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PROJECT SUMMARY:
A critical goal in heart research is to elucidate the mechanisms that promote clinically significant atherosclerosis and then use this knowledge to design novel therapies. We believe it is essential to couple new concepts with new drug delivery strategies, and we have thus formed a unique multi-PI team with complementary expertise in atherosclerosis and nanomedicine. The overarching concept is that plaque progression represents a pathologic process called defective inflammation resolution. The nanomedicine theme is based on the concept that encapsulation of biologics inside biodegradable, targeted polymeric nanoparticles (NPs) protects the cargo until it is delivered to atheromata and then facilitates controlled release of the biologic. We have demonstrated this principle using a peptide mediator of resolution called Ac2-26. To move closer to human translation, we now propose iterative NP optimization, in-depth mechanistic studies, and application to another type of biologic. The overarching hypothesis is that clinically translatable polymeric NPs packaged with various types of resolution mediators will, via specific molecular mechanisms related to cellular processes of resolution, prevent advanced plaque progression. In Aim 1, we will iteratively optimize and evaluate collagen IV (Col IV)-targeted NPs for effective delivery of Ac2-26 to atherosclerotic plaques. Modifications to NP size, charge, loading capacity, and targeting properties will be carried out to increase delivery of bioactive Ac2-26 to atherosclerotic lesions in a manner that optimizes prevention of plaque progression. In Aim 2, we will elucidate athero-protective mechanisms of Ac2-26 NPs focusing on oxidative stress, collagen formation, defective efferocytosis, and inflammation. In Aim 3, we will explore the molecular-cellular mechanisms of the pro-resolving protective effects of IL-10 in advanced atherosclerosis using atherotargeted IL-10 NPs, which will be optimized for controlled release kinetics, optimal bioactivity, and efficacy. At the conclusion of this project, we hope to have elucidated mechanistic links between inflammation resolution and atherosclerosis while simultaneously developing nanomedicines capable of blocking plaque progress in high-risk humans.