Novel Peptide-Drug Conjugates for Breast Cancer Targeted Delivery of Doxorubicin
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Purpose
Cancer treatment using chemotherapy is constantly challenged by poor selectivity and limited access of drugs to the cancer cells. Targeted drug delivery methods have been explored to improve drug efficacy and selectivity by directing the drug to tumor site. In recent years, a number of peptides have been identified for delivering drugs and diagnostic elements specifically to tumor site. Using peptide array-whole cell binding assay, we have identified several cancer targeting peptides which selectively bind breast cancer cells [Ahmed, Mathews, Byeon, Lavasanifar, Kaur, Anal. Chem., 2010, 7533; and Soudy, Ahmed, Kaur, ACS Comb. Sci., 2012, 590]. In addition, a novel strategy was applied to develop proteolytically stable peptide analogues that retain targeting ability of the peptides in vivo [Soudy, Gill, Sprules, Lavasanifar, Kaur, J. Med. Chem., 2011, 7523]. In this study, we have synthesized and evaluated novel peptide-doxorubicin (Dox) conjugates as well as peptide-liposomal doxorubicin formulations to deliver active drug in a cell-specific fashion, and overcome multidrug resistance.

Methods
Peptide-Dox conjugates were synthesized using Fmoc solid phase peptide synthesis and were purified and characterized using HPLC and mass spectrometry. The tumor targeting ability was studied using breast cancer cell lines (MDA-MB-435, MDA-MB-231 and MCF-7), while non-cancerous cell lines (HUVEC and MCF-10A) were used as control. In addition, the peptide-conjugated liposomal Dox formulations were evaluated in mice bearing MDA-MB-435 xenografts.

Results
The cell uptake studies using flow cytometry showed that the peptide conjugates were about 10 times more selective for breast cancer cells compared to noncancerous cells, and displayed similar toxicity as free Dox toward the cancerous cells. The conjugates were also toxic to the Dox resistant cells. Further, the mice treated with peptide conjugated liposomal Dox showed 4.8 folds reduction in the mean relative tumor volume compared to non-targeted DOX liposomes.

Conclusion
The results presented here show that the conjugates and the liposomal formations are safe and efficient targeting vectors for tumor specific delivery of Dox, and such constructs can be used for other chemotherapeutic drugs for targeted delivery to breast cancer site.