Heteromultivalent Approaches to Clot-Targeted Nanomedicine: Combination Targeting of Platelets and Fibrin

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Thrombus formation leading to blood vessel occlusion is a pathological event in cardiovascular diseases. Therefore, it is critical to remove the clot and restore blood flow to vital organs. One way to remove clots is by administering clot-busting drugs, but this strategy often results in off-target drug action and hemorrhagic risks, which can be minimized by localizing the drug to the clot site. A nanoparticle technology that can bind to active platelets and thereby provide a way to deliver drugs to areas of active platelet localization has previously been developed in the lab. Building on this, the focus of this project is to explore other components of a clot that can enhance nanoparticle targeting beyond active platelet targeting. One component is fibrin, which is the product of coagulation that happens on the surface of clot-associated active platelets. The hypothesis of the project is: Combining fibrin targeting with active platelet targeting can lead to a superior design of clot-targeted vehicles of clot-busting drugs. To test this hypothesis, two different peptides binding to either GPIIb/IIIa or fibrin were evaluated on liposomal nanoparticle surfaces. Resultant peptide-decorated liposomes were studied for their abilities to bind and stay retained on platelet and fibrin rich clots, under simulated blood flow environment using microfluidic chambers. Binding to a non-specific substrate was used as control condition. In vitro studies show that decorating liposomes with only platelet-binding or only fibrin-binding ligands results in increased binding to clots, and combining these decorations increases their clot-binding ability over time.

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