

Abstract # C168

Cancer-selective mitochondrial copper transport by elesclomol results in potent single agent efficacy in multiple tumor types.

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Background: Elesclomol is a first-in-class investigational drug that exerts potent anticancer activity through the elevation of reactive oxygen species (ROS) levels and is currently under clinical evaluation as a novel anticancer therapeutic. We recently demonstrated that elesclomol preferentially binds extracellular copper (Cu) and selectively transports this metal ion to the mitochondria of tumor cells to promote mitochondrial ROS generation and subsequent apoptosis. Here we report that elesclomol-induced copper transport and apoptosis is tumor selective.

Results: Comparative analysis using human PBMCs and the promyelocytic tumor cell line HL-60 demonstrated increased Cu levels in the mitochondrial fraction of HL-60 cells following elesclomol-Cu treatment, but not in donor PBMCs. Further, elesclomol-Cu induces ROS in HL-60-derived mitochondria but not in those isolated from PBMCs. These results suggest that elesclomol-Cu selectively targets cancer cell mitochondria to ultimately produce critical elevations in oxidative stress. To evaluate increased exposure to elesclomol-Cu *in vivo*, elesclomol was administered continuously to tumor-bearing mice using an Alzet pump at a clinically relevant dose. Upon release, elesclomol immediately chelates copper from the blood to form an elesclomol-Cu complex *in situ*, achieving 10-fold higher levels of elesclomol-Cu compared to those following bolus injection. Even with this increased formation of elesclomol-Cu *in situ*, no signs of toxicity have been observed.

Conclusions: In five different tumor xenograft models tested, elesclomol consistently demonstrated marked single agent activity with significant tumor growth suppression, indicating that increased elesclomol-Cu levels result in selective and enhanced antitumor efficacy. These findings highlight a unique mechanism of action of elesclomol and support potential single agent activity of this compound in a variety of tumor types.