SAMUEL WAXMAN CANCER RESEARCH FOUNDATION PROGRAM ON TARGETED BREAST CANCER THERAPY

Although diets rich in **vitamin A** have been associated in some studies with decreased likelihood of breast cancer, the first definitive link between vitamin A and breast cancer came from a study by our group. In this study, published in the Journal of the National Cancer Institute in 2000, we showed that a protein that binds vitamin A (this protein goes by the acronym CRBP) is present in normal breast cells but is missing in breast cancer cells (this defect occurs in breast cancers from 1 in 4 women).
We think that women who lack the CRBP protein may be at a greater risk of developing breast cancer because they are unable to use vitamin A from their diets to protect against cancer.

In a series of follow-up studies we found out that putting the CRBP protein back into cancer cells made them behave like normal cells. For instance, the cells no longer formed tumors when injected into mice. We also found out why the CRBP protein is not present in cancer cells. It turns out that it is because of a reversible "epigenetic" change in the DNA. This is good news because it means that drugs already in clinical use for other cancers may be used to treat breast cancer. These studies were published in 2004-2005 in the Journal of the National Cancer Institute, the internationally recognized Oncogene journal, and the Molecular Cancer journal, which is available free online to scientists in any part of the World.

Despite our progress, we still have not proven whether women who lack the CRBP protein are at a greater risk of developing breast cancer. The experiments we need to do cannot be done on human subjects for ethical reasons. However, they can be done using mice. Mice are good "stand-ins" for humans and are humanely treated to minimize any discomfort. We will use mice that are prone to breast cancer. The CRBP protein is also missing in mouse breast cancers. We want to find out what happens first: is the CRBP protein lost and then the cancers appear or is it the way around? We expect that the CRBP protein is lost first. These experiments are labor-intensive and time consuming because it takes one year for the mice to develop cancer (for a mouse, one year is roughly the same as 50 years for us). We already have the mice we need in order to do this experiment and look forward to sharing our results with you next year.

Further information has been obtained on how a large amount of a gene and protein called cyclin D make breast cancer cells more sensitive to a new drug called Velcade. For the first time, we may be able to select which women with breast cancer should receive this drug which is relatively non-toxic and could augment the effect of chemotherapy more selectively to breast cancer cells. We are finding that Velcade could also be useful in women with hormonal resistant advanced breast cancer if the tumor has a large amount of cyclin D. This is an exciting observation and may become a part of the clinical trail to test this hypothesis.

Finally, the SWCRF is supporting new research on the identification and properties of breast cancer stem cells. These cells feed the tumor and are difficult to

eradicate with standard chemotherapy. Breast cancer stem cells may be responsible for late recurrences in women with breast cancer. The initial approach is using engineered mouse models of breast cancer. Thereafter, the breast cancer stem cells will be separated and analyzed to find out which mechanisms protect them from standard chemotherapy. Once established, new drugs will be developed to overcome this resistance.