

PEOPLE



Michelle M. Le Beau, PhD, director of the University of Chicago Comprehensive Cancer Center (UCCCC), assumed a 2-year term as president of

the Association of American Cancer Institutes on November 1. She succeeds William S. Dalton, MD, PhD, former head of the Moffitt Cancer Center in Tampa, FL.

Representing 95 academic and independent cancer research centers in the United States, the organization educates policy leaders, major funders, and the public about the importance of cancer research.

Le Beau also directs the cancer cytogenetics laboratory at UCCCC. Her research focuses on cytogenetic abnormalities in malignant hematologic diseases, defining subsets of leukemias and lymphomas, and identifying genetic pathways that lead to myeloid leukemias.



Janis L. Abkowitz, MD, a professor of medicine and the head of the Division of Hematology at the University of Washington in Seattle, became

president of the American Society of Hematology at the organization's annual meeting this month. Serving a 1-year term, she succeeds Armand Keating, MD, a professor of medicine and director of the Division of Hematology at the University of Toronto in Canada.

Abkowitz's research interests include hematopoietic stem cells, the clonal evolution of hematologic disorders, the molecular and cellular control of erythropoiesis, and heme physiology and trafficking. Her clinical interests include marrow failure, myelodysplastic syndrome, and myeloproliferative disorders.

In addition, Abkowitz acts as an advisor to the NIH. She has also served on the editorial boards of *Blood* and *Leukemia*.

From TCGA to Treatment

After The Cancer Genome Atlas (TCGA) Research Network released a comprehensive molecular analysis of tumor samples from 825 patients with primary breast cancer, "we have to rethink everything," says Matthew Ellis, MB, BChir, PhD, director of breast oncology at Washington University in St. Louis, MO. "Breast cancers are so fundamentally different from each other that we have to rewrite the textbook on how we treat them," adds Ellis, one of the lead investigators for the TCGA study (*Nature* 2012;490: 61-70).

Integrating DNA copy number, methylation, exome sequencing, mRNA, microRNA sequencing, and proteomic data, the TCGA team uncovered numerous new significantly mutated genes and deepened our understanding of the 4 main molecular subtypes of the disease: basal-like; luminal A and luminal B, which are both estrogen receptor (ER) positive; and HER2 enriched.

One immediate clinical implication arises from the surprising finding that basal-like breast cancer bears a striking molecular resemblance to serous ovarian cancer. The discovery suggests that patients with these diseases should receive the same therapies, says Ellis. Both diseases are currently treated with a taxane, such as paclitaxel (Taxol; Bristol-Myers Squibb). In addition, patients with ovarian cancer usually receive a platinum-based therapy, but breast cancer patients typically receive an anthracycline, such as doxorubicin (Adriamycin; Pfizer), a class of drugs that can cause heart damage and leukemia, and cyclophosphamide.

Eager to avoid those side effects, and citing anecdotal evidence, some oncologists have started using platinum drugs to treat patients with basal-like breast cancer. However, "no one's done the definitive trial of platinum-based chemotherapy replacing the old-fashioned Adriamycin-cyclophosphamide combination that we use in breast cancer," notes Ellis. "That's obviously very low-hanging fruit. We absolutely must do that experiment."

Based on the TCGA results, researchers will also want to reexamine therapy for patients with ER-positive breast cancers. For these tumors, oncologists often turn to endocrine therapies such as tamoxifen or aromatase inhibitors, drugs that are initially effective. Unfortunately, many women ultimately die of the disease after they develop resistance to the drugs.

The high rate of mutations in *PIK3CA* in ER-positive disease suggests that inhibitors of this activated kinase or its pathway may be helpful, says Charles Perou, PhD, lead author of the study and a professor of genetics and pathology at the University of North Carolina at Chapel Hill. He notes that the site of the *PIK3CA* mutation may be subtype specific. For example, nearly all of the patients with the *PIK3CA* E545K mutation had the luminal A subtype, which has a better prognosis.

In addition to studying PI3K-AKT-mTOR pathway inhibitors like everolimus (Afinitor; Novartis) in patients with either the luminal A or B subtype, Ellis says TCGA data point to a role for agents that work through other mechanisms. For example, the use of MDM2 inhibitors could be a promising approach for treating wild-type TP53 luminal B tumors. Fibroblast growth factor receptor inhibitors and Smac mimetics could also be helpful. "These agents might achieve what endocrine therapy doesn't do—kill cancer cells," he notes.

The TCGA analysis also highlights the existence of at least 2 types of clinical HER2-positive tumors: One subgroup is associated with high levels of EGF receptor and HER2 protein phosphorylation, tends to be ER negative, and tends to be of the HER2-enriched mRNA subtype; the other group is associated with lower DNA amplification and protein-based signaling, tends to be ER positive, and tends to be of the luminal subtypes. That may explain why only about half of patients with HER2-positive tumors respond to trastuzumab (Herceptin; Genentech), says Perou.

"We need to look at the effectiveness of trastuzumab in patients and see if we can find a biomarker of responsiveness," he adds. ■

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