TEXAS TECH UNIVERSITY
HEALTH SCIENCES CENTER
Graduate School *of* Biomedical Sciences™

Dissertation Defense

Stealth Protein and Lipid Based Nanoconstructs of tPA for Site Specific Thrombolysis

Presented by:

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ABSTRACT: Thrombolytic drugs have been widely used in acute thrombotic events. However, bleeding complication–caused by the indiscriminate action of the drugs–remains a major limitation for thrombolytic therapy. In this dissertation, we have proposed several novel strategies for targeted/triggered delivery of tissue plasminogen activator (tPA)–the most widely used thrombolytic agent. An albumin-camouflaged and heparin triggered delivery system for tPA has been developed that suppresses the enzymatic action of tPA, which however, can be regenerated by heparin–a common anticoagulant. To eliminate the use of triggering agents, a peptide-decorated lipid based carrier system has also been developed so that a large amount of tPA is released shortly upon accumulation on thrombus but the remaining fraction releases over an extended period of time. Liposomal tPA demonstrated favorable pharmacokinetic profile and optimum thrombolytic efficacy by minimally affecting systemic fibrinogen level. Finally, an albumin-camouflaged thrombin-triggered delivery system was designed from which tPA release can be modulated by thrombin at the clot-site, and thrombolysis can be produced without depleting systemic fibrinogen level. Overall, this study proposes several novel delivery systems for localized delivery of tPA, which has the potential for translating to a clinically viable thrombolytic therapy.

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