a spacer, to overcome the steric hindrance for the steroid at the crowded dendrimer periphery. The use of the spacer appears to increase the reactivity of MP for subsequent conjugation with dendrimer, leading to high payload of the drug. 1H NMR estimates indicate that 12 molecules of MP are present in the drug-dendrimer conjugate. This represents a drug payload of approximately 32% w/w, which is among the highest reported for dendrimers.

The cellular transport and the therapeutic activity of the conjugates were also investigated. The conjugates were further fluorescent-labeled with fluoroisothiocynate (FITC) to evaluate the dynamics of cellular entry. Fluorescence and confocal microscopy images on A549 human lung epithelial carcinoma cells treated with the conjugates show that they enter the cells rapidly and are mostly localized in the cytosol. The MP-dendrimer conjugates showed comparable pharmacological activity to free MP, as measured through prostaglandin suppression. The conjugates are amenable for further conjugation with a targeting moiety for targeted drug delivery, and could improve the circulation time for the drug in vivo. We have developed methods to formulates the water-insoluble conjugates to be soluble in a IV and intra-nasal form, to be administered to mice, for evaluation in an ovalbumin-induced lung inflammation model. The model Preliminary results suggest that the dendritic polymer provides superior drug residence times in the lung, compared to free drug. When physically targeting the lung by delivering intra-nasally, the resident times for the dendrimers are significantly higher than free drug. For example, more than 35% of the dendrimer was recovered from the lung in 24 hours.

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