An effective FASN inhibitor

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Value Proposition

Many tumors are dependent on de novo fatty acid synthesis as a source of long chain fatty acids to maintain growth and interdicting at key steps in this pathway may have therapeutic benefit. Fatty acid synthase I (FASN) catalyzes the final step leading to the synthesis of fatty acids in vivo. In rapidly proliferating cells, such as cancer, FASN is needed to provide sufficient lipids for membrane formation and energy production as well as lipid modification of proteins. FASN is highly expressed in cancer, including colorectal, breast, lung, prostate, ovarian, and many more. Elevated FASN expression has been correlated with poor prognosis and reduced disease-free survival in colon cancer, prostate cancer, and sarcomas. Furthermore, FASN has been shown to serve as a bona fide oncogene in prostate and breast cancer, which may result from activation of the WNT/β-catenin pathway by FASN. Thus, blocking FASN represents a unique opportunity to effectively treat multiple tumor types.

Technology

In order to find an effective FASN inhibitor, the inventors panned 3,379 purine based compounds against mammary gland extract (rich source of FASN). The 20 highest hits were tested for anti-FASN activity in a [3H]glucose incorporation assay and the molecule with the highest activity, HS-106, was designated as lead compound. HS-106 is a thiophenopyrimidine that inhibits FASN by binding to its purine-binding cofactor domain. Cellular inhibition of FASN leads to apoptosis in cells dependent on FASN. Thus, this technology can inhibit cancer cell growth and may treat patients with cancer. Global lipodomics studies of breast cancer cells treated with HS-106 showed profound changes in cellular lipid profiles and sharply increased ceramide uptake. The increase in ceramide levels contributed to the apoptosis that reduced tumor growth in a Her2+ breast cancer mouse model.

Other Applications

Additionally, inhibition of FASN could also be effective against various viruses, including HIV, that are dependent on FASN for completing intracellular replication.

Advantages

FASN is considered an attractive target for cancer therapy due to the selective dependence of many tumors on de novo fatty acid synthesis. Many trials for the development of FASN inhibitors had previously failed to advance to translational studies, and only one FASN inhibitor was able to progress forward in clinical trials and is currently being evaluated in a Phase 2 trial for treating HER2 positive breast cancer. The molecule described here effectively inhibits FASN, leading to lipidomic changes and increased ceramide uptake and inhibits tumor cell growth in a clinically relevant breast cancer mouse model.