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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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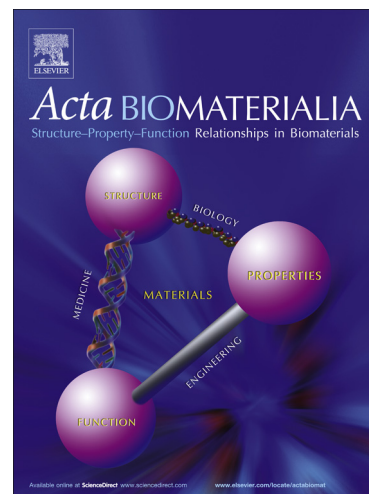
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20 ***Running Title: Overcoming cisplatin resistance in NSCLC by *Mad2* silencing***
21

22 **Abstract**

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

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