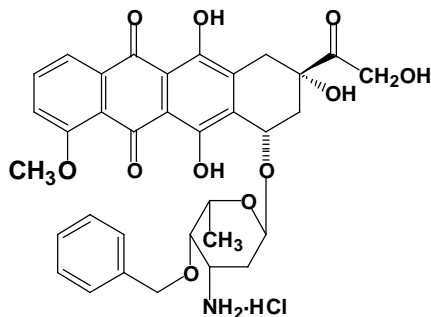


**WP744, A NOVEL HIGHLY APOPTOTIC AND ANTI-  
PROLIFERATIVE AGENT AGAINST STI-571-RESISTANT LEUKEMIC  
CELLS**

WALDEMAR PRIEBE, GILAD EVRONY, IZABELA FOKT, SANGYOU  
LEE, MOSHE TALPAZ and NICHOLAS J. DONATO

Department of Bioimmunotherapy, The University of Texas M. D. Anderson  
Cancer Center, 1515 Holcombe Blvd. Houston, TX 77030, USA

STI-571 is a novel tyrosine kinase inhibitor that targets BCR-ABL and other tyrosine kinases. Clinical studies have shown that STI-571 is very effective in controlling chronic myelogenous leukemia and other diseases and has limited clinical toxicity. However, while most patients derive longstanding benefit from this drug, patients with advanced disease often continue to progress on STI-571 therapy. These observations suggest that additional therapies may be required to control leukemia in advanced stage patients. To understand STI-571 resistance, K562 cells were selected for resistance to STI-571 (K562-R), and specimens from STI-571-resistant patients were collected to determine their sensitivity to other agents that mediate apoptosis through distinct mechanisms. Our studies were focused on WP744, previously shown to induce apoptosis in other multidrug-resistant cells. WP744 is a 10-fold more potent inducer of apoptosis than clinically used doxorubicin and it requires a 50-fold higher concentration to induce apoptosis in human fibroblasts [1]. We tested WP744 *in vitro* against a panel of doxorubicin (DOX)-sensitive, as well as MDR-type leukemia and solid tumor, cell lines. In all cases, WP744 was more cytotoxic than the structurally related drug DOX, and in the MDR1 and MRP1 models it was 60- to 90-times more potent than DOX. WP744 was also able to inhibit colony formation of blasts isolated from fresh bone marrow samples of patients with acute myelogenous leukemia more strongly than DOX [1].



**WP744**

WP744 appeared to be very effective against STI-571-resistant cells, and induced apoptosis and inhibited the growth of both K562 and K562-R cells. WP744 was significantly more cytotoxic against K562-R than DOX, and was significantly cytotoxic towards patient-derived STI-571 resistant cells [2]. These results suggest that WP744 may be effective in treating advanced leukemia patients who continue to progress on STI-571 therapy.

#### REFERENCES

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