Anticancer Compound that Is More Effective and Less Toxic than Available Treatments

Published date: May 14, 2019

Technology description

Thymidylate Synthase Inhibitor Employs Small Molecules to Inhibit Tumor Cell Growth

These potential anticancer compounds offer an effective treatment that is less likely to cause resistance and recurrence of cancer and is less toxic to normal tissues than available chemotherapeutic agents. Thymidylate synthase inhibitors are a class of antineoplastic agents widely used in the clinical treatment of gastrointestinal, breast, ovarian and other cancers. While thymidylate synthase is essential for DNA biosynthesis and normal cell reproduction, the enzyme’ s overexpression has been associated with a wide range of human cancers. Chemotherapy agent 5-flourouacil targets overexpression of thymidylate synthase and has some success in prolonging the survival of patients with colorectal, breast, and lung cancer, but it has been strongly associated with induction of thymidylate synthase expression that results in resistance to treatment and recurrence of cancer. Researchers at the University of Florida have discovered a strategy that takes advantage of high thymidylate synthase subunit cooperativity and used it to identify small allosteric inhibitors that will freeze the dimer structure and inhibit enzymatic activity.

Technology

Thymidylate synthase is a key enzyme in synthesis of 2-deoxythymidine-5-monophosphate, an essential precursor for DNA biosynthesis. Disruption in enzyme’ s activity in abnormally proliferating cancer cells impairs production of dTMP, a building block for DNA biosynthesis and results in thymineless death, a phenomenon by which cells undergo irreversible cell death, thus stopping the spread of cancer. Thymidylate synthase is an enzyme with two symmetrical active sites. Thymidylate synthase binding of a substrate at one active site initiates a conformational change in the activation loop that informs the interface to close the second active site. As a result the enzyme functions in a see-saw fashion; when one active site is occupied, the other is closed. This technology provides small molecule allosteric inhibitors designed to disrupt the thymidylate synthase cooperatively by over-stabilizing the structure and limiting see-saw-like motions to preserve the enzyme in the semi-open conformation so that the enzyme becomes unable to proceed through catalysis, further preventing the proliferation of cancer.

Application area

Anticancer compounds that employ small molecules to inhibit growth of tumor cells

Advantages

Decreases toxicity to normal tissues, enhancing its viability as a therapeutic drug
Can be used with thymidylate synthase inhibitor chemotherapeutic agents or alone, providing multiple treatment combinations
More potent than currently used folate-based thymidylate synthase inhibitors, allowing for smaller dosages
Less likely to cause resistance compared to 5-flourouracil, increasing the effectiveness of treatment

Institution

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