Prodrug Strategy for PSMA-Targeted Delivery of TGX-221 to Prostate Cancer Cells
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Purpose
TGX-221 is a potent, selective and cell membrane permeable inhibitor of PI3K. Recent studies have showed that TGX-221 has anti-proliferative activity against PTEN-deficient prostate cancer cells. The purpose of this project is to develop a prostate-specific membrane antigen (PSMA)-targeted drug delivery platform to deliver TGX-221 to the target tissue with minimal systemic toxicity.

Methods
TGX-221 was physically encapsulated in different nanocarries. To prolong the in vitro release half-life and the stability of the drug delivery platform, a prodrug strategy was applied. Pharmacokinetics of an intravenous micelle formulation and naked drug were determined in male Balb/c mice. For efficacy study, four prostate cancer cell lines, androgen-responsive (LAPC-4 and LNCaP) and non-responsive (C4-2 and 22RV-1), were used to generate the subcutaneous xenografts in nude mice. Tumor growth was monitored twice per week.

Results
A hydrophobic form prodrug, BL05-HA, was synthesized and Western blot showed that the prodrug had similar bioactivity in PTEN-deficient tumor cells compared to TGX-221. BL05-HA was successfully encapsulated in PSMA-targeted PEG-PCL micelles with particle sizes ca. 50 nm. By encapsulating with a more hydrophobic form, the in vitro release half-life was improved from less than 1 hour to 5 days. Fluorescence imaging demonstrated that the cellular uptake of both drug and nanoparticles were significantly improved by targeted micelles in PSMA-positive cell lines. In vivo pharmacokinetics studies indicated that area under the curve of micelle formulation was 2.27-fold greater than naked drug and drug clearance rate was 6.16-fold slower. In addition, the PSMA-targeted micelle formulation of TGX-221 prodrug, BL05-HA, significantly suppressed tumor growth in all four cell lines-derived xenografts.

Conclusion
These findings suggest a PSMA-targeted formulation of TGX-221 may improve prostate cancer treatment.