Chemo-RNAi-Therapy Combining Hybrid siRNA Nanocarrier and Docetaxel: Evaluation of In Vivo Efficacy and Adverse Effects in a Prostate Cancer Model
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Purpose
Prostate cancer in advanced stage is nearly incurable by standard chemotherapy due to frequent occurrence of chemoresistance. In recent years, there has been renewed interest in using RNAi therapeutics to target specific pathways that cause difficulties to standard drug treatment of cancer. In our previous studies we have shown that lipid-polymer hybrid nanocarriers (LPN) carrying anti-survivin siRNA can achieve sustained knockdown of the expression of survivin, a critical factor causing chemoresistance, both in vitro and in vivo. In this study, we aim at (i) studying whether this nanoformulation can effectively sensitize advanced prostate cancer to docetaxel, and (ii) evaluating its in vivo immunogenicity and liver toxicity.

Methods
Nanocarriers were prepared with a combination of solid lipids, oil, alkylated polyethylenimine/anti-survivin-siRNA complex using emulsification/solvent evaporation technique, and further modified with 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[amino(polyethylene glycol)-2000] conjugated with epidermal growth factor (EGF) for prostate cancer targeting. Treatments included docetaxel alone administered using different dosing schedules and different routes, LPN carrying anti-survivin siRNA, and their combinations. Their anti-tumor effects were studied in murine model inoculated with PC-3M, a highly metastatic human prostate cell line. We also studied the effects of LPN treatment on the plasma levels of several interleukins and liver function indicators such as ALT and AST.

Results
LPN of about 110 nm in diameter with or without EGF decorated were prepared and the nanosystems were stable in serum-enriched cell culture medium. Using this system, we showed that: (1) The impact of different docetaxel dosing schedules (lower dose, more cycles vs higher dose, fewer cycle) was not strong (p>0.05). All 3 dosing schedules are likely useable. IV administration appeared to be moderately superior to IP. (2) The chemo-RNAi combination was found to be more effective than chemo drug (docetaxel only) alone (p<0.05). The finding indicated effective RNAi-based chemosensitization. (3) The in vivo immunogenicity of LPN RNAi therapy was generally low. Except IL1B, the plasma levels of all interleukins tested (IL1A, IL2, IL4, IL6, IL10) did not significantly increase. The effects of LPN/docetaxel combination on liver function were also not significantly higher than docetaxel alone (p>0.05).

Conclusion
The chemo-RNAi combination therapy of hybrid siRNA nanosystem and standard docetaxel chemotherapy has demonstrated significant in vivo efficacy for treating advanced, highly metastatic prostate cancer, and the adverse effects detected so far are moderate at most.