In Vivo Anti-Tumor Efficacy Study of a Novel Wnt pathway Inhibitor Packed in RH40 Micelles

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ABSTRACT SUMMARY
Many potential drug candidates pose potent anti-tumor activities, but they have either low solubility or high toxicities. We identified a novel Wnt pathway inhibitor, which displays anti-tumor activities through inhibition of tumor cell proliferations. However, it has low solubility and high toxicity. In our current study, we prepared RH40 micelles to encapsulate the drug, in order to improve its solubility and reduce its toxicity in animals. The micelle formulation could be administered intravenously and improve the drug distribution in tumor tissue/cells. Potentially, this strategy may allow us to overcome the hurdle of low solubility of drugs in order to improve their anti-tumor efficacy and reduce non-target toxicity.

INTRODUCTION
We have identified a novel compound CL010, which is an inhibitor targeting at the Wnt pathway. It was discovered through screening efforts using cell models for inhibiting signaling Wnt pathway. Our in vitro study indicated that it is highly potent in inhibiting growth and proliferation of cancer cells over-expressing of RSPO2/3. A few in vivo primary tumor models were established in order to test in vivo anti-tumor activities of CL010.

However, CL010 was found to have very poor water solubility, which would restrict investigation of its dose responses in vivo. Therefore, improving the aqueous solubility of CL010 is essential before we can initiate in vivo studies to test its efficacy in animal models via different dosing schemes.

In addition, the compound CL010 appeared to be toxic to mice when administered in vivo. Thus, the current study aims to improve the compound solubility and reduce its toxicity through micelle technology.

EXPERIMENTAL METHODS
1. Preparation of micelle formulations containing the compound CL010: CL010 were dissolved in tert-butyl alcohol and mixed with water containing 20% cremophor RH40 and 5% mannitol. The solvents were removed by lyophilization. The lyophilized powder was then rehydrated with water. The anti-wnt compounds in micelles could increase its concentration to 3 mg/ml. This is a big improvement over its maximum solubility in water. (Table 1. Size distribution of the micelle)

2. Animal model setup: We select two gastric and one liver primary tumor samples, cut human tumor samples into 1 mm × 1 mm × 1 mm fragments, implant in 6-8 weeks old nude mice, start treatment when tumors reach 200 mm³ (length × width × width) / 2, dose mice via IV, and PO, and measure tumor size and bodyweight twice a week.

RESULTS AND DISCUSSION
We used the micelle formulation to prepare the CL010 compounds to dose animal via IV (Figure 1). The results show that there is difference in tumor sizes in the group treated with micelle-formulated CL010 compound, while the bodyweight of the treated mice were not reduced. Therefore, above studies demonstrated that micelle formulation improved the solubility of the compound CL010, and reduced its toxic effects on mice.
Table 1. Size distribution of the micelle with CL010

**CONCLUSION**

Using an anti-Wnt pathway inhibitor, we have demonstrated that micelle formulations containing compound CL010 had improved its solubility. In addition, the micelle formation appears to reduce its toxic effects *in vivo* when given via IV. Therefore, we conclude that micelle formulation strategy may facilitate anti-tumor therapy by overcoming the hurdle of low solubility of drugs in order to improve their anti-tumor efficacy and reduce non-target toxicity. Currently, we are performing additional studies to search for better compositions of micelle formation, and to provide more solid *in vivo* data to provide evidence to support this strategy.

**REFERENCES**