Molecular Dynamics Investigation of Nanoparticle Translocation through Pulmonary Monolayer for Gene Delivery

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Introduction

Pulmonary Gene Delivery

•Introduces genetic material directly into the lungs. [1]

•Provides high efficacy with reduced systemic side effects.

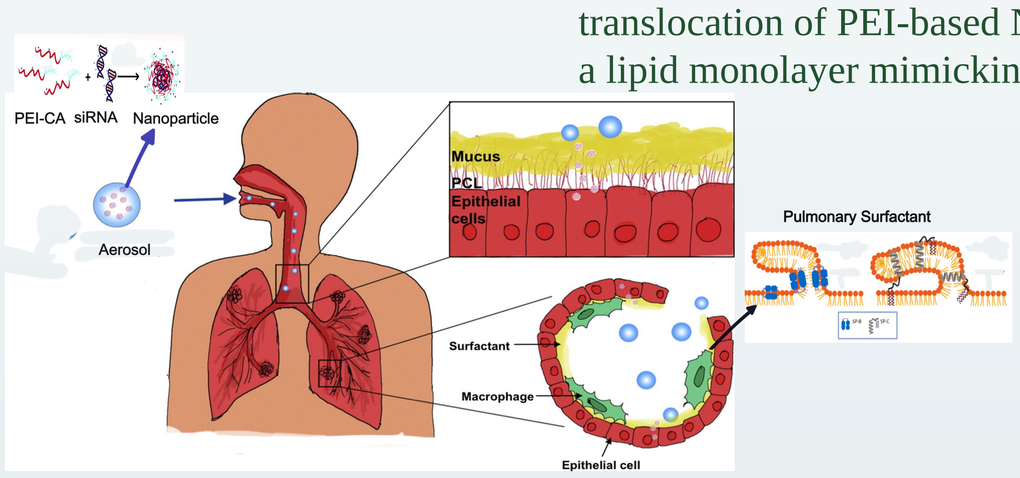
Challenges in Pulmonary Gene Delivery [2]

•Complex airways limit efficient delivery.

•Mucus entrapment traps particles.

•Pulmonary surfactant (PS) forms lipid monolayers/multilayers that act as a barrier.

•Macrophage Engulfs and neutralizes therapeutic agents.



Recent Advances in Pulmonary Gene Delivery

•Nanoparticles (NPs) encapsulate genetic material, enhancing transport and stability across biological barriers.

•Cationic polymers (e.g., Polyethylenimine (PEI)) condense siRNA and protect it.

PEI-Based Gene Delivery

•Advantages: High transfection efficiency, versatile applications.

•Challenges: Cytotoxicity, limited specificity.

Research Objective

•Use coarse-grained (CG) molecular dynamics (MD) to study the translocation of PEI-based NPs through a lipid monolayer mimicking the PS.

Methods

Martini Force Field Parameterization:

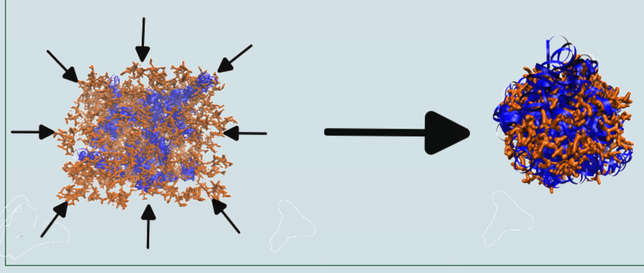
•PEI and PEI-CA modeled with CG beads; smaller PEI/PEI-CA fragment used for efficiency. Simulations conducted with water and NaCl at 300 K and 1 bar.

•Parameters adjusted until the CG potential of mean force (PMF), based on the center-of-mass (COM) distance between PEI/PEI-CA and siRNA as well between PEI/PEI-CA and lipids, matched the all-atom (AA) results.

Nanoparticle Formation:

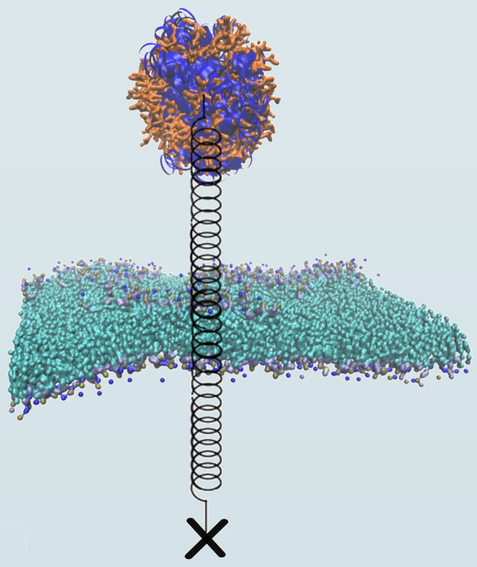
•Compact NP formed by pulling the COM of PEI-CAs and siRNAs together.

•NPs with PEI and siRNA, and with PEI-CA and siRNA, were equilibrated; drifting PEIs were removed afterward.



Pulmonary Monolayer Setup:

•Monolayer composed of DPPC and DPPG (5:1 ratio), simulated under constant surface tension (γ) from 10–30 mN/m.



NP Translocation Simulations:

•Steered MD utilized a spring constraint to pull the NP toward the origin.

•Monitored forces, monolayer integrity, NP properties, and various stages of NP delivery.

Results

Preparation and Validation of simulation system

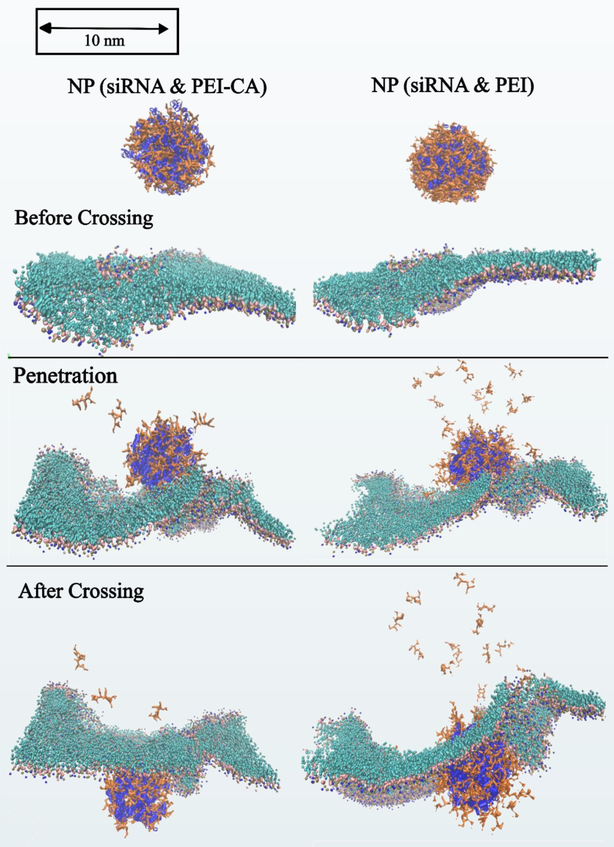
•CG force field reproduced AA simulation results with minimal RMSD, confirming accuracy.

γ was maintained at target values with minimal monolayer damage.

NP delivery:

•For NP (siRNA/PEI-CA), N/P ratio decreased from 3.49 to 3.23, and for NP (siRNA/PEI) from 7.7 to 6.

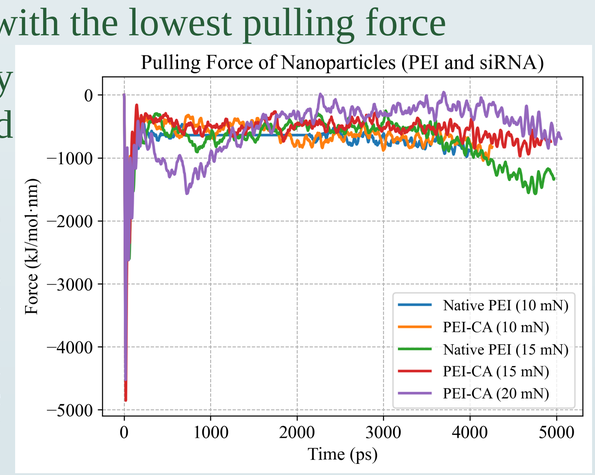
•Radius of gyration increased for both NPs, with a more significant increase for PEI-siRNA NP. RNAs radius of gyration remained relatively constant in both cases.



Pulling Force at Varying γ:

•γ impacts NP translocation, with the lowest pulling force observed at 20 mN/m, likely due to more pores generated in the monolayer.

•CA tails in PEI-CA enhance hydrophobicity, facilitating easier translocation by promoting interactions with the hydrophobic regions of the monolayer.



Conclusion

•Forcefield validation

•NP translocation through the monolayer is influenced by γ and lipid substitution on PEI.

•PEI-CA's hydrophobic tails facilitate easier translocation.

•Higher γ reduces the required force.

References

[1] M. Bisserier, X. Q. Sun, S. Fazal, I. C. Turnbull, S. Bonnet, and L. Hadri, Cells, vol. 11, no. 6, pp. 9842022. doi:10.3390/cells11060984.

[2] C. C. Ruge, J. Kirch, and C. M. Lehr, Med., vol. 1, no. 5, pp. 402-413,2013. doi: 10.1016/S2213-2600(13)70072-9.