

## **Monepantel a new first in class potent inhibitor of P70S6K potentiates the anti-tumor effects of gemcitabine and doxorubicin: In vitro and in vivo studies.**

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**Aims:** Monepantel (MPL) is a new nematode-specific anthelmintic agent. We have recently communicated the preliminary results showing the anti-tumor activity of this agent in ovarian cancer through attenuation of mTOR/P70S6K pathway. As emerging data indicate that mTOR inhibitors are most effective when combined with other target agents, we evaluated whether MPL could favorably be combined with the clinically approved chemotherapeutic agents to improve therapeutic efficacy.

**Methods:** The effects of MPL and/or chemotherapeutic agents gemcitabine (Gem)/ doxorubicin (Dox) on the growth of a panel of cancer cell lines were determined using SRB assay. In vitro drug synergy was determined using combination index (CI) methods derived from Chou-Talalay equations using CalcuSyn software. For in vivo studies, we evaluated the effect of MPL, alone and in combination with Gem/ Dox on the growth of established human ovarian (OVCAR-3) tumors implanted subcutaneously in BALB/C nude mice. Toxicity was evaluated measuring animal weight. In vivo combination effects was determined using Fractional Tumor Volume (FTV) method.

**Results:** In vitro, MPL in combination with Gem or Dox synergistically reduced survival rates of a panel of malignant cells from different origins while having no additive effect upon non-malignant cell (HOSE) survival rates. In vivo, antitumor activity was observed in all treatment groups compared to the mock-treated animals after 4 weeks of treatment. However combination therapy with MPL and chemotherapeutics significantly attenuated tumor growth, compared to monotherapy without showing any toxicity. Combining MPL (50 mg/kg) increased the tumor inhibitory effect of low dose Gem (2 mg/kg), high dose Gem (5 mg/kg), low dose Dox (2 mg/kg) and high dose Dox (5 mg/kg) by 32.29, 35.1, 15.2 and 24.38% respectively. Moreover, MPL (25 mg/kg) enhanced the tumor inhibitory rate of Gem (5 mg/kg) by 36.26%. These resulted in complete tumor growth inhibition in Gem 5 mg/kg + MPL 25 or 50 mg/kg and Dox 2 or 5 mg/kg+ MPL 50 mg/kg treatment groups. Assessment of therapeutic synergy with FTV method revealed strong synergy in Gem 5 mg/kg + MPL 25 or 50 mg/kg, Gem 2 mg/kg + MPL 50 mg/kg and Dox 2 or 5 mg/kg+ MPL 50 mg/kg treatment groups with odds ratio of 2.48, 2.59, 1.48, 1.63 and 2.97 (>1 indicates synergy) respectively.

**Conclusion:** These findings provide a rational to further investigate MPL in combination with standard chemotherapeutics as novel combination regimens which could hopefully provide strong anticancer synergy.