



## **Synta Announces Results Presented at AACR Further Elucidate Mechanism by Which Elesclomol Targets Cancer Cell Metabolism**

April 4, 2011

- Elesclomol induces cancer cell apoptosis by elevating oxidative stress directly within cancer cell mitochondria, disrupting mitochondrial energy metabolism-*
- Biomarkers related to cellular metabolic state, LDHA and TRX-1, are predictive of elesclomol activity in models of lung cancer-*

LEXINGTON, Mass., Apr 04, 2011 (BUSINESS WIRE) -- Synta Pharmaceuticals Corp. (NASDAQ: SNTA) today presented five posters at the American Association for Cancer Research (AACR) 102nd Annual Meeting. Three posters reported results from studies of ganetespib (STA-9090), a novel Hsp90 inhibitor, and two posters reported results from studies of elesclomol.

Elesclomol is a novel small molecule inhibitor of cancer cell metabolism that kills cancer cells with normoxic, or normal oxygen, metabolism. In three randomized clinical trials elesclomol has shown clinical activity in patients whose cancers show signatures of the normoxic metabolic state. Elesclomol is currently being evaluated in clinical trials in leukemia and ovarian cancer, with a trial in lung cancer expected to initiate later this year.

"The results presented today demonstrate that elesclomol induces apoptosis through a unique means of selectively targeting cancer cell mitochondria and elevating reactive oxygen species," said Vojo Vukovic, M.D., Ph.D., Senior Vice President and Chief Medical Officer, Synta Pharmaceuticals. "The anti-cancer activity of elesclomol is highly dependent on the redox potential of its copper complex. This observation suggests a unique means of selectively targeting cancer cells: exploiting electrochemical differences between cancer cell and normal cell mitochondria. This represents an entirely novel approach to treating cancer, distinct from chemotherapy or cell signaling inhibition."

"Additional results presented today show that two serum markers directly related to tumor metabolic state are predictive of elesclomol *in vitro* activity in lung cancer," said Dr. Vukovic. "Our collaborators at the University of Miami, the V.A. Medical Research Center in Miami, and the M.D. Anderson Cancer Center have shown that low levels of thioredoxin reductase 1 (TRX-1), an antioxidant, which is associated with resistance to cisplatin - a common first-line treatment of lung cancer - leads to high levels of reactive oxygen species (ROS) in lung cancer cells and enhanced sensitivity to elesclomol. Results also showed that low levels of LDHA were associated with increased sensitivity to elesclomol, consistent with results observed in clinical trials. These results further validate the mechanism of action, and suggest promising potential for using biomarkers to select those patients most likely to benefit from treatment."

"All ongoing and planned trials with elesclomol incorporate the use of biomarkers related to tumor metabolic state," continued Dr. Vukovic. "We are excited to pioneer a novel personalized medicine approach for this first-in-class, promising drug candidate."

Clinical trials of elesclomol in acute myeloid leukemia (AML) and ovarian cancer are currently underway and Synta expects to initiate a Phase 2 trial of elesclomol in non small cell lung cancer later this year. The ovarian cancer trial is being conducted by the Gynecologic Oncology Group (GOG) and supported by the National Cancer Institute (NCI).

Elesclomol posters and publications are available at [www.syntapharma.com](http://www.syntapharma.com) or by contacting Synta directly.

**Title: Elesclomol-Cu chelate selectively targets mitochondria to induce oxidative stress**

Poster Presentation April 4, 1:00 p.m. ET

Abstract Number: 2093

Abstract:

**Introduction:** Elesclomol is a first-in-class investigational drug that exerts anticancer activity through elevating the level of reactive oxygen species (ROS) and oxidative stress. We recently reported that elesclomol selectively chelates Cu(II) in plasma, which causes a change in conformation that enables its uptake into cells. A cell-free assay system showed that elesclomol-Cu(II) generated ROS via the reduction of Cu(II) to Cu(I). A correlation has been observed between the redox potential and anticancer activity for Cu chelates of elesclomol and its analogs, suggesting that the ability to promote redox cycling of Cu(II) to Cu(I) is necessary for anticancer activity. Here, we demonstrate that elesclomol-Cu carries copper into mitochondria, leading to an increase in oxidative stress and apoptosis due to mitochondrial stress.

**Results:** The subcellular distribution of elesclomol was tracked using preformed elesclomol-Cu chelates. Cytosolic, nuclear and mitochondrial fractions of HL60 cells were prepared from cells treated with elesclomol-Cu, and total copper levels were determined for each cellular fraction. Elevated copper levels were observed only in the mitochondrial fraction, suggesting that elesclomol-Cu selectively transported copper into the mitochondria. To verify that the increased mitochondrial copper levels were from elesclomol-Cu, a copper complex of elesclomol was preformed with  $^{65}\text{Cu}$ . This elesclomol- $^{65}\text{Cu}$  complex was incubated for 2h with HL60 cells that were previously enriched with  $^{63}\text{Cu}$  using  $^{63}\text{Cu}$ -supplemented media, and subcellular distributions of  $^{63}\text{Cu}$  and  $^{65}\text{Cu}$  determined by ICP-MS. Control mitochondria contained minimal levels of endogenous  $^{65}\text{Cu}$ . In contrast,  $^{65}\text{Cu}$  was markedly increased in the mitochondrial fraction of elesclomol- $^{65}\text{Cu}$  treated cells but not in the cytosolic or nuclear fractions, confirming the selective mitochondrial uptake of copper with elesclomol-Cu. Next, we compared the mitochondrial uptake of elesclomol-Cu and disulfiram(DSF)-Cu using isolated mitochondria. DSF is a Cu chelator, and Cu has been shown to enhance DSF-mediated growth inhibition and apoptosis in cancer cells through the generation of ROS. As expected, an increase in copper levels was observed in mitochondria treated with elesclomol-Cu, yet no increase in mitochondrial copper was seen following treatment with DSF-Cu at its cytotoxic concentration, emphasizing the novel mitochondrial selectivity of elesclomol-Cu. To investigate whether the mitochondrial entry of elesclomol-Cu triggered the generation of ROS, ROS in isolated mitochondria was measured. Mitochondrial ROS was immediately increased by adding elesclomol-Cu while no change in mitochondrial ROS was seen using DSF-Cu or free  $\text{Cu}^{2+}$ . These results show that elesclomol induces apoptosis through elevating ROS directly in cancer cell mitochondria.

**Title: Downregulation of thioredoxin-1 confers resistance to cisplatin and sensitivity to the**

## **ROS generating agent elesclomol**

Poster Presentation April 4, 8:00 a.m. ET

Abstract Number: 1692

Abstract:

We have previously discovered a unique and important finding that all of our cisplatin resistant (CR) lung cancer cell lines, regardless of their signaling mechanisms, possess high levels of ROS (Reactive Oxygen Species) when compared to their parental cancer cell counterparts as well as normal cells. Importantly, these CR cells are sensitive to elesclomol, a new compound which kills cancer cells by generating ROS(2). The question remains why these CR cells possess intrinsically higher levels of ROS.

It is known that one of the pharmacologic actions of cisplatin is the disruption of redox system through inhibition of thioredoxin reductase-1 (TrxR1) TrxR catalyses the NADPH-dependent reduction of the redox protein thioredoxin-1 (TRX1). TRX-1 is an important protein that acts as an antioxidant by facilitating the reduction of other enzymes. Using our CR cell models, we have found that TrxR1 activities as well as TRX-1 levels are significantly decreased. To further verify that TRX-1 is an important contributory factor to the higher ROS levels seen in CR cells, we knocked down TRX-1 protein expression in parental cells using siRNA. These TRX-1 knocked down cells generated significantly higher levels of ROS and were resistant to cisplatin as well as hypersensitive to elesclomol treatment. Correspondingly, over-expression of TRX-1 protein in the CR cells using the pCMV6 vector containing full length TRX-1 cDNA, resulted in decreased ROS production but increased sensitivity to cisplatin. These TRX-1 overexpressing cells also became more resistant to elesclomol treatment.

Moreover, we found that all CR cells have 3-5 fold lower levels of lactate dehydrogenase A (LDHA) levels. Interestingly, it has been reported that diminished elesclomol activity is influenced by high LDHA levels. Here, we found that TRX-1 overexpression cells also exhibit higher LDHA levels and confer resistance to elesclomol. Our findings suggest another novel approach to selectively kill CR lung tumors which intrinsically produce higher ROS and express lower TRX-1 and LDHA levels.

### **About Elesclomol**

Elesclomol is a first-in-class, investigational drug candidate that triggers programmed cell death (apoptosis) in cancer cells through a novel mechanism: disrupting mitochondrial energy metabolism.

Elesclomol binds copper in plasma, which causes a change in conformation that enables its uptake through membranes and into cells. Elesclomol binds copper in an oxidative, positively charged, state called Cu(II). Once inside mitochondria, an interaction with the electron transport chain reduces the copper from Cu(II) to Cu(I), resulting in a cascade of redox reactions, a rapid increase of oxidative stress, disruption of mitochondrial energy production, and the initiation of the mitochondrial apoptosis pathway.

Mitochondria generate energy for cells, but also can induce apoptosis under certain conditions, such as a high level of oxidative stress. By sensitizing mitochondria and reducing barriers to apoptosis, elesclomol may provide a means to overcome resistance to traditional chemotherapy or targeted therapy.

## **About Synta Pharmaceuticals**

Synta Pharmaceuticals Corp. is a biopharmaceutical company focused on discovering, developing, and commercializing small molecule drugs to extend and enhance the lives of patients with severe medical conditions, including cancer and chronic inflammatory diseases. Synta has a unique chemical compound library, an integrated discovery engine, and a diverse pipeline of clinical- and preclinical-stage drug candidates with distinct mechanisms of action and novel chemical structures. All Synta drug candidates were invented by Synta scientists using our compound library and discovery capabilities. For more information, please visit [www.syntapharma.com](http://www.syntapharma.com).

## **Safe Harbor Statement**

This media release may contain forward-looking statements about Synta Pharmaceuticals Corp. Such forward-looking statements can be identified by the use of forward-looking terminology such as "will", "would", "should", "expects", "anticipates", "intends", "plans", "believes", "may", "estimates", "predicts", "projects", or similar expressions intended to identify forward-looking statements. Such statements, including statements relating to the timing, developments and progress of our clinical and preclinical programs, reflect our current views with respect to future events and are based on assumptions and subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such forward-looking statements, including those described in "Risk Factors" of our Form 10-K for the year ended December 31, 2010 as filed with the Securities and Exchange Commission. Synta undertakes no obligation to publicly update forward-looking statements, whether because of new information, future events or otherwise, except as required by law.

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