PEOPLE


Martha Stewart

Richard Van Etten, MD, PhD, began his new role as director of the Chao Family Comprehensive Cancer Center at the University of California, Irvine, on October 1. He succeeds the center's founding director, Frank Meyskens Jr., MD, and interim director, Sheldon Greenfield, MD.

Van Etten previously served as chief of the division of hematology/oncology and director of Tufts Cancer Center in Boston, MA. Internationally recognized for his research, he studies the molecular pathogenesis of leukemia, particularly dysregulated kinases such as the BCR-ABL, FGFR1, and JAK2 V617F kinases. In addition, he has an interest in oxidative stress and the role of the peroxiredoxin family of antioxidant enzymes in cell signaling.

After postgraduate training in internal medicine and hematology at Boston's Brigham and Women's Hospital, he completed a fellowship at the Whitehead Institute in Cambridge, MA.

Norman Sharpless, MD, has been appointed director of the University of North Carolina (UNC) Lineberger Comprehensive Cancer Center in Chapel Hill, effective January 1. He will succeed H. Shelton Earp, MD.

A graduate of UNC and the UNC School of Medicine, Sharpless is currently Lineberger's deputy director, Wellcome Distinguished Professor of Cancer Research, and professor of medicine and genetics. A practicing medical oncologist, he studies the role of the INK4/ARF tumor suppressor locus in human cancer and aging. In addition, he codirects UNCSeq, a large clinical trial at UNC that uses next-generation sequencing of tumor DNA to define optimal chemotherapy regimens in patients with advanced cancer.

A recipient of numerous awards, Sharpless holds 12 patents and has authored more than 100 research papers.

Avoiding Overdiagnosis and Overtreatment

A group of experts advising the National Cancer Institute recommends revising the definition of cancer and refining how cancers are detected and treated in an effort to curb overdiagnosis and overtreatment of conditions that may not be life-threatening (JAMA 2013;310:797–8).

Among the proposals is a call to no longer define indolent or low-risk lesions as cancer. Rather, the term "cancer" should be used only to describe "lesions with a reasonable likelihood of lethal progression if left untreated," the authors write.

The group says, for example, that premalignant conditions such as ductal carcinoma in situ (DCIS) or high-grade prostatic intraepithelial neoplasia should be renamed "indolent lesions of epithelial origin."

Taking the word "cancer" out of such diagnoses could lead to a more thoughtful, less frightening discussion between patients and their doctors about what to do next, says Laura Esserman, MD, lead author of the report and director of the Carol Franc Buck Breast Care Center at the University of California, San Francisco (UCSF).

When patients are told that their condition is "cancer," they tend to be much more aggressive with therapy, Esserman comments. "Treatment decisions shouldn't be made out of fear," she says.

The national push for increased cancer screening in recent decades has meant that more early-stage cancers are being found and treated. But data generally have shown that screening has not led to a drop in mortality rates. Detection and removal of precancerous colon polyps and cervical lesions are exceptions, the authors note.

"Our assumption back in the 1980s was if you found it early, you could fix the problem. But cancer is a lot more complicated than we thought," Esserman says.

The report suggests that the Institute of Medicine or another independent group convene a multidisciplinary panel made up of pathologists, imaging specialists, surgeons, oncologists, and other experts to discuss these issues.

The working group also calls for research to predict which lesions are destined for a serious outcome and which are not, and how to best confront each scenario with strategies such as active surveillance or chemoprevention.

Other recommendations include focusing screening on high-risk populations, raising the thresholds for biopsy, and creating registries for low-risk lesions. Esserman and her colleagues at UCSF plan to launch a DCIS registry in early 2014.

"I'm not saying cancer isn't serious," Esserman sums up. "I'm saying it's time for us to start focusing our interventions on the things that are lethal." ■

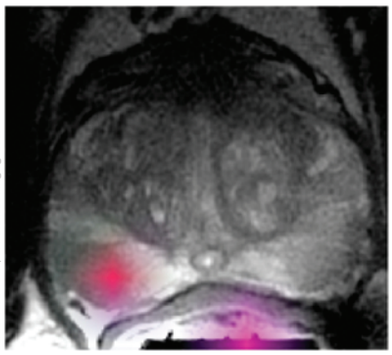
Metabolic Imaging Points Out Prostate Cancers

The first clinical trial of imaging tumor metabolism using hyperpolarized MRI shows that the technique is safe in humans and can highlight differences in how normal and cancerous prostate tissues metabolize sugars (Sci Transl Med 2013:198,198ra108). If confirmed in further studies, the approach may provide a noninvasive way to analyze the aggressiveness of prostate tumors and monitor response to therapy.

"We know that metabolism is a good way to assess the aggressiveness of a tumor," says Sarah Nelson, PhD, a professor of radiology at the University of California, San Francisco (UCSF), and lead author on the paper. Tumor tissue has a different metabolism from healthy tissue and tends to convert the sugar pyruvate into lactate rather than into other metabolites, she explains. This conversion is more pronounced in more-aggressive tumors.

The effect is invisible in conventional imaging scans but can be observed by MRI with a special contrast agent treated to generate a hyperpolarized spin state in a carbon-13 nucleus in pyruvate. This results in a 10,000-fold enhancement in image contrast relative to conventional MRI.

While hyperpolarized pyruvate has been used to image abnormal metabolism in tumors in animals, it hasn't been safe to use in humans. The agent can be created only at temperatures nearing absolute zero—much too cold



Surbeck Laboratory of Advanced Imaging, UCSF

In this hyperpolarized MRI image of early-stage human prostate cancer, the bright color on the left side shows an area of elevated lactate, indicating cancerous tissue, which corresponds to a region of biopsy-proven cancer. The color to the right is not from prostate tissue but from blood vessels surrounding the rectum.

to inject into the human body—and must be warmed and injected quickly because its half-life is only about 60 seconds.

Nelson's group at UCSF developed a way to rapidly filter and warm the hyperpolarized pyruvate so that it can be injected in an arm within 66 seconds, with observable uptake following within 20 seconds. The group also designed special pulse sequences for the MRI scanner, and coils to create the pulses.

The researchers and their colleagues tested the safety of the agent in a clinical trial of 31 men with biopsy-proven early-stage prostate cancer. They found no dose-limiting toxicity. Areas known to be cancerous had higher levels of lactate relative to pyruvate than normal tissues, and in some cases cancer was identified in regions where it had not been seen by other imaging methods.

With the current widespread use of prostate-specific antigen blood tests, "a lot of men are getting a diagnosis of cancer, and we don't know if it's going to be aggressive or benign," says Nelson. She hopes that metabolic imaging will help doctors make better treatment decisions and monitor therapeutic responses.

Robert Gillies, PhD, vice-chair of radiology and director of imaging research at the Moffitt Cancer Center in Tampa, FL, is excited to see hyperpolarized MRI in human studies. "We can follow not only where these substrates go but what they get turned into, and measure the flux of metabolic reactions in real time," he says. Gillies adds that the technology allows more extended tracing of metabolites over time than does positron emission tomography (a common tool for imaging tumors) and is likely to be less expensive. ■

FDA Gives Drug Codevelopment Guidance

As drug combinations play a steadily increasing role in cancer treatment, the U.S. Food and Drug Administration (FDA) is encouraging the development of investigational agents that will be used only as part of a novel combination, even if the agents show minimal efficacy on their own.

In one example of the promise of such combinations, researchers from Massachusetts General Hospital in Boston and Wellcome Trust Sanger Institute in Hinxton, UK, reported in March that the BH3 mimetic ABT-737 and the deacetylase inhibitor vorinostat (Zolinza; Merck), when combined, synergized to kill squamous cell carcinoma (SCC) cells *in vitro* and dramatically shrank established SCCs *in vivo* (Cancer Discov 2013;3:324–37). The findings support the idea of testing the combination in patients with head and neck SSC (HNSCC), a disease with poor overall survival.

Although vorinostat is approved for cutaneous T-cell lymphoma, a related commentary noted that both drugs "are likely to fail (or have already failed) in single-agent trials in HNSCC. Only the combination therapy is expected to show benefit. However, it is very difficult to initiate a clinical trial using two failed therapeutics" (Cancer Discov 2013;3:258–9).

In June, the FDA issued a guidance document, "Codevelopment of Two or More New Investigational Drugs for Use in Combination," that should help create a smoother clinical-trials process for such novel therapies.

Codevelopment is the concurrent development of multiple drug products intended only to be used together and not as monotherapies. It might be an appropriate option if, for example, therapy with one of the agents rapidly leads to drug resistance, or if the agents are likely to have limited efficacy when used alone, making their individual approval unlikely, the document notes.

One goal of the guidance document is to "address general uncertainty in industry about how the existing regulatory paradigm for single-agent development would apply to development of a novel combination," says Stephen King, an FDA spokesperson. He adds that there are also concerns that current FDA regulations "would be an impediment to development of combinations of novel agents where it may not be possible to extensively study and characterize the activity of individual components of the combination in clinical trials. The guidance is intended to signal that there is flexibility in the amount and types of data that could be relied on to demonstrate the contributions of the components."

According to the guidance document, codevelopment may be appropriate if these criteria are met:

- The combination is intended to treat a serious disease or condition.
- There is a strong biologic rationale for the use of the combination.
- A full nonclinical characterization of the activity of the combination and the individual drugs suggests that the combination may provide a significant advance over available therapies and is superior to the individual agents.
- There is a compelling reason why the new drugs cannot be developed independently.

Although industry has shown some interest in the codevelopment of drugs for use in oncology, infectious diseases, and other specialties, no codeveloped drug combinations have been approved yet, says King.

Given the financial risk of developing drugs for use in a combination when they show minimal efficacy as single agents, codevelopment is "virtually unnavigated" by industry, says Fadlo R. Khuri, MD, deputy director of the Winship Cancer Institute of Emory University in Atlanta, GA, and codirector of its Cancer Discovery and Developmental Therapeutics Program.

"I can't overstate how important it is that the FDA put out this document and supports this approach," Khuri