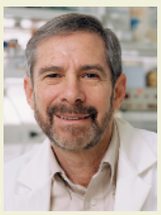
PEOPLE

Paul Workman, PhD, was named chief executive and president of the Institute of Cancer Research (ICR) in November, replacing Alan Ashworth, PhD. Workman was previously the ICR's deputy chief executive and director of the Cancer Research UK Cancer Therapeutics Unit. In addition, he has worked as an academic researcher at the Universities of Cambridge and Glasgow in the UK, and at Stanford University in the United States.

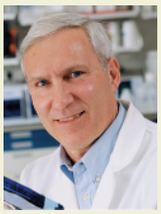
Through the ICR's new Centre for Evolution and Cancer, Workman aims to outpace cancer evolution and drug resistance by discovering drugs that act on currently untargeted cancer proteins; finding and implementing the best drug combinations; and developing drugs that tackle more than one signaling pathway.

President Barack Obama awarded the National Medal of Technology and Innovation, bestowed upon "visionary thinkers whose creativity and intellect have made a lasting impact on the United States and its workforce," to nine scientists and inventors, including two from the NCI, late last fall.



NCI

Douglas R. Lowy, MD



NCI

John T. Schiller, PhD

Douglas R. Lowy, MD, chief of the Laboratory of Cellular Oncology, and **John T. Schiller, PhD,** deputy chief of the Laboratory of Cellular Oncology, were recognized for their research on the human papillomavirus (HPV). Together, they studied the life cycle of HPV and led the initial development of the prophylactic vaccines that laid the groundwork for the subsequent development of the commercial HPV vaccines Cervarix (GlaxoSmithKline) and Gardasil (Merck). The vaccines protect against the HPV types that cause nearly all cervical cancers.

Two Drugs Beat Back Lung Tumors

Two new EGFR-blocking drugs shrink lung tumors that have developed resistance to standard therapy with tyrosine kinase inhibitors (TKI), according to a pair of new studies.

TKIs such as erlotinib (Tarceva; Genentech) are first-line therapies for patients with metastatic non–small cell lung cancer (NSCLC) whose tumors have certain *EGFR* mutations. However, the tumors usually become resistant to these therapies, often due to the T790M mutation. Erlotinib and related drugs obstruct EGFR's ATP-binding pocket, but the T790M mutation prevents the drugs from interacting with the pocket, allowing cancer cells to continue growing.

At the recent 2014 Symposium on Molecular Targets and Cancer Therapeutics in Barcelona, Spain, sponsored by the European Organization for Research and Treatment of Cancer, the NCI, and the American Association for Cancer Research, two research groups presented evidence on the effectiveness of separate investigational drugs that can bind to and inactivate EGFR despite the T790M mutation.

In a phase I/II trial, Jean-Charles Soria, MD, PhD, of the Institut Gustave Roussy in France, and colleagues in Europe, Australia, and the United States tested the EGFR inhibitor rociletinib (CO-1686; Clovis Oncology), which inhibits activated EGFR with or without the T790M resistance mutation. The researchers enrolled 193 patients with NSCLC, who had received three prior therapies on average, in the ongoing trial.

Among the 27 rociletinib-treated patients who received optimal doses of the drug and for whom the team had CT scan results, 18 had a confirmed response to the drug; the median progression-free survival was 10.4 months.

"Sixty-seven percent activity lasting nearly a year is very good," says Soria, who presented the group's findings. In some patients, the drug triggered high blood glucose levels, which were controlled with the diabetes drug metformin.

Several other studies of rociletinib are under way, including a phase III trial comparing it to chemotherapy.

The second group, led by Haruyasu Murakami, MD, PhD, of the Shizuoka Cancer Center in Japan, reported results from a phase I trial of another drug, ASP8273 (Astellas Pharma), that also inhibits mutant EGFR. So far, 31 patients with NSCLC, all of whom received prior therapy with a TKI, have been enrolled in the trial.

The researchers found that tumors shrank in 7 of the 9 patients who had both the EGFR and T790M mutations. Although the drug spurred gastrointestinal symptoms such as diarrhea and nausea, it didn't lead to high blood sugar.

"Although the number of patients is still small, ASP8273 would be expected to have clinical benefits," says Murakami, adding that phase II trials of the drug are being planned.

Two other drugs that are effective against EGFR harboring the T790M mutation, AZD9291 (AstraZeneca) and HM61713 (Hanmi Pharmaceutical), have also shown promise in patients with NSCLC in phase I and phase I/II clinical trials. ■

Pembrolizumab Shows Potential in Breast Cancer

With no approved targeted agents for triple-negative breast cancer (TNBC), women diagnosed with this disease have few treatment options besides chemotherapy. However, the immune checkpoint inhibitor pembrolizumab (Keytruda; Merck) may be effective in some patients, according to a report from the 2014 San Antonio Breast Cancer Symposium (SABCS) in San Antonio, TX, December 9–13.

By binding to the PD-1 receptor and blocking its ligands, PD-L1 and PD-L2, pembrolizumab—approved by the FDA in September for advanced melanoma—prevents tumor cells from using this pathway to escape immune surveillance.

In the phase Ib study presented at SABCS, 18.5% of 27 evaluable patients responded to pembrolizumab, "an encouraging signal that's worthy of

Rita Nanda, MD, presents findings of a study on the use of pembrolizumab for the treatment of triple-negative breast cancer at the San Antonio Breast Cancer Symposium.

further evaluation," said principal investigator Rita Nanda, MD, associate director of the Breast Medical Oncology program at the University of Chicago. All participants had advanced TNBC and were PD-L1–positive; most had previously received and progressed on multiple lines of therapy. One patient achieved a complete response to pembrolizumab, four had partial responses, and seven saw their disease stabilize.

The median progression-free survival was just under 2 months. Three patients remained on pembrolizumab for at least 11 months, which "speaks to the response durability," Nanda said. Although one patient died of treatment-related disseminated intravascular coagulation, pembrolizumab's main side effects—including low-grade joint and muscle pain, fatigue, and nausea—were largely well-tolerated, Nanda added.

Oncologists are optimistic about the use of pembrolizumab for TNBC, an aggressive, difficult-to-treat disease. "When it comes to harnessing the immune system in breast cancer, we've just started scratching the surface," said Jennifer Litton, MD, director of the Breast Medical Oncology Education program at The MD Anderson Cancer Center in Houston, TX. "This disease, intrinsically, is not like melanoma and other cancers that have higher immune infiltrates."

Edith Perez, MD, deputy director at large for the Mayo Clinic Cancer Center, agreed. "Breast cancer has not typically been considered targetable with immunotherapy," she said, "so it's gratifying to have proof-of-principle data showing a glimpse of [pembrolizumab] activity in patients with refractory disease."

Nanda noted that "the degree of PD-L1 positivity and response [to pembrolizumab] didn't appear to correlate, so PD-L1 alone may not be the most appropriate biomarker." Research is under way to investigate the relationship between outcome and PD-L2 expression, and a phase II trial to further evaluate pembrolizumab in TNBC will begin enrolling patients in the first half of 2015.

"This was a small study," said Eric Winer, MD, director of Dana-Farber Cancer Institute's Breast Oncology Center in Boston, MA, "but the fact that a handful of patients responded durably to pembrolizumab is a signal saying, 'Look into this further,' which is where the next study, and the one after that, should go." ■

Somatic Mutations May Predict Blood Cancers

Two teams of researchers independently discovered that somatic mutations in the DNA of peripheral blood cells associate with an individual's risk of developing hematologic cancers later in life.

In both studies, researchers conducted whole-exome sequencing of DNA in blood samples taken from individuals not known to have cancer or blood disorders. They found that more than 10% of individuals over age 70 carried somatic mutations common in hematologic cancers, resulting in an overall 5% risk of a cancer diagnosis within 5 to 10 years. Most of the mutations occurred in three genes recognized as drivers of blood cancers: *DNMT3A*, *ASXL1*, and *TET2*.

One study, led by Siddhartha Jaiswal, MD, PhD, clinical fellow at Massachusetts General Hospital in Boston, analyzed more than 17,000 DNA samples from patients enrolled in type 2 diabetes and heart disease studies to determine whether it is possible to detect early somatic mutations that may initiate hematologic cancers (N Engl J Med 2014;371:2488–98).

"*DNMT3A*, *ASXL1*, and *TET2* seem to be initiators of malignant progression," says Jaiswal, who presented his team's findings last month at the American Society of Hematology Annual Meeting in San Francisco. The findings corroborate earlier studies in mouse models, he says, which show that loss of *TET2* or *DNMT3A* results in an increase in blood stem cells and a selective growth advantage.

After a median follow-up period of 8 years, Jaiswal's group assessed DNA samples and found that carrying a mutation was also associated with all-cause mortality.

"We found that individuals with mutations were about 40% more likely to die in the follow-up period, and the causes extended beyond cancer to cardiovascular disease," says Jaiswal. "When we looked deeper, we found that people with the mutations were 2 to 2.5 times more likely to have cardiovascular events than people without the mutations."

A second study, led by Giulio Genovese, PhD, a computational biologist at the Broad Institute of MIT and Harvard in Cambridge, MA, set out to examine somatic mutations that may contribute to risk for schizophrenia using a database of DNA samples from more than 12,000 people, about half of whom had schizophrenia or bipolar disorder; the rest served as controls (N Engl J Med 2014;371:2477–87).

After realizing that somatic mutations were concentrated in cancer genes, Genovese's team examined patients' medical histories and found that those with the mutations had a higher risk of blood cancer than healthy controls. They detected the somatic mutations in 42% of study participants who were diagnosed with a blood cancer more than 6 months after the DNA samples were taken.

Researchers emphasize that it is premature to screen otherwise healthy people for premalignant somatic mutations, because the absolute risk of progressing to cancer is very low, and there is no way to prevent the development of cancer. However, the studies may have immediate implications for cancer diagnostics.

"When you suspect someone might have a malignancy like myelodysplastic syndrome, screening for these mutations can have negative predictive value," says Jaiswal. "However, the