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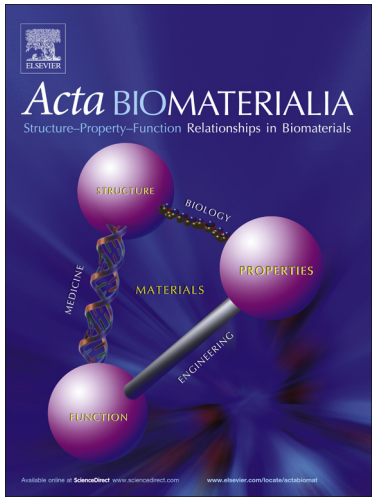

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Overcoming Cisplatin Resistance in Non-Small Cell Lung Cancer with *Mad2* Silencing siRNA Delivered Systemically using EGFR-Targeted Chitosan Nanoparticles

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Abstract

Efficiency of chemotherapy is often limited by low therapeutic index of the drug as well as emergence of inherent and acquired drug resistance in cancer cells. As a common strategy to overcome drug resistance, higher doses of chemo-agents are administered. However, adverse side effects are usually increased as a consequence. A potentially effective approach is to combine chemotherapy with other therapeutic strategies such as small interfering RNAs (siRNAs) that allow the use of lower yet efficient doses of the anticancer drugs. We previously developed epidermal growth factor receptor (EGFR)-targeted chitosan (CS) nanoparticles as a versatile delivery system for silencing the essential mitotic checkpoint gene Mad2, and induce cell death. Here, we tested this system as a single therapy and in combination with cisplatin in cisplatin sensitive and resistant lung cancer models, and characterized its *in vivo* efficacy and safety. Combination treatment resulted in significant improvement in tumor inhibition that was strikingly more effective in cisplatin-resistant tumors. Importantly, effective cisplatin dosage