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“Second-Generation Inhibitors of Fatty Acid Synthase for Lung Cancer Treatment”

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Fatty acid synthase (FAS) is highly expressed in many human cancers, including lung cancers. Previous our work has shown that blocking FAS activity by cerulenin, a natural antibiotic, or C75, a first-generation synthetic small molecule, leads to apoptosis in cells that overexpress this enzyme. However, the use of C75 is limited by the dose-dependent anorexia that appears to be associated with stimulation of carnitine O-palmitoyltransferase-1 (CPT-1). Pharmacokinetics studies (using PET scans and FAS activity assays) show that the activity of C75 peaks within hours of administration and by 24 hours, approximately 80% of activity is lost. Thus, the effectiveness of C75 is limited by short duration of activity and anorexia, which requires several days for recovery.

Several second-generation novel FAS-inhibitory compounds have been synthesized that show significant inhibition of FAS, without parallel stimulation of CPT-1. Among the most promising of the compounds is FAS93, which inhibits FAS at nearly equal potency as C75, but has significantly less stimulation of CPT-1. When tested for weight loss in Balb/C mice, FAS93 induced only 6% weight loss at 50mg/kg, compared to 15% weight loss for C75 at a dose of 30 mg/kg.

For *in vivo* experiments, we treated mice with xenografts developed from 3 different lung cancer cell lines, H460, A549, and LX-7. Daily intraperitoneal injections of FAS93 (5 days/week) at 50 mg/kg for 4 weeks resulted in significant (up to 70%) inhibition of tumor growth, H460 ($p=0.027$), A549 ($p = 0.058$), LX7 ($p = 0.007$). No organ-specific toxicity was recognized in treated animals. These results suggest that it is possible to pharmacologically uncouple inhibition of FAS from stimulation of CPT-1, and thus achieve anti-neoplastic activity by inhibition of FAS without significant drug-induced anorexia.

Recognizing that FAS93 did not completely abolish the tumors, we have also initiated investigations regarding possible combination therapy using FAS93 with Docetaxel, a cytotoxic microtubule-interfering agent. Remarkably, in clonogenic assays, there is striking synergy when cells are treated simultaneously with FAS93 and docetaxel, or when treatment with docetaxel precedes FAS93, but not when FAS93 precedes docetaxel. Collectively, these data indicate that FAS93 has independent antineoplastic activity, and this agent might be more effective when used in combination with docetaxel.