Oncogenes Give Breast Cancer Prognosis

The amplification of an oncogene in breast cancer cells correlates with time to relapse and survival time, and therefore provides a potential tool for judging prognosis

In this issue of *Science*, Dennis Slamon of the UCLA School of Medicine and his colleagues report that the amplification of an oncogene correlates with a shorter time to relapse and lower survival rate in women with breast cancer. The finding may help physicians decide how aggressively to treat breast cancer patients. And it may be a clue to what causes this cancer in the first place.

The breast cancer work, which appears on page 177, is the third finding that amplified oncogenes in human cancers may indicate poor prognoses. Previously, researchers reported a similar finding for the childhood cancer, neuroblastoma, and, very recently, others found it is also true for lung cancer.

These clinical studies build on a large body of research on the role of oncogenes in cancer. These are genes from animal cells that were picked up by certain RNA tumor viruses and that allow these viruses to cause cancer. Since these genes are always present in cells, molecular biologists suspect that they may play a role in causing cancer, even when no viruses are present.

Molecular biologists have two working hypotheses to explain how cellular oncogenes may be involved in cancer. The first says that when a cell becomes cancerous, the cellular oncogenes may be either overexpressed or expressed at the wrong time. The second says that the genes are subtly altered through mutations so that the gene products cause cells to lose control of their growth. There is evidence to support both hypotheses.

Recently, molecular biologists began reporting that some oncogenes are overexpressed following gene amplification—cells from cultured cancer cell lines make extra copies of oncogenes and subsequently make large amounts of the gene products.

The first clinical application of this work was reported about 1½ years ago by Robert Seeger and his colleagues at the UCLA School of Medicine. The oncogene, N-*myc*, they found, is present in multiple copies in some human neuroblastomas and this N-*myc* amplification correlates with the stage of the disease.

Oncologists classify this rare nerve cell tumor, which occurs in one out of every 125,000 children, in stages I through IV. Stage I is a tumor confined to the organ or structure of origin, and stage IV is a primary tumor that has spread to other sites in the body. Seeger found that N-*myc* amplification is an independent prognostic index and that the more copies of N-*myc* that are present in cancer cells, the worse the prognosis. In fact, patients with stage II cancer but with N-*myc* amplification had prognoses like those of stages III and IV patients, indicating that N-*myc* amplification is an even better predictor of survival time than the best clinical data.

Oncogene amplification, says Clark, is "the first prognostic factor I've seen that, by itself, is that powerful."

At about the same time as the neuroblastoma work was progressing, John Minna and Bruce Johnson of the National Cancer Institute looked at oncogene amplification in lung cancer. About 25% of the 140,000 lung cancer cases that are diagnosed each year are classified as small cell tumors, and these cancers typically have the worst prognoses. "Until 5 or 10 years ago, everyone thought that small cell cancer was virtually incurable by any mechanism," Minna says. But Minna's group and about ten other groups have now shown that as many as 10% of all these patients can actually be cured by appropriate combinations of chemotherapy and radiation.

The prognosis depends on the stage of the cancer. Twenty to 25% of patients with limited stage cancer, which remains in the chest, are cured whereas about 1% of those with extensive stage disease are cured.

Johnson and Minna looked for amplification of the c-*myc* oncogene in patients with extensive stage disease. They found that those with oncogene amplification survive only one-half to one-third as long as patients whose tumors do not have this amplification. In addition, says Minna, they have "no examples of patients with oncogene amplification who were cured."

Johnson and Minna continue to treat all their small cell patients, even those with oncogene amplification. "We have to be optimistic," Minna says. "It may be that we used the wrong drugs or the wrong drug combinations in the past with these patients."

Meanwhile, knowing of his colleague Seeger's results with the neuroblastoma oncogene, Slamon decided to look for a similar effect in breast cancer. "Neuroblastoma is a very bad disease, but it is very rare," Slamon says. "One out of every 14 women in this country will develop breast cancer. That's a frightening statistic."

Slamon and his colleagues had reason to believe that oncogenes might be amplified in breast cancer because Stuart Aaronson of the National Cancer Institute has found that such a gene is amplified in one out of ten breast cancer cell lines. "I saw Aaronson's report and decided it would be interesting to look at fresh human cancers, because all kinds of things can happen in cell lines," Slamon recalls.

Slamon worked in collaboration with oncologist William McGuire and statistician Gary Clark of the University of Texas Health Science Center in San Antonio, where there is a bank of breast cancer tissue and computerized information on the patients' clinical status and the course of their disease. The group also included Axel Ullrich of Genentech, who cloned the human breast cancer oncogene.

In its initial study, the group looked at 103 primary breast tumors. They found that the oncogene HER-2/*neu* was amplified in 18% of them. The result was encouraging, but what Slamon needed to know next was whether oncogene amplification correlated at all with clinical signs.

They found, says Slamon, that "the amplification correlated with the number of positive lymph nodes. The number of positive nodes is the best predictor of relapse and survival time. That was our first inkling that there may be a lead here."

Next, Slamon and his associates decided to ask whether the oncogene amplification gave any clinical information among women whose cancer had already spread, as indicated by positive lymph nodes. They therefore looked at tumors from an additional 86

women in the San Antonio data bank who had positive lymph nodes and for whom relapse and survival information was available. Without knowing anything about the patients' clinical status, Slamon and his associates did DNA analyses, looking for oncogene amplification. The oncogene was amplified in 40% of the patients.

When the group then looked at the clinical data, it found that the more the oncogene was amplified, the more likely the woman was to relapse and the shorter her survival time. "Oncogene amplification was a better indicator than hormone receptor status, age of the patient, and size of the tumor. And it was independent of the number of positive nodes," Slamon says. Statistician Clark remarks that oncogene amplification is "the first prognostic factor that I've seen that, by itself, is that powerful." The more the oncogene is amplified, the worse the prognosis.

The clinical implications, if the result is confirmed, can be important, particularly in women whose cancer has not spread to the lymph nodes. Physicians now classify breast cancer patients as being in stage I through stage IV of the disease. Stage IV is the most advanced. But these stages are not foolproof, and oncologists would like to break down the classification still further. They are particularly interested in getting better prognostic information on stage I women who have negative lymph nodes and who generally have such a good prognosis that they are not given radiation or chemotherapy after their breast cancer is removed. Yet, according to Clark, breast cancer will recur in 25 to 30% of these women with negative nodes.

A consensus conference on breast cancer held at the National Institutes of Health in September of 1985 debated the question of whether women with negative lymph nodes should receive chemotherapy or radiation and concluded that there were not enough data to decide. If the oncogene finding holds up in node-negative women, it could provide a means of deciding.

In addition, the oncogene finding could be important in deciding on therapy for postmenopausal women with positive lymph nodes. Most of these women, according to McGuire, do no better when they receive chemotherapy than when they do not. But, says McGuire, "we would like to know which postmenopausal, node-positive women will have an early recurrence of their cancer. Then we would treat them very aggressively."

The oncogene that is amplified in breast cancer cells also could be telling researchers what causes the disease in the first place and how to devise a molecularly targeted treatment. The gene codes for a protein kinase, an enzyme that adds phosphate to tyrosines of certain proteins. "It is most closely related to the EGF [epidermal growth factor] receptor, but it is not the EGF receptor," Slamon notes. No one knows what binds to this receptor protein, but if the EGF receptor plays a role in the development or progress of breast cancer, blocking it could possibly arrest or cure the disease.

Slamon, McGuire, and their associates are now expanding their study, looking particularly at node-negative women from the tissue bank in San Antonio for whom long-term relapse rate and survival are known. There are more than 9000 breast cancers stored in the data bank at San Antonio, so the investigators are optimistic that they will be able to do a definitive study. ■

GINA KOLATA

Materials Scientists Seek a Unified Voice

The rise of materials science as a recognizable discipline paralleled the growth of the Materials Research Laboratories now run by NSF, but funding and identity problems remain

LAST year was the 25th anniversary of the interdisciplinary Materials Research Laboratories, established by the Defense Advanced Research Projects Agency (DARPA) but administered by the National Science Foundation (NSF) since 1972. The just published proceedings of a symposium that was held a year ago at the National Academy of Sciences to celebrate the occasion contain another of what is becoming an increasingly frequent call for the broad and diverse materials science community to organize itself more formally.*

The hope expressed in contributions by C. Peter Flynn of the University of Illinois and William Nix of Stanford University is that, with an appropriate mechanism for arriving at a community consensus, funding decisions can be made in the context of an overall national program and the field can present its needs effectively in the national arena.

At the moment, the primary means for arriving at anything like a consensus are the committees assembled when the academy or some other body sets out to study a materials-related issue. Two years ago, for example, the academy turned out a report for the Office of Science and Technology Policy titled "Major Facilities for Materials Research and Related Disciplines."

Now under way is a massive academy study involving five subpanels and a steering committee, all under the direction of Praveen Chaudhari of IBM's Yorktown Heights laboratory and Merton Flemings of the Massachusetts Institute of Technology (MIT). The report, not due to be published for another 2 years, will be an attempt to present a unified view of materials science and engineering in the spirit of the recent academy overviews "Opportunities in Chemistry" and "Physics through the 1990's."

As valuable as these ad hoc efforts are, they cannot provide the kind of continuous guidance that, for example, the High Energy Physics Advisory Panel has given for about two decades. This group, which was chartered to advise the Department of Energy on the needs and wants of high-energy physicists, has become an oft-mentioned model for how a relatively homogeneous scientific community that has its act together can express itself to the federal agency that funds its operations.

Whether materials science, which is a far less homogeneous and a much newer discipline, can adapt this or some other model has become a frequently debated question as the field has matured, the cost of facilities grown, and the competition for funds increased. In particular, while providing state-of-the-art instrumentation is a problem across the board, the expanding role of so-called "big science" facilities, such as synchrotron light sources, has generated much tension in the community. Beyond the admonishment that major facilities must not come at the expense of individual and small-group research, the academy's study on the subject did not address the issue of how to

**Advancing Materials Research* is available from the National Academy Press, 2101 Constitution Avenue, NW, Washington, DC 20418, for $47.50. Also see *Science* editorial, 2 January, p. 9.