

Peptide-mediated Membrane Fusion for Gene Therapy

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INTRODUCTION

- Gene delivery efficiency is limited by endocytosis, which promotes lysosomal degradation of therapeutic cargo.
- Membrane fusion provides a strategy to bypass endocytosis and directly release cargo into the cytoplasm.
- Engineered peptides (E4 and PK4) can mimic SNARE proteins and “zipper” membranes together to induce fusion.
- HIV-1 capsids naturally protect genetic material and efficiently deliver it into the nucleus, including in non-dividing cells.

Theory

- Dimerization of E4 (liposome anchored) and PK4 (cell membrane anchored) peptides will drive enforced membrane fusion
- Purified HIV-1 capsids encapsulated within engineered liposomes will be efficiently delivered into target cells.
- Fusion-mediated delivery will bypass endocytosis and enhance nuclear gene expression.

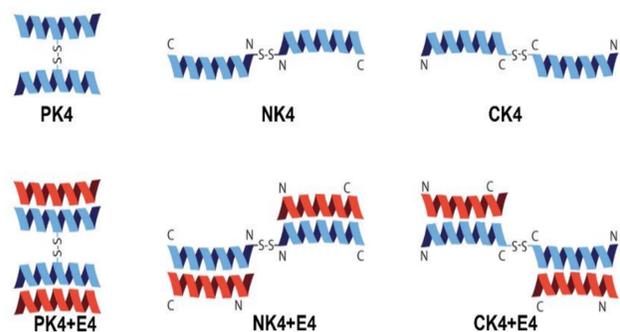


Figure 1: Schematic representation of K4-dimers and coiled-coil structures of K4-dimers with complementary E4 peptides

Can a peptide-mediated, non-viral fusion platform improve the safety and efficiency of gene delivery compared to traditional lentiviral vectors?

METHODS

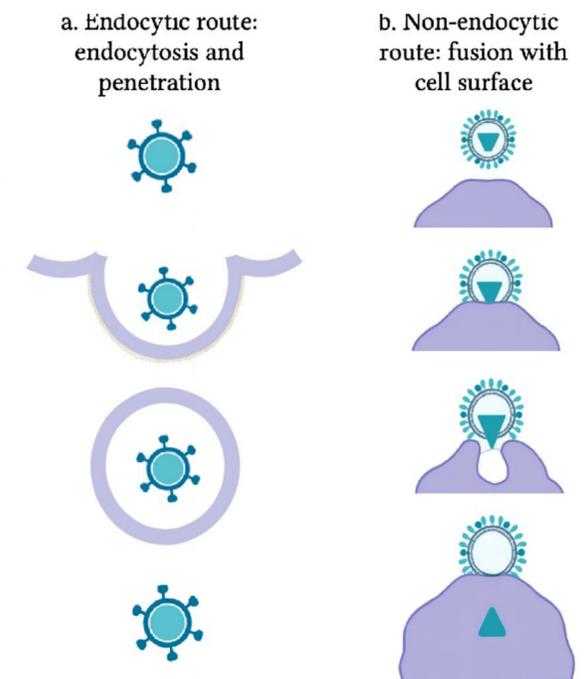
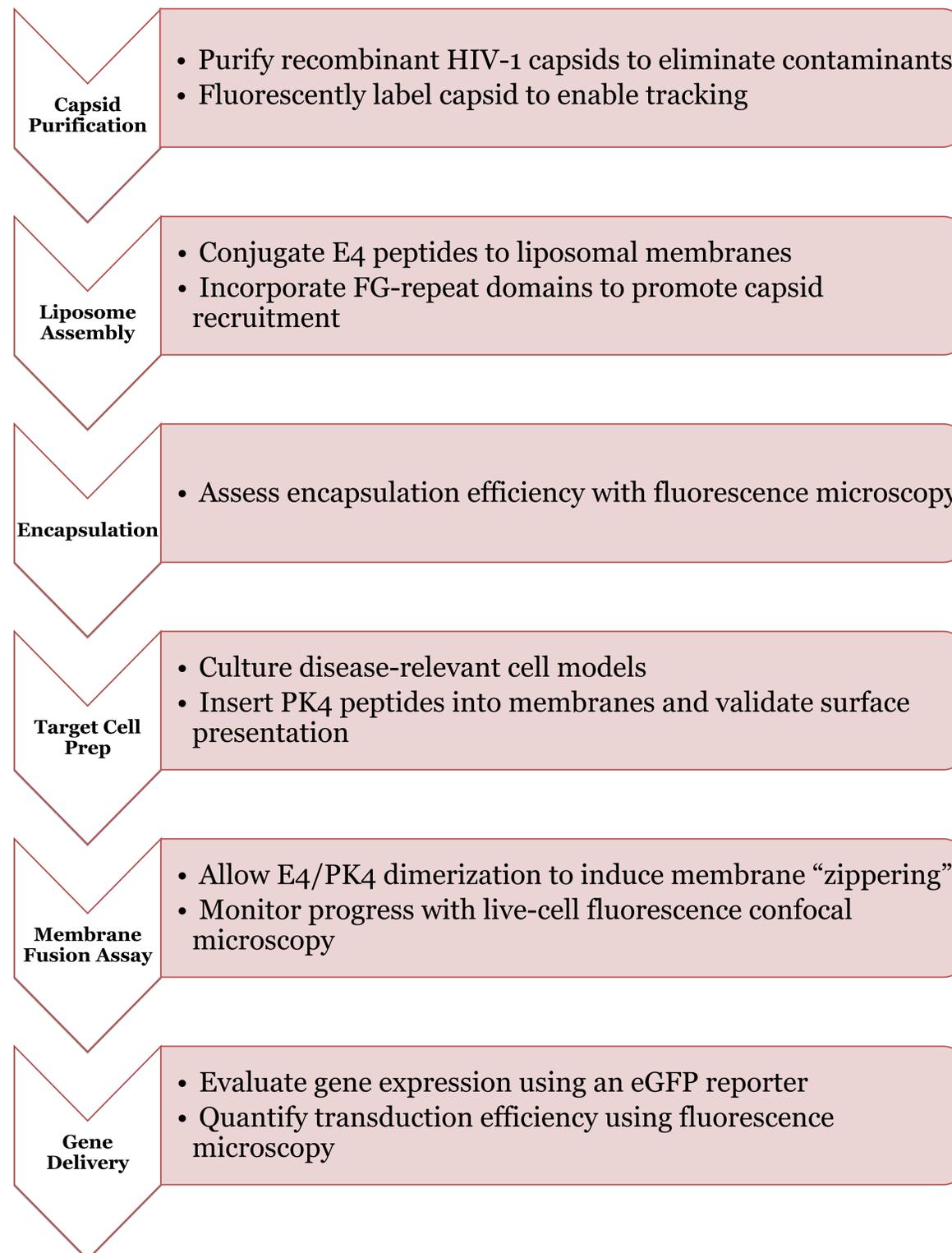


Figure 2: Juxtaposition of endocytosis vs. membrane fusion for capsid delivery

DISCUSSION

- Enforced membrane fusion may significantly enhance cytoplasmic and nuclear gene delivery efficiency.
- This approach reduces reliance on full viral vectors, potentially improving safety and purity.
- The system is modular and adaptable for delivering customizable genetic cargo.
- Successful implementation could advance non-viral gene therapy platforms for difficult-to-target cells (e.g., stem cells, neurons).
- Provides a foundation for engineering capsid-like particles for therapeutic applications.

REFERENCES

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