Fatty acids are the major constituent of membrane lipids and are used for energy storage and signaling compounds. Fatty acids can be obtained from the diet or synthesized de novo in a series of reactions catalyzed by the multifunctional enzyme fatty acid synthase. Fatty acid synthase overexpression has been observed in a variety of human cancer types (breast, prostate, colon, and ovarian tumors) and has been associated with tumor progression, aggressiveness and metastasis. In addition, higher levels of palmitate, the product of the fatty acid synthase (FAS) enzyme, have been detected in more advanced cancers of the prostate. Importantly it has been shown that some cancers preferentially synthesize palmitate de novo rather than importing this 16 carbon fatty acid. FAS is the sole human lipogenic enzyme capable of de novo synthesis of long-chain fatty acids from acetyl-CoA, malonyl-CoA and NADPH precursors. Together these data identify FAS as a therapeutic target.

We have discovered novel potent and selective inhibitors of FAS. These inhibit the β-ketoacyl reductase activity of FAS. At the molecular level, the FAS inhibitors cause an increase in malonyl-CoA and a decrease in phospholipid production. At the cellular level these inhibit the proliferation of cancer cell lines, result in an increase of cleaved polyADP ribose and lead to an increase in the population of cells with a sub2N DNA content. To further understand the biological consequences of FAS inhibition we have performed a global metabolic analysis with and without the inhibition of FAS. Inhibition of FAS resulted in dose and time dependent changes of greater than 10 fold in the pool sizes of multiple metabolites across multiple metabolic pathways. In the same timeframe FAS inhibition altered the mRNA expression of metabolic genes. This data will be discussed from the perspective of the biological consequences of inhibiting fatty acid synthase.