

Abstract # 4525

## Targeting ROS to kill cisplatin-resistant cells.

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Cisplatin (CP) resistance remains a major problem in the treatment of both small cell and non small cell lung cancer. We have previously shown that inhibiting mTOR can restore CP sensitivity; however, not all CP resistant cell lines are sensitive to mTOR inhibitor. Our findings have led us to search for an alternative target in these CP resistant cells. We have discovered that CP resistant cells share one common biochemical parameter which is increased reactive oxygen species (ROS) when compared to normal cells and their parental cells counterpart. Thus, further increased ROS in these CP resistant cells can push them beyond their tolerance limit which ultimately leads to cell death. We have found that increased expression of NADPH oxidase 4 (NOX4) and lower levels of thioredoxin (Trx) correlate with the high levels of ROS seen in CP resistant cell lines. Using elesclomol (N',N'-bis[1,3-dimethyl-5-phenylcarbonothioyl]propanedihydrazide (formerly STA-4783, provided by Synta Pharmaceuticals)), an agent which is known to increase ROS, we demonstrated that elesclomol can increase H<sub>2</sub>O<sub>2</sub> levels in CP resistant lung cancer cell lines (CP-R). Moreover, elesclomol is also significantly more cytotoxic toward CP-R with the ID<sub>50</sub> dosage of 4-10 fold less than their parental cells (PC) counterpart and normal cells, BJ-1 (see table below). The percentage of apoptosis is also significantly higher in CP-R (65%) vs. PC (3%). The cytotoxic effect of elesclomol in CP-R is accompanied by further decrease in Trx and glutathione (GSH) antioxidant systems, while opposite results were found in PC and normal cells. This cytotoxic effect can be reversed by an antioxidant, N-acetylcysteine (NAC, 0.1mM). Furthermore, we have also found that elesclomol also increased intracellular CP and hence enhanced CP sensitivity in CP-R cells. We conclude that elesclomol is highly effective in CP resistant cells which express high basal levels of ROS and should be considered for treatment of CP resistant tumor.

**ID<sub>50</sub> Dosage of Elesclomol in Parental (PC) vs. Cisplatin Resistant (CP-R) Lung Cancer Cell Lines**

	SCLC1(PC)	SCLCSR2(CP-R)	SCLCB(PC)	SCLCBC (CP-R)	NSCLCS(PC)	NSCLCSC(CP-R)	BJ1
Elesclomol(nM)	50+/-2.5	5+/-0.5	41+/-3.8	9+/-1.2	59+/-4.6	10+/-2.2	65+/-5.5