Design of a Novel, Dual-Functioning, Tissue Plasminogen Activator and Anticoagulant Therapeutic for Rapid Ischemic Stroke Treatment

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Stroke is the second leading cause of death worldwide, with 15 million people suffering from its debilitating effects each year. 87% of strokes are ischemic, where an artery narrows or becomes wholly blocked due to a thrombus. Tissue Plasminogen Activator (tPA) is a protein that activates the conversion of plasminogen to plasmin, an enzyme responsible for the breakdown of clots. While tPA is the leading emergency treatment for ischemic stroke, it possesses several shortcomings, including a non-localized nature and increased risk of hemorrhage. Similarly, no existing therapeutic candidates have both dissolved the thrombus and simultaneously deterred the coagulation cascade, the process by which a thrombus is actively built. Herein, a rapid, clot-specific, and dual-functioning microbubble system, utilizing tPA and anticoagulant Dicumarol, was engineered to create a more effective emergency therapeutic. Fabrication of the magnetic interior nanoparticles was completed by synthesizing Dicumarol-Carboxylic-acid-coated Fe_3O_4 nanoparticles. SiO_2-tPA was fabricated and added to complete the subsequent encapsulation layer of the nanoparticles. Peptides CGSSSGRGDSPA and GRGD were conjugated to the nanoparticle's surface, to promote selectivity for platelets and fibrin, and ensure clot-specific adhesion and release. A vertical gel channel-system, composed of fibrinogen, thrombin, and agarose, was developed to validate the clot dissolution function of the new therapeutic, which was 2x that of tPA alone. As a final verification component, in-vitro clots were created using ~100µl of whole-blood, in a 96-wellplate. Successful therapeutic-induced dissolution of thrombus was observed via increased absorbance throughout the visible spectral region at 300-700nm, due to clot liquifying.

Awards Won:
First Award of $5,000