Thrombus-Directed Drug Delivery Systems for Targeted Fibrinolysis

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The primary cause of cardiovascular disease, like myocardial infarction and ischemic stroke, is the blockage of blood vessels by blood clots. Treatment requires fibrinolytic agents, like tissue plasminogen activator (tPA), to rapidly remove clots and restore blood flow. Although effective, fibrinolytic drugs pose unwanted side effects like intracranial hemorrhage due to off-target action. Such side effects can be avoided by specifically targeting clots and releasing the drug at the target site through packaging fibrinolytic agents within drug delivery systems (DDS). In this framework, previous studies have shown the benefit of modifying the surface of liposomal nanoparticle-based DDS with ligand motifs that bind to active platelets or fibrin, allowing for clot-relevant binding. Building on this, it was hypothesized that DDS which simultaneously bind to active platelets and fibrin will significantly enhance targeting of clots compared to DDS which bind to platelets or fibrin only. To test this, liposomal DDS surfaces were decorated with platelet integrin GPIIb-IIIa-binding peptide GSSGRGDSPA (IRGD), with fibrin-binding peptide cyclo-AC-Y(DGl)C(HPr)YGLCYlQGK-Am (FBP) (homomultivalent decorations), or with a combination of both (heteromultivalent decoration). Liposomes bearing various ligand densities and ratios were flowed over human blood clots in microfluidic channels, and liposome binding was analyzed by fluorescence microscopy. Studies showed that heteromultivalent decorations had enhanced binding and reached peak binding with lower ligand density compared to homomultivalent decorations. Future studies will focus on adapting this heteromultivalent targeting strategy on unique DDS that, upon binding to clots, will release fibrinolytic agents via local stimuli.