Supplementary Information:

Thymidylate Synthase (TS) is an enzyme of metabolism which is part of the DNA synthesis pathway in both normal and tumor cells. It has been known for decades that TS is expressed in tumor cells in quantities that are significantly higher than most noncancerous tissues. There has been much research into developing chemotherapeutic drugs which attempt to block or inhibit TS in tumor cells in an effort to shrink or slow their growth in vivo. Drugs such as fluorouracil and flouxuridine are examples of this class of TS inhibitors.

The problem with enzyme inhibiting drugs is that over a short period of time, if the tumor cells are not killed, they become tremendously resistant to the inhibitors by various mechanisms. Usually the tumors boost expression of TS to overcome the inhibitor, but many other avenues are available to the tumor, such as pumping the drug out of the cell and mutating the enzyme to minimize the drug effect. At present, once the treated tumors start producing high levels of TS there is no effective therapy available.

Instead of inhibiting TS, this new strategy involves using TS to turn a uracil analog with low toxicity into highly toxic thymidine analog. The treatment would benefit patients with resistant tumors who were previously treated with TS inhibitors. The benefits of this type of prodrug are obvious. Patients could be treated with relatively high doses of the low toxicity prodrug thus ensuring high enough concentrations to penetrate the patients tissues and only the tumor cells will be actively converting the prodrug to its toxic metabolite thus dramatically lowering the severity of chemotherapeutic side effects. Moreover, there is less chance of the cells becoming resistant because they cannot down-regulate TS synthesis without slowing their own growth while making more and more toxic metabolites which in turn will kill the cancer cells.

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