Enhancing Chemotherapy Response with Sustained EphA2 Silencing Using Multistage Vector Delivery

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ABSTRACT SUMMARY
In this study, we describe experimental therapy of metastatic ovarian cancer in murine tumor models with a combination of chemotherapy and siRNA targeting the EphA2 gene. Tumor enrichment of siRNA is achieved by multistage vector delivery.

INTRODUCTION
RNA interference has the potential to specifically knock down the expression of target genes, and thereby transform cancer therapy. However, lack of effective delivery of small inhibitory RNA (siRNA) has dramatically limited its in vivo applications. We have developed a multistage vector (MSV) system, composed of discoidal porous silicon particles loaded with nanotherapeutics, that directs effective delivery and sustained release of siRNA in tumor tissues. In this study, we evaluated therapeutic efficacy of MSV-loaded EphA2 siRNA (MSV/EphA2) with murine orthotopic models of metastatic ovarian cancers as a first step towards development of a new class of nanotherapeutics for the treatment of ovarian cancer.

EXPERIMENTAL METHODS
Tumor accumulation of MSV/EphA2 and sustained release of siRNA from MSV were analyzed after i.v. administration of MSV/siRNA. Nude mice with metastatic SKOV3ip2 tumors were treated with MSV/EphA2 and paclitaxel, and therapeutic efficacy was assessed. Mice with chemotherapy-resistant HeyA8 ovarian tumors were treated with a combination of MSV/EphA2 and docetaxel, and enhanced therapeutic efficacy was evaluated.

RESULTS AND DISCUSSION
Treatment of SKOV3ip2 tumor mice with MSV/EphA2 biweekly for 6 weeks resulted in dose-dependent (5, 10 and 15 µg/mice) reduction of tumor weight (36%, 64%, and 83%) and number of tumor nodules compared with the control groups. In addition, tumor growth was completely inhibited when mice were treated with MSV/EphA2 in combination with paclitaxel. Furthermore, combination treatment with MSV/EphA2 and docetaxel inhibited growth of HeyA8-MDR tumors which were otherwise resistant to docetaxel treatment.

Figure 1. Therapeutic efficacy of MSV/EphA2 siRNA in combination with paclitaxel on tumor growth in murine model of SK-OV-3ip2 metastatic ovarian cancer.
CONCLUSION
These results indicate that 1) MSV is an effective delivery vector for tumor-enrichment of therapeutics, and 2) MSV/EphA2 is efficacious in treating metastatic ovarian cancer. MSV/EphA2 merits further development as a novel therapeutic agent for the treatment of ovarian cancer, and most likely, other types of human cancer.

REFERENCES