Development of Biomimetic Nanoparticles for Smooth Muscle Cell Dysfunction

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Background and Objective

Coronary Artery Disease (CAD) is the leading cause of mortality in the U.S. It's associated with 17.8 million death annually Worldwide[1]. Mechanical interventions are common procedures for CAD; however, they often lead to endothelial denudation exposing the collagen layer in the vessel wall. The injury promotes smooth muscle cells (SMC) dysfunction where they undergo an unregulated migration and proliferation to the intima layer introducing neointima hyperplasia and stenosis. The predominant challenge stems from the lack of pharmacotherapeutic alternatives to effectively combat in-stent restenosis [4]. Verteporfin (VP), an FDA-approved pharmacological agent, presents a promising trajectory in attenuating YAP/TAZ activity which have been identified as the key regulator of cell signaling including migration and prefoliation in SMC [3][5]. **This project aims to** develop a biomimetic nano-drug for SMC dysfunction in vascular diseases by targeting the YAP/TAZ signaling pathway through collagen binding at the lesion site, with the ultimate goal of reducing the need for restenosis surgery.

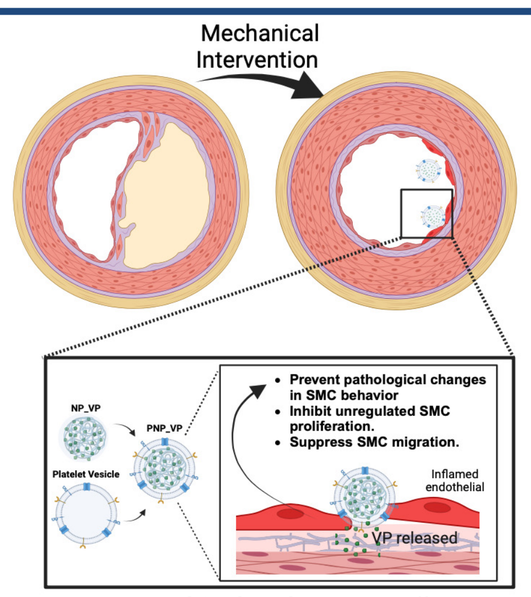


Figure 1. Graphical abstract. Illustration highlighting the project's approach to suppress SMC dysfunction by binding to collagen for targeting delivery and inhibiting YAP signaling.

Methodology

PNP-VP Synthesis

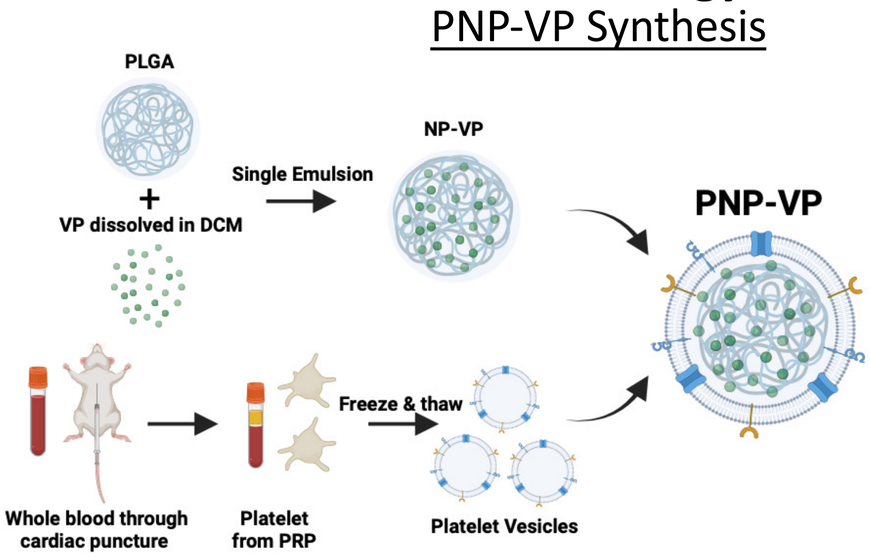


Figure 2 PNP-VP formulation: Schematic diagram illustrating the preparation process of platelet membrane verteporfin nanoparticles (PNP-VP) through a single emulsion [6].Platelet membrane collection procedure from mouse whole blood.

In Vitro Assessments

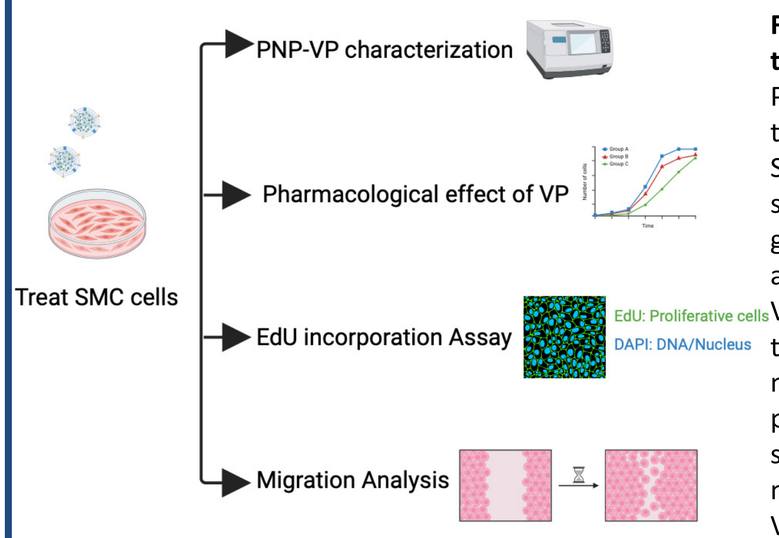


Figure 3 Experimental design to assess PNP-VP on SMC: PNP_VP are characterized through the Dynamic Light Scattering (DLS) in terms of size, charge, and PDI. Both cell growth assay and western blot analysis are utilized to assess VP effect on SMC and optimize the dose. EdU incorporation measured the DNA synthesis in proliferation cells. Migration scratch assay examined the migratory behavior of cells post VP treatment.

Results

Optimization of PNP-VP Dose

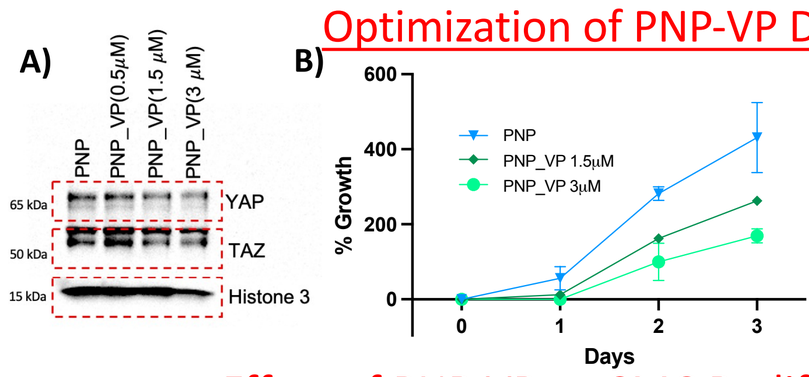


Figure 5. Dose Optimization. (A) Inhibition effect of PNP_VP on SMC through western blot analysis. **(B)** Effect of various PNP_VP dosages on SMC growth over time.

Effect of PNP-VP on SMC Proliferation

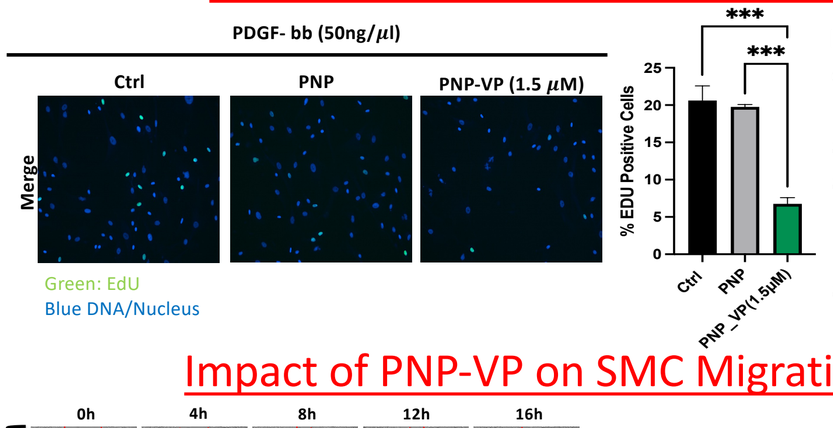


Figure 6. PNP_VP effect on SMC proliferation. Representative images and quantitative analysis of SMC proliferation through EdU incorporation assay.

Impact of PNP-VP on SMC Migration Rate

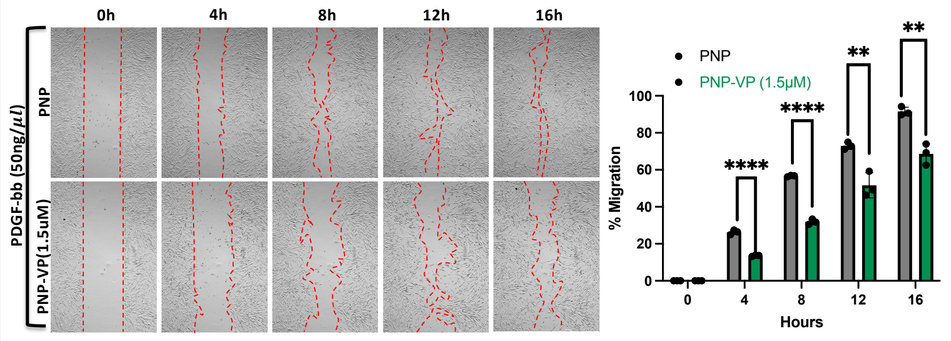
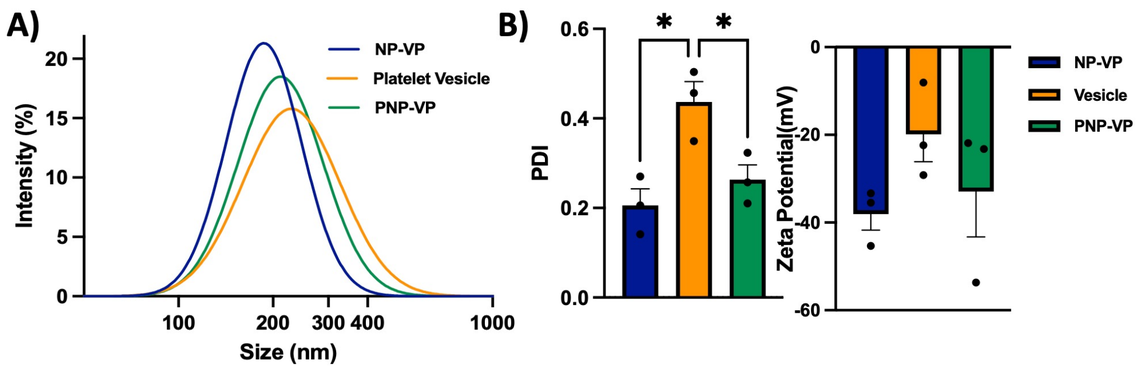


Figure 7. SMC Migration post treatment. Representative images and quantitative analysis of scratch assay for SMC post treatment.

Results

PNP-VP Characterization through DLS and TEM



C)

NP-VP EE %	79.37 %
NP-VP LC %	17.69 %

D)

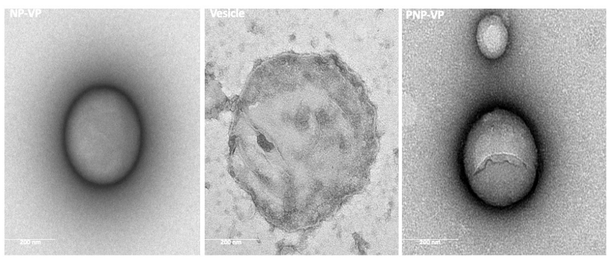


Figure 4: Formulation and characterization of PNP-VP. (A) Hydrodynamic size of NP-VP, platelet vesicle, and PNP-VP through the dynamic light scattering (DLS). **(B)** Polydispersity (PDI) and surface charge of NP-VP, platelet vesicle, and PNP-VP. **(C)** Percentage of the encapsulation efficiency and loading capacity of NP-VP. **(D)** Representative transmission electron microscopy (TEM) images of NP_VP, platelet vesicle, and PNP_VP (scale = 200 nm).

Conclusion

- At lower doses, PNP_VP effectively inhibited cell growth without triggering apoptosis.
- PNP-VP reduced the proliferation rate in SMC, indicating its potential to suppress unregulated cell division.
- PNP-VP demonstrated a notable reduction in cell migration rate, suggesting its potential to modulate cytoskeletal dynamics and hinder cellular motility.

Ongoing Work

- Utilizing quantitative polymerase chain reaction (qPCR) to elucidate the molecular mechanisms underlying the PNP-VP on the expression of migration and proliferation genes.
- Conducting a study in a neointima hyperplasia animal model to validate the efficacy of PNP-VP *in vivo.*

Acknowledgment

I would like to express my sincere gratitude to Dr. Wang for the opportunity to contribute to this project, and to all lab members for their time and support. Special thanks to W.L. Gore & Associates for sponsoring this project.

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