



Fatty Acid Synthase Inhibition for Ovarian Cancer

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Fatty acid synthase (FAS), the enzyme responsible for the *de novo* synthesis of fatty acids, is highly expressed in many human cancers, including ovarian cancer. Prior studies have shown that pharmacological FAS inhibition is cytotoxic to a variety of human cancer xenograft models without overt toxicity. Thus, FAS has become a target for anticancer therapy. While successful xenograft studies suggest that FAS inhibition is not substantially toxic to normal tissues, formal toxicity data has not been described. Utilizing a novel small molecule FAS inhibitor, FAS 31, in preliminary toxicity studies, we report no observable toxicity to normal tissues in the rat or mouse. FAS31 inhibits fatty acid synthesis in SKOV3 human ovarian cancer cells *in vitro* ($IC_{50} = 6.09 \pm 0.4 \mu\text{g/ml}$) at a concentration similar to induce cytotoxicity ($LC_{50} = 5.2 \pm 2.0 \mu\text{g/ml}$). FAS 31 (50 mg/kg/day) for 2 weeks substantially inhibited SKOV3 xenograft growth by >90% compared to vehicle. FAS activity in the treated tumor xenografts was reduced by 82%. This is consistent with published *in vitro* studies where inhibition of FAS pathway activity by at least 20% led to brisk apoptosis in human cancer cells. No gross or microscopic organ toxicity was identified. In maximally tolerated dose studies, male and female rats were challenged with increasing single doses of FAS 31 ranging from 0 (vehicle) to 1000 mg/Kg ip or po and followed for 8 days. Aside from one death in the female rats treated with 1000 mg/Kg (ip), no overt toxicity was noted in any other animals; normal motor activity was recorded. In a five-day rat toxicology study, male and female rats were challenged with twice-daily doses of FAS 31 from 0 to 500 mg/Kg ip or orally. No abnormal behavior or distress was noted attributable to FAS 31. The following chemistry and hematology studies were within normal limits: Na^+ , K^+ , Cl^- , HCO_3^- , creatinine, AST, ALT, ALP, glucose, bilirubin, hemoglobin, hematocrit, white blood cell count and differential, platelets, and coagulation profile. No gross or microscopic organ toxicity was seen. Finally, we conducted pharmacokinetics and bioavailability studies of FAS 31 in rat and dog. In dogs, FAS-31 half-life is between 2.5 h in the fasted state and 3.6 h in the fed state with 16% and 51% plasma bioavailability respectively. In rats, FAS-31 half-life is 5 h in males and 3.8 h in females with 17% plasma bioavailability. Toxokinetic analysis of FAS 31 in rats treated with doses of FAS 31 used in xenograft models (50 mg/kg), demonstrate blood levels of FAS 31, which if applied to cancer cells, would inhibit FAS pathway by approximately 50%. Thus, the blood levels of FAS 31 achieved in the toxicological studies are sufficient to induce apoptosis in human cancer cells and were non-toxic. From these studies, we conclude that FAS is a viable pharmacological target for anti-cancer therapy.