National Surgical Adjuvant Breast and Bowel Project

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Ground-Breaking Study by the Pittsburgh Based National Surgical Adjuvant Breast and Bowel Project (NSABP) Demonstrates Novel Way to Use Common Cancer Gene to Trigger Death of Breast Cancer Cells

--First Time Gene's Dual Roles Demonstrated in Patients --

--Large NSABP Tumor Bank Facilitates Study --

Pittsburgh, PA – December 15, 2005 – The National Surgical Adjuvant Breast and Bowel Project (NSABP) has announced the results of a ground-breaking laboratory study performed on human breast cancer specimens collected as part of a clinical trial evaluating the breast cancer drug, Herceptin™, that suggests a cancer-causing gene, called cMYC, can be triggered to cause the death of breast cancer cells.

The study led by Soonmyung Paik, MD, Director of the NSABP Institute of Molecular Pathology, evaluated the breast cancers of more than 3,000 patients treated on two large adjuvant breast cancer clinical trials conducted by the NSABP.

Funding for the laboratory study came in part from the Tobacco Settlement Act (ACT 77 of 2001), which authorizes the Pennsylvania Department of Health to allocate a portion of the tobacco settlement fund for health and related research.* The results of the study were presented December 8th at the San Antonio Breast Cancer Symposium by Dr. Paik.

This finding is the end result of a three-year-long project that required screening more than 51,000 individual test samples. The research team began by searching for cancer chromosomal abnormalities called gene amplification which were thought to influence the behavior of breast cancer. All people are born with two sets of all genes, one copy from each parent. For some

unknown reason, over time, some genes increase their copy number (a process called amplification) resulting in normal cells becoming cancerous. After screening for gene amplifications in 1,900 cases of breast cancer treated with chemotherapy as part of the NSABP B-28 trial, amplification of three genes (HER2, cMYC, and HTPAP) was found to lead to a poorer prognosis even after the use of standard chemotherapy.

Clinical Benefit from Herceptin

In May 2005, the NSABP and the North Central Cancer Treatment Group, another research group also funded by the National Cancer Institute (NCI), announced the results from a joint analysis of data from the two similar clinical trials (NSABP B-31 and NCCTG N9831) conducted by the groups. The analysis showed significant clinical benefit by adding Herceptin, a monoclonal antibody that targets the HER2 protein, to standard chemotherapy in patients diagnosed with breast cancer with increased copies (amplification) of the HER2 gene. Adding Herceptin resulted in a 53% reduction in the recurrence rate – a result hailed by one expert as “revolutionary rather than evolutionary.”

Since cMYC was frequently amplified together with the HER2 gene in the initial study of the cancers from patients in the B-28 study, Dr. Paik's team examined cMYC amplification in the tumor specimens collected in the NSABP B-31 Herceptin study. The benefit of adding Herceptin to chemotherapy in these patients whose tumors had amplification of the HER2 gene was examined according to the presence or absence of cMYC amplification. Those with cMYC amplification had achieved a much larger reduction in recurrence rate (76%) compared to those without cMYC amplification (37%).

Out of the 237 patients with cMYC amplified cancers who received Herceptin along with chemotherapy, only .5% had developed recurrent breast cancer within 4 years after start of treatment and .3% of these patients died within 4 years of their diagnosis. In contrast, of the 234 patients with cMYC amplified cancers treated only with standard chemotherapy, four times as many recurred and three times as many died within 4 years of starting therapy. More intriguing is the finding that while recurrences and death continue to happen beyond two years after initiation of standard chemotherapy, there were no recurrences after two years in cMYC amplified Herceptin-treated patients. These results suggest the potential impact of Herceptin on survival in patients with

co-amplification of HER2 and cMYC will be very substantial. "Since patients with cMYC amplified tumors start with a worse prognosis, it is remarkable that their fortune is essentially reversed due to the addition of Herceptin to chemotherapy," Dr. Paik noted.

Dr. Paik describes this finding as not completely surprising given the body of laboratory evidence collected over the years regarding the apparent dual role of cancer-causing genes such as cMYC. Notably this is the first time that this concept has been demonstrated in a large study conducted in breast cancer patients. The activity of the cMYC gene is normally tightly controlled because gene activity causes cells to rapidly divide and increase in number. Uncontrolled growth caused by unregulated activity of genes such as cMYC plays an important role in the development of breast and other cancers.

As a natural defense against cancer, potentially cancer-causing genes such as cMYC, which play important roles in normal cells, are equipped with a capability to not only stimulate cell proliferation, but also to trigger the death of the cell (a process called *apoptosis*). When cMYC becomes expressed in an unregulated manner, cMYC triggers cell death instead of continuing cell proliferation so the cell will not develop into cancer.

The existence of this natural defense mechanism explains why cancer doesn't develop in the majority of people. However if there is activation of other genes, such as HER2, that suppress the cell death pathway while cMYC is stimulating cell proliferation, an aggressive cancer may eventually develop. The results of this study suggest that when HER2 activity is inhibited by the antibody Herceptin, cMYC regains its ability to trigger cellular death. "This probably explains why Herceptin added to chemotherapy worked so well in cMYC amplified tumors," Dr. Paik said.

Applicability in Other Cancers

Dr. Paik believes that this finding has important potential applicability in other cancers, including breast cancers without HER2 amplification. About 30% or more of all human cancers have problems of abnormal expression of cMYC. Such tumors tend to have a worse prognosis compared to the cancers without cMYC abnormalities. The data from Dr. Paik's lab suggests that these aggressive tumors could be triggered to die if active co-conspiring cancer genes could be identified and effectively blocked, as Herceptin does by blocking the activity of HER2.

"The possibility that a cancer gene can be manipulated to trigger the death of cancer cells themselves is a fascinating one and may potentially lead to development of substantially more effective treatment strategies for many kinds of cancer with fewer side effects," Dr. Paik said. Dr. Paik and his colleagues at the NSABP are actively searching for other cancer genes that interact with cMYC.

NSABP Tumor Bank Facilitates Trial

These important molecular NSABP studies were made possible by the commitment of the NSABP scientific leadership and member institutions to the development of the NSABP Tumor Bank, one of the largest annotated breast and colorectal cancer tissue banks in the world which contains over 65,000 specimens. These valuable research samples have all been donated by patients who participated in clinical trials conducted by the NSABP during the past 40 years. Each year about 3,000-4,000 specimens are added to the Tumor Bank. The Tumor Bank is mainly funded by grants from the National Cancer Institute (NCI).

The Tumor Bank has contributed significantly over the years in the clarification of the importance of various tumor molecular markers and the development of practical prognostic tests. The NSABP Tumor Bank is an open resource for the scientific community that is available to any investigator in the world with an innovative scientific proposal approved through a transparent review process by an external scientific review panel of experts. The Tumor Bank is currently supporting a number of projects conducted by investigators from institutions throughout the United States.

*The Pennsylvania Department of Health specifically disclaims responsibility for any analysis, interpretations or conclusions.

About NSABP:

Headquartered in Pittsburgh, PA, the NSABP is a not-for-profit, clinical trials cooperative group, which includes a network of over 10,000 professionals and 750 institutions located in the U.S., Canada and Puerto Rico. Research conducted by the NSABP is supported primarily by grants from the NCI. For more than 40 years, the NSABP has successfully conducted large-scale, randomized

clinical trials in colorectal and breast cancer that have altered and improved the standard of care for men and women with these diseases. To learn more about the NSABP, please visit http://www.nsabp.pitt.edu.

Editors Note: High Resolution Jpegs illustrating the study are available upon request. Please contact Frank Catanzano at 412-965-5269 or email fcatanzano@truebaseline.com or visit www.nsabp.pitt.edu to download the images.