



Bay Area Breast Cancer SPORE Newsletter

Specialized Program of Research Excellence at the University of California San Francisco

UCSF Professor Elizabeth Blackburn Awarded Nobel Prize By Joe W. Gray, PhD, Adjunct Professor of Laboratory Medicine, UCSF

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“The joyous occasion to award the Nobel Prize in Physiology or Medicine to UCSF’s Elizabeth Blackburn, PhD—among 10 women in history to receive that prize—marks the triumph of her extraordinary journey as a scientist,” read the UCSF news release on December 10, 2009. Dr. Elizabeth H. Blackburn, Dr. Carol W. Greider, and Dr. Jack W. Szostak, received the 2009 Nobel Prize in Physiology or Medicine on December 10 “for the discovery of how chromosomes are protected by telomeres and the telomerase enzyme” by the Nobel committee in Stockholm, Sweden.

The entire UCSF and UC communities celebrated this extraordinary triumph and came together to applaud this great achievement of their fellow colleague, mentor, professor, and peer: Dr. Elizabeth Blackburn. UCSF Chancellor, Susan Desmond-Hellmann, MD, commented that “Dr. Blackburn’s research over the course of more than three decades has revolutionized scientists’ understanding of the way in which cells function.”

UC President Mark Yudof remarked, “The entire University of California community could not be more proud of Dr. Elizabeth Blackburn. Her path-breaking work is yet another reminder of the life-changing contributions UC makes to California and to the world.”

We in the Breast Oncology Program are especially proud of Dr. Blackburn for her achievements as a long-standing member of the UCSF Breast Cancer SPORE.

In 1985, as an Associate Professor in the Department of Molecular Biology at the University of California Berkeley, Dr. Blackburn discovered the ribonucleoprotein enzyme, telomerase. Telomerase was found to create the end caps of DNA to protect DNA from being whittled away through repeated cell divisions; this is kind of like trying to quickly move water back and forth

between two containers – each transfer may result in spilling a couple drops, and after some time, you will be left with significantly less than what you started with.

Similarly, as DNA is replicated to “fill up” newly created cells, a small piece of the DNA at each end has the potential of being lost with each transfer. Telomeres buffer and protect DNA strands from shrinking during this process.

After this great discovery, Dr. Blackburn came to UCSF in 1990 and joined the Departments of Biochemistry and Biophysics, and Microbiology and Immunology. In 1995, Dr.

Blackburn was awarded funding for a developmental project from the Breast Cancer SPORE to look at the role of telomerase in breast cancer and to determine whether telomerase inhibitors would be useful in the clinic to prevent and/or treat breast cancer.

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The 70-gene Breast Cancer Gene Signature and MammaPrint

By Laura J. Van 't Veer, PhD, Professor of Laboratory Medicine, UCSF

Dr. Laura Van 't Veer's development of the 70-gene breast cancer gene signature, and subsequent molecular diagnostic test, MammaPrint, has helped to lead the cancer community into a new era of personalized medicine. This groundbreaking scientific tool began with a 2002 article titled "Gene expression profiling predicts clinical outcome of breast cancer" published in *Nature*, and has since evolved into a tool now used in clinical practice to guide the use of adjuvant chemotherapy.

The conventional approach to cancer therapy has been to provide treatment according to the organ or tissue in which the cancer originates and its histopathological appearance (i.e., tumor stage, type, grade). This approach was appropriate when there was only a rudimentary understanding of the molecular origins of cancer and the different intracellular signaling pathways that are perturbed in the various types of cancer. In the past two to three decades, however, the genetic events that lead to cancer have been dissected, and it has become clear that cancer develops as a result of multiple genetic defects and that individuals with the same type of cancer often have dissimilar genetic defects in their tumors. This finding explains why patients diagnosed with seemingly similar cancers may respond in varying manners to anticancer agents. Such differences clearly demonstrate the huge obstacles to providing effective treatments for cancer.

In the past decade, cancer therapy has slowly but steadily begun to shift from a 'one size fits all' approach to a more personalized approach, in which each patient is treated according to the specific genetic defects in the tumor. Such an individualized approach requires the discovery and

development of biomarkers (biological indicators) that help doctors to decide which patients to treat (known as prognostic biomarkers) and which therapy is most likely to be effective for a given patient (known as predictive biomarkers). More specifically, prognostic biomarkers predict the clinical outcome for a patient if no anticancer drugs are administered, whereas predictive biomarkers predict the outcome while a specific therapy is given to the patient. An example of why such biomarkers are needed to improve patient management is that, for some tumors, surgical removal alone of the primary tumor may be curative; thus, systemic therapy to eliminate any remaining tumor cells (also known as adjuvant therapy) would not be needed. By contrast, for more aggressive primary tumors, systemic therapy--often chemotherapy--might be required after surgery in order to reduce the risk of tumor recurrence. The distinction between these is not so easily made, so prognostic biomarkers that enable the likelihood of recurrence to be determined can be of great benefit.

In the case of breast cancer, large meta-analyses studies have shown that recurrence is likely in 20–30% of young women with early-stage, lymph-node negative breast cancer who undergo only surgery and localized radiation treatment. In the United States 85–95% of women with this type of cancer receive adjuvant chemotherapy, mostly because conventional medical parameters fail to reliably identify those patients who are likely to have a recurrence. Over 50% of women with early-stage breast cancer in the United States may undergo a toxic therapy from which they will not benefit but will experience the side effects.

The advent of DNA-microarray technology has made it possible to assess the expression of tens of thousands of genes in a single experiment and to develop gene tests for patients. Systematic analysis of the gene-expression patterns of tumor samples enabled researchers to identify characteristic expression patterns of groups of genes that are associated

with specific tumor traits. These patterns are known as gene-expression signatures.

Implementing gene-expression profiles in the clinic

Translating biomarker research into clinically useful tests has often been a frustrating activity. Many of the biomarkers identified in the initial tumor studies failed to be validated in subsequent studies. Some of the more recent gene expression signatures were derived from large data-driven, genome wide studies with excellent data quality, so these biomarkers are far more likely to be validated than previously identified biomarkers from knowledge-driven studies.

Both the US Food and Drug Administration (FDA) and the medical community have recognized that multigene signatures are better biomarkers than single molecules, so why are so few gene-expression signatures available in the clinic? First, on the basis of past failures, doctors are often reluctant to use biomarkers that have been validated only by retrospective studies; they insist on validation by prospective studies before biomarkers are used in routine clinical practice. A second impediment is that DNA-microarray technology was initially not very robust and, to many scientists and doctors, it still has a poor reputation, which has been unfounded since industry became involved in production. Third, the correct regulatory path for using multigene tests in clinical practice is unclear. For two of the three multigene tests that are commercially available large prospective validation studies are in progress: the study TAILORx is validating the 16-gene signature marketed as Oncotype DX; and the study MINDACT is validating the 70-gene signature marketed as MammaPrint. But the results of these large studies, which require

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News from the 2009 San Antonio Breast Cancer Symposium

By Diane Heditsian, UCSF Breast SPORE Advocate



In December I attended the 2009 San Antonio Breast Cancer Symposium as a patient advocate through the support of UCSF Breast SPORE Advocacy Core (BSAC). As one of 8,400 attendees from almost 100 countries, I was grateful to hear the results of the latest breast cancer research. Fellow SPORE advocates, Joni Venticinque, Susan Samson and I didn't stop for five days straight. We attended breakfasts that highlighted clinical trials, scientific poster discussions, general sessions, lunchtime panels where physicians such as UCSF's Dr. Laura Esserman provided input to colleagues on their most challenging patient cases, and evening mentor sessions where breast cancer luminaries such as Dr. Susan Love answered our questions and explained the significance of what had been reported during the day. Here, I highlight a few of the many studies. You can listen to webcasts, podcasts or read in depth about these and other studies at www.sabcs.org. And, if you'd like to learn about the UCSF Breast SPORE Advocate Core, I encourage you to contact Sarah Goins at sarah.goins@ucsf.edu.

No Difference in Aromatase First or in Sequence

The results of a large trial of post-menopausal, hormone receptor-positive women found that women who took tamoxifen for 2.5 to 3 years and then switched to the aromatase inhibitor, Aromasin, for 2 to 2.5 years (for a total of 5 years) had the same risk of recurrence as women who took Aromasin for the full five years. Time to recurrence and overall survival

were almost identical for the two strategies when patients were followed up after five years. This is good news because the decision on which treatment approach to take can now be based on side effect profile, since the efficacy for both is the same. Women can feel comfortable switching treatments if they need to due to side effects or the cost of the drug. Researchers are now looking at biomarkers to find out if certain subgroups of patients benefit more from one strategy than the other.

Combining Targeted Therapies for HER2-positive Breast Cancer

Another interesting study showed that for metastatic Her2 positive breast cancer, combining Tykerb with Herceptin resulted in a more than four-month improvement in survival when compared to using Tykerb alone. This was the first Phase III trial to show effectiveness when combining two targeted therapies without the use of endocrine therapy or chemotherapy. Not only did overall survival significantly improve among the patients who used the combination therapy compared with those who were treated with Tykerb alone, but also, there was a trend toward a 25% reduction in risk of death. This combination therapy is now being compared to either drug alone for recurrence prevention in patients with

HER2-positive *early stage* breast cancer. These results were encouraging to me. Perhaps we are moving closer to the day when women can be treated with targeted therapies alone and chemotherapy can be eliminated.

Obesity is Linked with Worse Breast Cancer Outcomes

In one of many studies focusing on the effects of lifestyle on breast cancer it was shown that the women with early stage breast cancer who were overweight or obese at the time of diagnosis had a higher risk for distant recurrence and poorer survival rates. Women with a body mass index (BMI) of $\geq 25 \text{ kg/m}^2$ had an increased risk of distant metastasis by up to 46% within ten years and obese patients had as much as a 38% greater risk of breast cancer mortality ten or more years after diagnosis compared to normal-weight breast cancer patients. This Danish study of almost 54,000 women who were followed for 30 years, also showed that being overweight or obese was associated with being diagnosed at a more advanced stage of breast cancer. Additionally, the study found that normal-weight women were as much as 77% more likely to benefit from adjuvant systemic therapy. There was no correlation

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About the Ida & Joseph Friend Cancer Resource Center

The Cancer Resource Center supports wellness and the healing process by providing patients and their loved ones with information, emotional support, and community resources.

The CRC maintains a multimedia library, provides access to specialized health databases, and offers research assistance. The CRC hosts diverse support groups and classes, and directs people to other community resources.

All CRC programs are free.

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San Antonio Breast Cancer Symposium continued...

between BMI and local-regional recurrence. These results underscore the importance of keeping body weight within a normal range.

Do Drugs for Osteoporosis Reduce the Risk of Breast Cancer?

Women taking oral bisphosphonates had a 30% lower risk of breast cancer than women who didn't take them, according to data from two retrospective studies reported at the symposium. Data from the huge Women's Health Initiative study showed that there was an overall risk reduction in invasive breast cancer, a significant reduction in the risk of estrogen receptor (ER)-positive breast cancer, and a trend toward a lower risk of ER-negative breast cancer in women taking a bisphosphonate. Surprisingly, in this same study, bisphosphonate treatment was associated with a 41% *increased* risk of ductal carcinoma in

situ. A smaller Israeli study of postmenopausal patients that compared breast cancer rates in women who took bisphosphonates for five years or more to women who didn't take them, showed similar benefits for invasive cancer but didn't show the increased risk for DCIS. This study also found that breast cancers that developed in bisphosphonate users were more likely to have favorable characteristics such as in situ versus invasive cancer, moderately or well-differentiated, strong ER positivity, and HER2 negativity.

This risk reduction benefit of bisphosphonates is a hypothesis based on reviews of databases and will now be tested in randomized clinical trials. One alternate explanation for these results is that women who take bisphosphonates have low bone density because of low estrogen levels, so they would have a

lower risk for breast cancer than the women who did not take bisphosphonates.

Vitamin D Reduces Aromatase Inhibitor Pain

There were a number of studies on vitamin D and breast cancer. One small, randomized clinical trial showed that high-dose vitamin D significantly reduced muscle and joint pain in breast cancer patients treated with Arimidex. After two months of weekly vitamin D supplementation, patients had significant improvement in their pain and mobility. However, the improvement began to disappear after they were switched to monthly supplementation, and it had almost completely disappeared by four to six months. Larger studies are needed to confirm these findings.



Breast SPORE Advocacy Core

By Sarah Goins, MS, Manager, Breast SPORE Advocacy Core, UCSF

The Bay Area SPORE's Advocacy Core is comprised of a dedicated group of individuals personally affected by breast cancer. The Core has been an integral part of SPORE research since its inception more than a decade ago. The Advocates have accomplished significant achievements within the program, from spurring on research endeavors, contributing to shortening the time it takes novel agents to go from bench to bedside, and inviting exemplary speakers to present at program events, such as inviting at-the-time, Netherlands Cancer Institute Investigator, Laura Van 't Veer to UCSF for a Breast SPORE/Avon sponsored conference in April 2003.

The Advocates provide enthusiasm to the program and help researchers target those areas of breast cancer science that patients are most

concerned about. Because most advocates have been patients, they offer an invaluable perspective to our researchers, junior investigators, and students. Since October of 2009, we are thrilled to have welcomed ten new advocates to our core. These new members enrich the program with their zeal and excitement to learn about the science, and their desire to have a positive impact on the scientific process. Advocates bring varied interests, levels of training, and experience in breast cancer research and survivorship, and therefore provide complimentary skills.

We are very proud of our advocates and appreciate their hard work, time and efforts, and their commitment to the SPORE program.

If you are interested in getting involved and volunteering as a SPORE Advocate, please contact Sarah Goins: sarah.goins@ucsf.edu.

The Bay Area Breast Cancer SPORE Newsletter is produced annually by the SPORE Advocacy and Tissue & Outcomes Core at UCSF.

It is mailed to all current study participants as well as breast care surgeons and oncologists at UCSF, CPMC and SFGH.

If you have questions or comments about the material printed in this newsletter, or if you would like to have additional copies sent, please call the Outcomes Office at: (415) 353-9763.

More information about SPORE and related studies, as well as archived newsletter editions, is available at:

http://cancer.ucsf.edu/breast_spore

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MammaPrint Article continued...

thousands of patients, are at least five years away, and the medical community seems to be divided about when to start using such tests in routine clinical practice. This dilemma has recently been exacerbated when the FDA cleared the first multigene assay (MammaPrint) on the basis of only retrospective validation.

An excerpt from Van 't Veer's 2002 Nature Journal article:

“Breast cancer patients with the same stage of disease can have markedly different treatment responses and overall outcome. The strongest predictors for metastases (for example, lymph node status and histological grade) fail to classify accurately breast tumors according to their clinical behavior. Chemotherapy or hormonal therapy reduces the risk of distant metastases by approximately one-third; however, 70–80% of patients receiving this treatment would have survived without it. None of the signatures of breast cancer gene expression reported to date allow for patient-tailored therapy strategies. Here we used DNA-microarray analysis on primary breast tumors of 117 young patients, and applied supervised classification to identify a gene expression signature strongly predictive of a short interval to distant metastases ('poor prognosis' signature) in patients without tumor cells in local lymph nodes at diagnosis (lymph node negative). In addition, we

established a signature that identifies tumors of *BRCA1* carriers. The poor prognosis signature consists of genes regulating cell cycle, invasion, metastasis and angiogenesis. This gene expression profile will outperform all currently used clinical parameters in predicting disease outcome. Our findings provide a strategy to select patients who would benefit from adjuvant therapy.”

References:

- 1) Van 't Veer, LJ, Bernard R. Insight Review: Enabling personalized cancer medicine through analysis of gene-expression patterns. *Nature* 2008, 452, 564-570
- 2) Van 't Veer LJ, Dai H, Van de Vijver MJ, He YD, Hart AAM, Mao M, Peterse HL, Van der Kooy K, Marton MJ, Witteveen AT, Schreiber GJ,

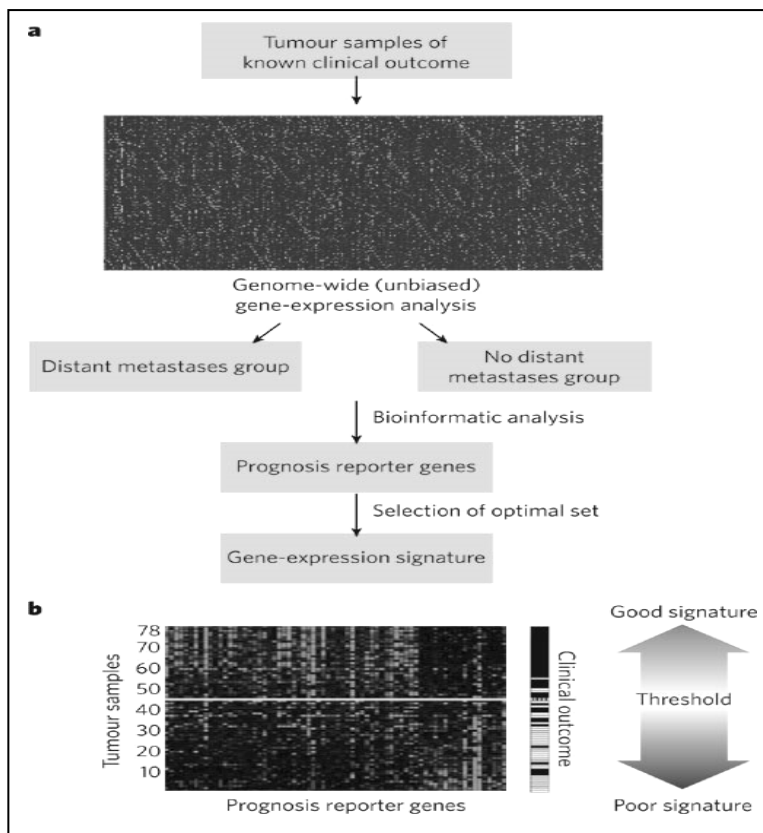
Kerkhoven RM, Roberts C, Linsley PS, Bernard R, Friend SH. Gene expression profiling predicts clinical outcome of breast cancer. *Nature* 2002; 415, 530-536

Explanation of model found below:

a, Generating a prognostic gene-expression signature by using supervised classification. The gene expression of cells in a set of tumors of known clinical outcome is analyzed by using whole-genome microarrays. Colours indicate the level of expression for each gene: red, gene is more active than the average for tumors of this type; green, gene is less active than average; yellow, gene is equally active; and, black, gene is not expressed. The results for each tumor sample are then classified into two categories: tumors with a gene-expression signature that predicts a good outcome (low

likelihood of distant metastases development), and tumors with a gene expression signature predicting poor outcome (high likelihood of distant metastases development). Using bioinformatic analysis, genes whose expression is significantly correlated with disease outcome are identified, and these are known as prognosis reporter genes. An optimal set of genes is then selected from the prognosis reporter genes by using bioinformatic algorithms, and the pattern of expression of this multigene set is known as a gene-expression signature (or classifier).

b, The gene-expression signature generated in a is shown as a 'heat map'. The expression of the 70 prognosis reporter genes (MammaPrint) selected as the optimal set (vertical columns) is shown for 78 tumors (horizontal lines). So each of the 70 x 78 intersection points of the heat map shows how a particular gene is expressed in a given tumor. A red spot indicates that the gene is expressed at a higher level than average for tumors of this type, and a green spot that the gene is expressed at a lower level. The outcome of the disease is shown on the right: white indicates metastasis; black indicates no metastasis; and yellow indicates the threshold between good (low risk) signature and poor (high risk) signature tumors. (Panel adapted)



Elizabeth Blackburn Nobel Prize Article continued....

She first looked at how much telomerase is present and how “active” it is in tumor cells. She then wanted to see if cells at different stages of cancer progression show any significant changes in telomerase levels that can be related to parameters used in diagnosis/treatment. Since increased telomerase activity is one hallmark of cancer that contributes to cancer cell immortality.

Dr. Blackburn’s SPORE project focuses on a therapeutic approach that forces cancer cells with active telomerase into making aberrant telomeres, which in turn will cause damaged surveillance

systems to activate cell death mechanisms. We hope that one day this approach will become an important cancer treatment.

Recently, Dr. Blackburn and colleagues also have looked at the possibility that life stress, the perception of life stress, and lifestyle behaviors could influence telomerase and telomeres. They have reported several studies with human participants that suggest a correlation. The findings may offer insight, at the cellular level, into the impact of stress on early onset of age-related diseases.

Dr. Blackburn’s work is of particular interest with Breast SPORE Research Advocates

who enjoy interacting with Dr. Blackburn and discussing her work. In the fall of 2009 a group of SPORE Advocates, led by Linda Vincent, held a workshop entitled: Understanding Medical Journals, where they focused their study on Dr. Blackburn’s latest publications, looking at the role stress can play on telomerase.

We are impressed with Dr. Blackburn’s momentous discoveries. Her impact on cancer research is a true reflection of the incredible work and character we’ve seen in our Breast Cancer SPORE program over the years.




Pharmacogenetics of Tamoxifen By Elad Ziv, MD, Associate Professor of Medicine, UCSF

UCSF investigators including Drs. Elad Ziv, Hope Rugo, Mary Beattie and Alan Go, are studying the “pharmacogenetics” of tamoxifen. “Pharmacogenetics” is a term that refers to how genetic variations in individuals may impact the effect of medications. There is a genetic test for a gene named CYP2D6 that affects how tamoxifen is processed by the body. CYP2D6 converts tamoxifen to a more active form of the drug, called endoxifen. Some individuals have variations in the CYP2D6 gene that decrease the processing of tamoxifen to endoxifen. Patients with genetic variations that decrease CYP2D6 activity have lower levels of endoxifen. Some studies have demonstrated that patients with genetic variations that decrease CYP2D6 activity have less benefit from tamoxifen. However, other studies have found no association between genetic variations of CYP2D6 and benefit from tamoxifen.

Thus, the use of the test prior to prescribing tamoxifen is still controversial.

The UCSF team is offering the CYP2D6 genetic test as part of a study. Prior to getting the test, women participate in an informational session about the background of the test and the data in the medical literature about the test. Participants who want to get the test can then undergo a blood test. The results are provided to the participant’s physician within several weeks. After three to four months a brief follow-up by telephone is conducted, to determine whether or not changes in therapy were made.

As part of a collaborative study with Kaiser the investigators are also testing associations between CYP2D6 genotype and breast cancer recurrence among women. In addition, the investigators will be testing additional genes that may




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have an impact on the effect of tamoxifen. The study plans to enroll 250 women and to date nearly 240 have been recruited. If you are looking to participate in this study or would like to learn more please contact Viktoriya Kovpak, CRC, at (415) 514-4983.