A Study on Gene Therapy: Using Poly (β-aminoesters)

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ABSTRACT

Gene delivery is the process of administering therapeutic genes to a patient’s cells, where upon uptake, their modulation of the protein expression patterns in the host can result in a desired phenotype. This is especially beneficial for the treatment of a large number of diseases at the genetic level, including cancer. Cationic polymers, which are known for their ease of synthesis that can allow for a large library of polymers to be created for studies, have garnered much attention as potential gene delivery vectors. One type of cationic polymer, poly (β-aminoesters) (PBAEs), is being utilized as a potential type of vector for gene delivery. Unlike other vectors that have been observed in the past, which include viral vectors, poly-lysine (PLL), and poly(ethylene imine) (PEI), PBAEs are structurally diverse and non-cytotoxic. In addition, PBAEs are easily synthesized (via Michael addition), biodegradable, and capable of controlled DNA release into the cell.

INTRODUCTION

PBAE Synthesis

Polymers are named according to monomers used. For example: for a reaction between diacrylate A and amine 1, the resulting base polymer is called “A1”

Reaction Scheme

We analyzed the effects of mannosylation on PBAEs of a wide range of molecular weights. As polymer molecular weight decreased, the surface density increased.

Mannosylation of PBAE

- Mannose is used as a grafting ligand.
- It has been previously shown that mannosylating PBAEs improved gene delivery efficiency.
- In these studies, we examine the effects of both mannosylation and molecular weight on the gene delivery efficiency of one specific PBAE – D4A4.

Polyplex Characterization

- To form polyplexes, three ratios of polymer to pDNA were used: 50:1, 100:1, and 200:1. Polyplexes are ordered on these graphs in descending molecular weight, with P1 having the highest molecular weight, and P14 having the lowest.
- Using dynamic light scattering (DLS), both the polyplex diameter (nm) and the polyplex zeta potential (mV) were measured. Sodium acetate (NaOAc) and PBS were used as solvents.
- As molecular weight decreases, both the polyplex diameter and zeta potential decrease.

RESULTS & DISCUSSION

NMR Spectroscopy

- Nuclear magnetic resonance spectroscopy (NMR) allows us to determine (and confirm) the structure and purity of each polymer
- NMR was also used to evaluate polymer degradation profiles. This significantly reduced instrumentation time, as well as experimental costs.

CONCLUSIONS & FUTURE DIRECTIONS

- As molecular weight increases, both zeta potential (mV) and diameter of polyplex (mm) decrease.
- NMR Spectroscopy also allowed us to determine the polymer degradation profiles at a significantly lower cost and time.
- Future experiments that can be considered include:
  1. Imaging using SEM, TEM, Confocal Microscope
  2. Antigen Presenting Cell (APC) Gene Delivery studies
  3. Infectious disease and cancer models

REFERENCES

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The NMR Spectroscopy of D4A4-Man-1