SYNTHESIS AND PERFORMANCE OF FLAVIVIRUS-DERIVED LIPOPEPTIDE AS COMPONENTS OF FUSOGENIC LIPOSOMES FOR BLADDER TUMOR THERAPY

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INTRODUCTION

Bladder cancer is the fourth most common cancer in men and eleventh most common in women in the US.[1] Because of it´s high recurrence rate and long progression interval, improved treatment options are needed. At present, intravesical infusion of live *Mycobacterium bovis* bacillus Calmette-Guerin (BCG)[2] is the treatment of choice for non-resectable superficial bladder tumors, in spite of the significant side effects that accompany this modality. The primary side effect is high local morbidity, which limits patient tolerance. Given the recurrent nature of the disease, multiple instillations of BCG are often required, greatly enhancing its toxicity and substantial increasing the risk of systemic infection in the patient. Ratliff *et al*. reported that fibronectin attachment protein (FAP) mediates the attachment of the BCG bacterium to the urothelial surface *via* the extracellular matrix protein, fibronectin (FBN).[3] It is also known that FBN-dependent attachment of BCG to bladder tumor cells is required for successful anti-tumor activity. To enable mechanistic and therapeutic aims of FAP binding, novel tris-nitrilotriacetic acid (NTA)-Alexa probes and NTA-PEG-lipids were prepared and tested for their ability to promote bladder cell internalization of his-tagged FAP.

RESULTS

To enable mechanistic and therapeutic aims of FAP binding, novel tris-nitrilotriacetic acid (NTA)-Alexa probes and NTA-PEG-lipids were prepared and tested for their ability to promote bladder cell internalization of his-tagged FAP.

A new family of non-viral vectors also has been developed to promote lipid-mediated membrane fusion for enhancing the bioavailability of the encapsulated cargo upon activation within the endosomal environment of target tissues. An integrated approach using theory, synthetic chemistry, membrane biophysics, and cell biology is being used to discover new pH-sensitive PEG lipids that rationally control the membrane fusion process. These latent fusogens, incorporated within host membranes as masked nonfusogenic compounds, are designed to fuse with target (endosomal) membranes upon receptor-mediated endocytosis, to increase the bioavailability and improve the intracellular delivery of therapeutic agents to the cytoplasm of the targeted cell. A mosquito-borne Flavivirus fusion peptide has been selected as a model fusion peptide for these constructs. We have designed these fusogenic lipopeptides to micro-aggregate into a fusogenic domain at low pH, thereby promoting aggregation and fusion of the host liposomal membrane

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REFERENCES

1) Jemal, A.; Tiwari, R. C.; Murray, T.; Ghafoor, A.; Samuels, A.; Ward, E.; Feuer, E. J.; Thun, M. J. *CA Cancer J. Clin.* **2004**, *4*, 8-29

2) Morales, A.; Eidinger, D.; Bruce, A. W. *J. Urol.* **1976**, *116*, 180-183

3) Schorey, J. S.; Holsti, M. A., Ratliff, T. L.; Allen, P. M., Brown, E. J. *Mol. Microbiol.* **1996**, *21*, 321-329

4) Coon, B. G.; Crist, S.; González-Bonet, A. M.; Kim, H.; Sowa, J.; Thompson, D. H.; Ratliff, T. L.; Aguilar, R. C.; *Int. J. Cancer* **2011**, *131* (3), 591-600

5) Mukhopadhyay, S.; Kuhn, R. J.; Rossmann, M. G., *Nat Rev Microbiol* **2005,** *3* (1), 13-22.