Evaluation of a Novel Small Molecular Drug in Vascular Dysfunction

Mark Orlando, Biomedical Engineering
Mentor: Dr. Kuei-Chun Wang, Assistant Professor
School of Biological Health Systems Engineering

Introduction

Atherosclerosis Plaque Progressed by Dysfunctional Vascular Cells

Atherosclerosis, the buildup of plaques within blood vessels, contributes to global mortality from cardiovascular disease. Currently, there are no effective medicines for alleviating the manifestation of plaque formation due to dysregulated inflammation and cell proliferation of vascular endothelial cells (ECs) and smooth muscle cells (SMCs). The objective of this project is to determine the pharmacological effects of IAG933 on ECs and SMCs and then formulate nanoparticles that encapsulates IAG933 and characterize its physiochemical properties.

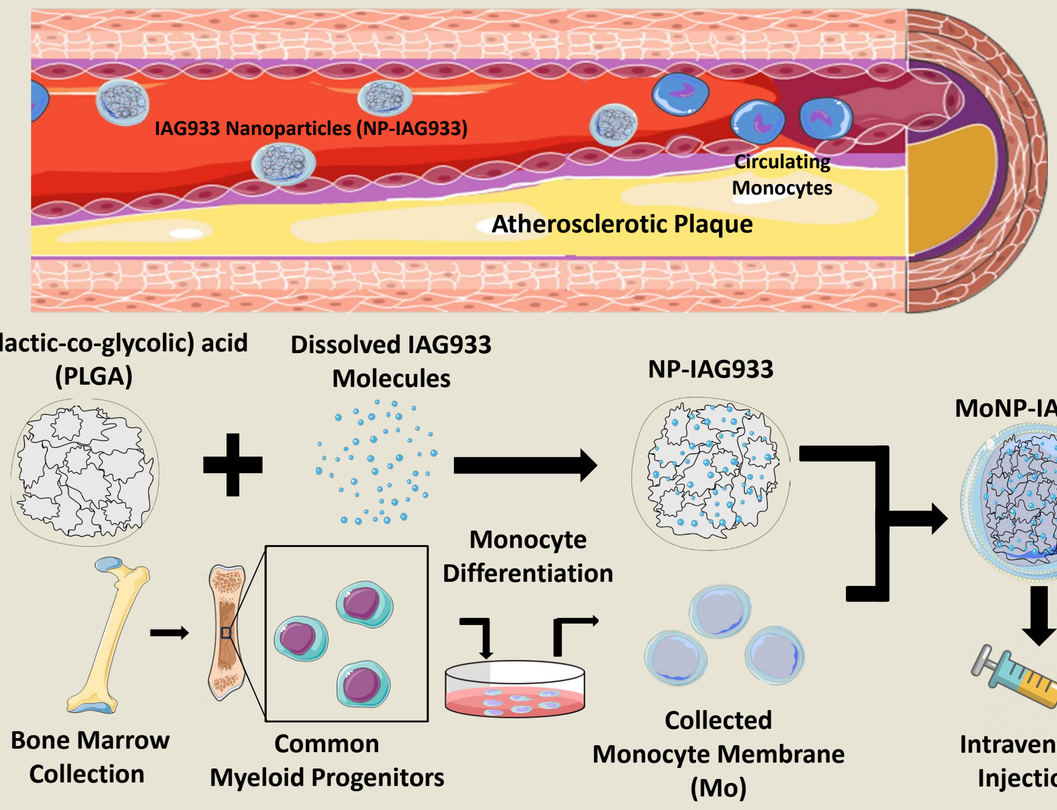

Figure 1: Proposed Regional Inflammatory Targeting Nanomedicine Treatment of Atherosclerotic Plaque through Monocyte Membrane Cloaking Guidance.

Methods

Detailed Protocols and Procedure

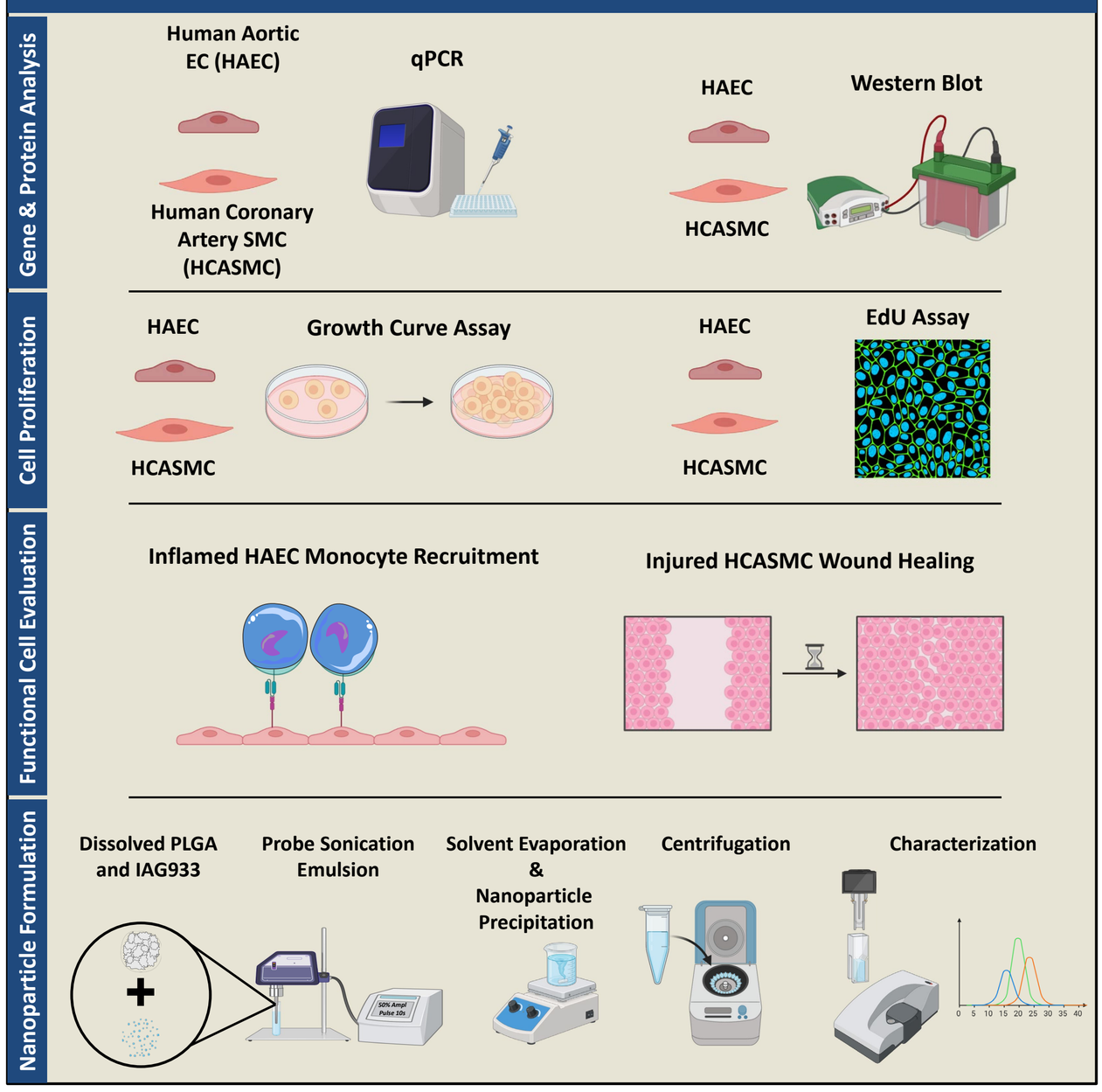

Figure 2: Experimental Design for Evaluation of Free Drug IAG933 Effects on Vascular HAECs and HCASMCs and Nanoparticle Formulation Process.

Results

In-Vitro Validation

Effects of IAG933 on YAP-TEAD Associated Downstream Expression

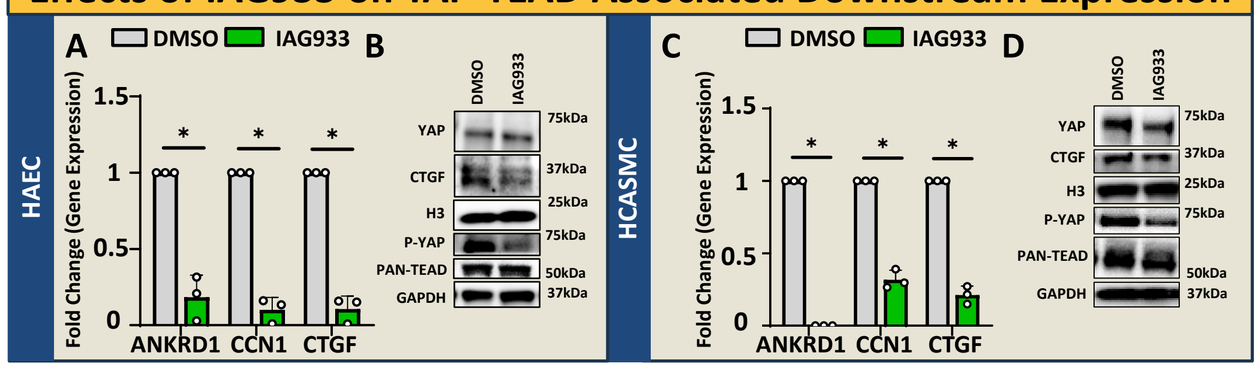

Figure 3: IAG933 Downregulates Downstream YAP-TEAD Genes and Proteins.

Effects of IAG933 on Cell Proliferation

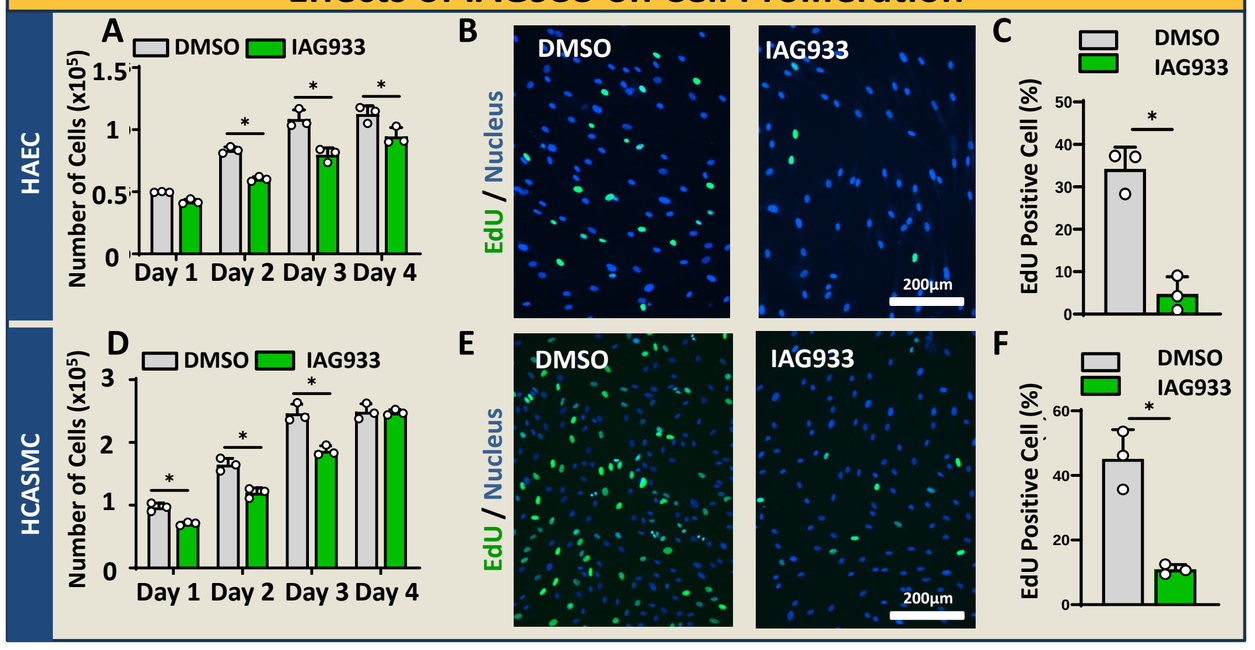

Figure 4: IAG933 Slows Cell Growth Rate and Suppresses New Cell Expansion.

IAG933 Enhances Vascular Cell Function in Response to Injury

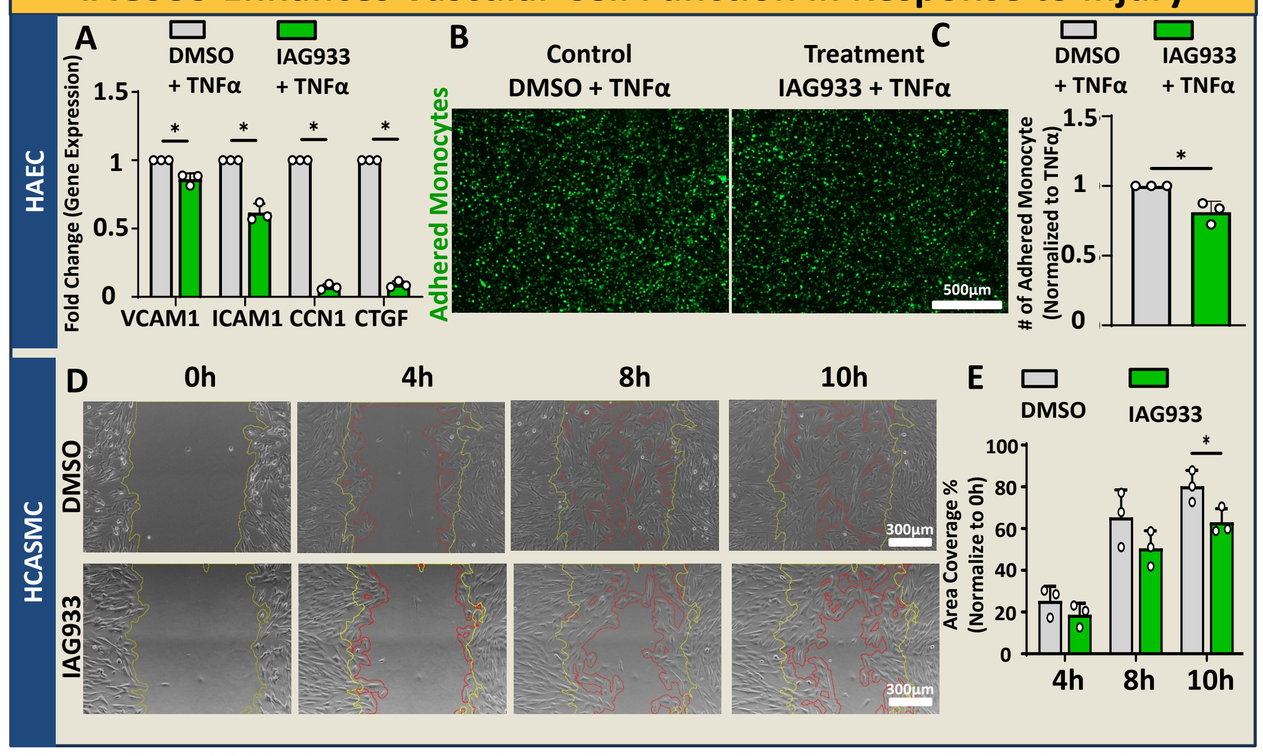

Figure 5: IAG933 Alleviates Induced Vascular Cell Phenotypic Dysfunction Post Inflammatory Stimuli and Post Scratch Injury Insult.

Particle Characterization

Monocyte Membrane Coats IAG933 Encapsulated Nanoparticles

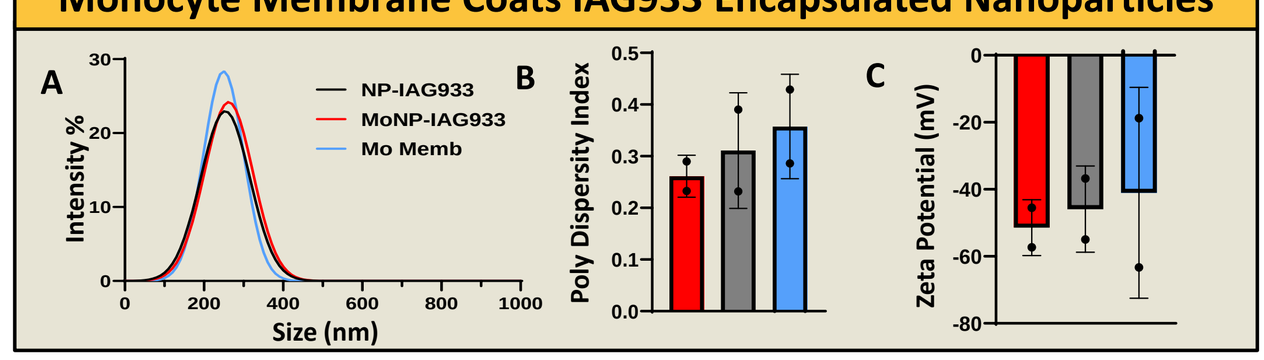

Figure 6: DLS Particle Surface Characterization of Size, Uniformity and Surface Charge Demonstrate Support fore Successful Membrane Coating.

References

[1] C. Sun *et al.*, "Yes-Associated Protein in Atherosclerosis and Related Complications: A Potential Therapeutic Target That Requires Further Exploration," *Front. Cardiovasc. Med.*, vol. 8, p. 704208, Aug. 2021, doi: 10.3389/fcvm.2021.704208.
[2] F. Daoud *et al.*, "YAP and TAZ in Vascular Smooth Muscle Confer Protection Against Hypertensive Vasculopathy," *Arterioscler. Thromb. Vasc. Biol.*, vol. 42, no. 4, pp. 428–443, Apr. 2022, doi: 10.1161/ATVBAHA.121.317365.
[3] K.-C. Wang *et al.*, "Flow-dependent YAP/TAZ activities regulate endothelial phenotypes and atherosclerosis," *Proc. Natl. Acad. Sci.*, vol. 113, no. 41, pp. 11525–11530, Oct. 2016, doi: 10.1073/pnas.1613121113.
[4] E. A. Chapeau *et al.*, "Author Correction: Direct and selective pharmacological disruption of the YAP–TEAD interface by IAG933 inhibits Hippo-dependent and RAS–MAPK-altered cancers," *Nat. Cancer*, vol. 5, no. 7, pp. 1130–1130, Jun. 2024, doi: 10.1038/s43018-024-00797-y.

Future Directions

It is current and ongoing work for optimization of nanoparticles formulation to improve yield and batch consistency. The future works of this project are to evaluate the effectiveness of IAG933 in nanoparticle form when surrounded by cell membrane cloaking to localize the nanomedicine to the atherosclerotic lesion site. Further investigation of the interaction of vascular cells and inflammatory immune cells along is also planned for the Wang Laboratory.

Acknowledgments: I would sincerely like to acknowledge the support and mentorship of Dr. Kuei-Chun Wang and the guiding efforts of the Wang Lab's PhD research students: Ting-Yun Wang, Joshua Rousseau, and Sin Pei Wu.

MORE
Masters Opportunity for Research in Engineering

Ira A. Fulton Schools of Engineering
Arizona State University