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Breast Cancer: Finding the Right Treatment

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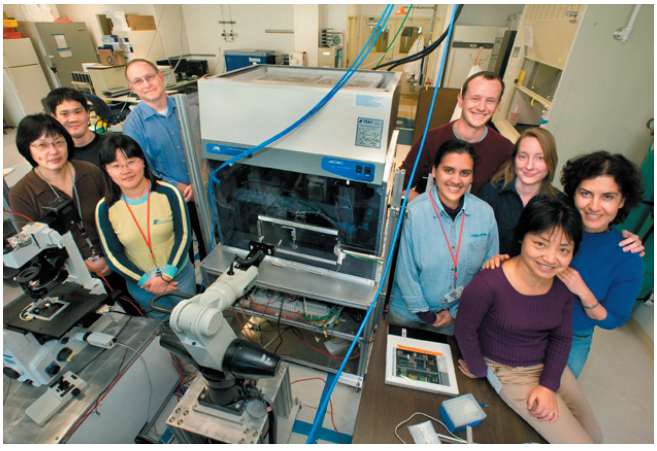
Despite all the efforts that have gone into diagnostics and treatments, breast cancer remains the leading cause of cancer deaths in women. One of the major challenges in bringing this pernicious disease under control is that each individual patient's breast cancer is unique. A treatment that is effective for one woman may be ineffective or even harmful for another, and there's been no reliable way of predicting which drug would best serve an individual patient.

That medical conundrum is about to change. In a potentially huge step towards advancing the concept of individualized cancer treatments, Berkeley Lab researchers have identified biomarkers —molecular signatures—that can be used to predict how a patient is likely to respond to two of the leading breast cancer drugs. Furthermore, the methodology used to identify these predictive biomarkers should also be applicable towards identifying similar biomarkers for other breast cancer drugs, as well as drugs used to treat other forms of cancer.

At the 2007 annual meeting of the American Association for Cancer Research (AACR), the Berkeley Lab researchers reported on a system they have developed for evaluating the response to therapeutic drugs in 50 different breast cell lines. These cell lines, 45 of which were cancerous and five of which were normal, mirrored the recurrent genetic abnormalities, as well as the biological variability, found in primary breast cancer tumors.

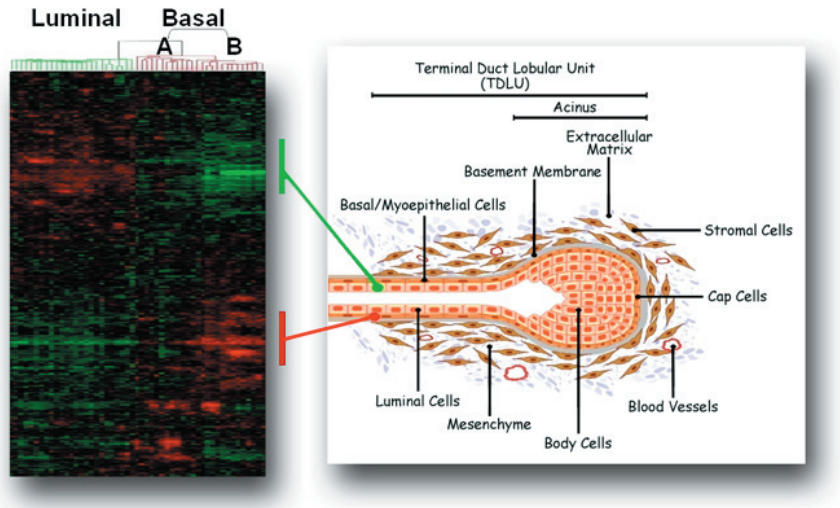
For each line, a detailed molecular profile was created that included genome copy-number abnormalities, gene expression patterns, and abundance measurements for more than 100 different types of proteins. Such features have been linked to either drug sensitivity or resistance. When these molecular profiles were correlated with cell responses to targeted therapeutic drugs, they yielded characteristic signatures that served as predictive biomarkers.

"Individuals respond differently to different therapeutics because there are substantial differences in the spectrum of genetic, biological, and epigenetic characteristics between breast cancers," says Joe Gray, director of Berkeley Lab's Life Sciences Division and Associate Laboratory Director for Life and Environmental sciences, who was the principal investigator for the research. "However, some recurrent abnormality patterns are emerging that define breast cancer subtypes."



Joe Gray's research group gathers around the automated cell culture system they use for plating and treating cells with different compounds. From left, Wen-Lin Kuo, Nick Wang, Zhi Hu, Joe Gray, Naina Shastri, Richard Neve, Heidi Feiler, Yinghui Guan, and Nora Bayani.
(Photo Roy Kaltschmidt)

Gray, who is also the co-leader of the breast cancer research program for the Comprehensive Cancer Center at the University of California's San Francisco campus, was one of the presenters at the AACR symposium, along with Yinghui Guan and Debopriya Das. Wen-Lin Kuo planned and coordinated the study and analyzed the raw data. Other collaborators included Zhi Hu, Nick Wang, Heidi Feiler, and Richard Neve. All are members of Gray's research group at Berkeley Lab.



The breast cancer cell lines developed by the Gray research group represent recurrent genetic abnormalities as well as biological variability in primary breast cancer tumors. For example, it was found that these cell lines can be classified into luminal (green) and basal (red) subtypes that strongly correlate with luminal and basal tumors, and can therefore be used to predict responses to new drugs for these subtypes of breast cancer.

"Many new therapeutic agents are emerging that must be prioritized for testing in these and other cancers and cancer subtypes," Gray says. "We need better ways to tailor existing therapies to individuals and to target experimental agents."

Says Guan, "Our assumption was that a large collection of breast cancer cell lines retains enough of the recurrent molecular abnormalities and individual heterogeneity of the tumor subgroups that their responses, in ensemble, will predict clinical behavior."

To test the hypothesis, Gray and Kuo and the other members of Gray's research group analyzed the responses of their 50 breast cell lines to two of the most powerful breast-cancer drugs on the market today, Lapatinib and CI-1040. Lapatinib, developed by GlaxoSmithKline, is a dual inhibitor of EGFR and ERBB2 oncogenes. CI-1040 inhibits the gene for the MEK enzyme, whose overexpression has been linked to breast cancer.

In this study the researchers reported that for Lapatinib, several biomarkers were identified exhibiting strong correlation with sensitivity to the drug. The strongest correlations were found for the amplification and overexpression of ERBB2, a result consistent with clinical experience. For CI-1040, the phosphorylation of MAPK1/3 and AKT were found to be accurate predictors of an individual cell line's response to the drug.

"It is logistically and financially impossible to test all of the experimental medicines in each cancer subtype," says Gray. "The concordance of our markers of response to Lapatinib with those observed clinically suggests that the molecular markers identified in the cell line collection can be used to guide the use and testing of other approved and experimental drugs. Our predictive biomarkers could be used to prescreen patients prior to receiving therapy and define tailored therapeutics for individual patients."

To further validate the effectiveness of their predictive biomarkers, Gray and his group will use their 50 cell lines to test scores of other therapeutic drugs. These biomarkers may also prove useful for finding new combinations of therapeutic drugs that could provide more effective treatments than any one drug alone.

Says Gray, "We know in the end that we are going to have to use combinations of drugs to be fully effective in treating many cancer patients."

The research reported at the AACR meeting was supported by funds from the National Institutes of Health and by GlaxoSmithKline. The work is an extension of research reported in detail in "Decoding Breast Cancer Genomes," in the January, 2007 edition of Science@Berkeley Lab.

This is an edited version of an article appearing in the April 2007 edition of Science@Berkeley Lab, the online science magazine of Lawrence Berkeley National Laboratory. The full-length version, including links to further information, may be accessed at http://www.lbl.gov/Science-Articles/Archive/sabl/2007/Apr/bc.html.