A promising novel drug for breast cancer

The reason cancer is so difficult to treat is that cancer cells are our own cells running wild, which means that they generally do not make any protein or other molecule that normal cells don't make. This means that a drug that targets a protein in a cancer cell will also target that same protein in a normal cell and thus cause side effects. Nevertheless, some drugs, such as taxol and vinblastine, have been shown to be very useful and in fact are among the most successful anti-tumor drugs. Our approach has been to understand why these drugs are successful and then build on that knowledge to design even better drugs. These drugs target the protein tubulin, which the cell uses to make structures that help cells divide, grow and move, everything that a cancer cell wants and needs to do, especially if it is metastasizing. What is special about tubulin is that there are several forms of it and they differ in their tissue distributions, their presence in cancers, and their ability to bind to these drugs. Taxol and vinblastine favor the beta-2 form of tubulin, which is found in nerves and muscles as well as in many tumors; hence, the usefulness of these drugs is limited by their neurotoxicity. (Other drugs target the beta-4 form of tubulin, which is very widespread; these cause too many side effects to be useful in treating cancer). We are more interested in targeting the beta-3 form of tubulin, since this form is found primarily in neurons (not other nerve cells) and testes (not relevant to women). Beta-3 is also found in many tumors, especially those that are aggressive and metastatic, precisely the ones where novel treatments are most urgent. It has also been shown that tubulin in neurons is likely to be less sensitive to drugs than tubulin in other types of nerve cells. Thus, beta-3 is likely to be a better target than beta-2.

CH-35 was designed to bind better to beta-3 than to beta-2. We purified beta-3 and beta-2 and measured their binding to CH-35. The bad news is that CH-35 binds pretty well to beta-3 but not quite as well as it does to beta-2. The good news is that CH-35 is equally active as taxol against a variety of cancer cells in culture. We have tested CH35 in mice bearing breast tumors, both of human and mouse origin, and have found that CH-35 is equally effective as taxol in inhibiting tumor growth at dosages where it is equally as toxic as taxol. The better news is this: we designed a novel breast cancer cell line that makes a lot of beta-3; the idea is that this could mimic some of the most dangerous breast cancers. This cell line causes very rapid growth of tumors in mice, much more rapid than an otherwise identical cancer cell line lacking beta-3. This demonstrates very clearly how dangerous beta-3 in a tumor is for a cancer patient. The best news is that CH-35 is much more effective than taxol for inhibiting the growth of this cancer in mice.

Our conclusion is that we have not yet found the ideal drug for aggressive breast cancer. However, CH-35 represents a step in the right direction. What we have done is a proof-of-principle experiment about the role of beta-3 and the effect of CH-35. We hope that CH-35 may serve as a starting point for the development of even better drugs for breast and other cancers.

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Publication

Effect of CH-35, a novel anti-tumor colchicine analogue, on breast cancer cells overexpressing the ?III isotype of tubulin.
Yeh LC, Banerjee A, Prasad V, Tuszynski JA, Weis AL, Bakos T, Yeh IT, Ludueña RF, Lee JC.
Invest New Drugs. 2016 Feb