

Abstract

Our goal is to develop a clinically applicable method to deliver anti-thrombotic agents to enhance their benefit:risk ratio. We propose to do this by taking advantage of the physiology of platelets as vehicles to deliver therapy to sites of incipient or ongoing pathological clotting, thereby bypassing the need to use high systemic drug levels to achieve locally desired concentrations. A genetically engineered fusion protein consisting of a thrombin-activated pro-drug, low molecular weight single-chain urokinase, fused to Fab anti-platelet specific antibodies will be injected IV into mice. Targeting will be accomplished through the antibody portion of the chimeric protein and the functional end will provide targeted fibrinolytic activity. Localization will be detected via magnetic resonance using prodrug targeted iron oxide nanoparticles. Platelet-bound pro-drug will be delivered to the clot through the recruitment of platelets and the drug will be activated when and where thrombin is formed. We will demonstrate that the chimeric protein binds to the target cell, we will quantify drug localization at sites of thrombosis *in vivo*, and we will examine its efficacy and safety in established models of stroke and pulmonary embolism.