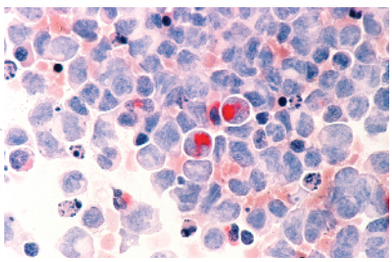

Researchers have identified ancestral pre-leukemic hematopoietic stem cells that may give rise to acute myeloid leukemia, shown here.

mutations, but not the *NPM1c* mutation. The presence of the *DNMT3A* mutations in both T cells, which are of the lymphoid lineage, and AML cells, of the myeloid lineage, coupled with the lack of the *NPM1c* mutation in T cells, led the researchers to theorize that the *DNMT3A* mutations were cancer drivers in ancestral HSCs that give rise to both lineages.

Further studies confirmed that suggestion, as they identified HSCs with *DNMT3A* mutations but without *NPM1c* mutations. *DNMT3A* mutations were also identified in HSCs in blood from patients who had already undergone chemotherapy—including patients in remission and those whose disease had recurred.

Researchers are already investigating DNMT3A as a target for therapy, but a drug can't come fast enough for patients who've already been diagnosed.

"The patients we need to follow are those in remission, because the recurrence rate is very high," Dick says. "In patients with these pre-leukemic cells, we want to know, what's the risk the disease will recur? We're working hard to answer that question." ■

Teaming Up to Engage the Immune System

Several of the biggest drug companies in the world have announced a collaborative effort to make the most of Merck's anti–PD-1 antibody MK-3475 by studying it alongside treatments of their own.

Pfizer has agreed to test MK-3475 in combination with its monoclonal anti-CD137 antibody PF-2566, which it hopes will further amplify the immune response, and, separately, with the targeted kinase inhibitor axitinib (Inlyta), aimed at VEGF receptors 1, 2, and 3, to optimize effectiveness in renal cell carcinoma. Amgen will test the drug with its oncolytic virus talimogene laherparepvec (OncoVex) in patients with previously untreated advanced melanoma; and Incyte will test it alongside its immunotherapy agent INCB24360, an indoleamine 2,3-dioxygenase inhibitor, in patients with metastatic and recurrent non–small cell lung cancer, among others. All the studies are phase I/II.

Glenn Dranoff, MD, a cancer immunologist at Dana-Farber Cancer Institute (DFCI) and Harvard Medical School, both in Boston, MA, and co-leader of the Cancer Vaccine Center at DFCI, says there's convincing preclinical data to suggest that all of these combinations are worth trying.

Although Merck continues to test MK-3475 as a monotherapy against late-stage tumor types, there is little doubt in the industry that combination therapy is the way forward. Because tumors are adept at escaping the immune system, combination therapies have the potential "to elicit much stronger responses," says Dranoff.

Competition in the cancer immunotherapy field is great, and companies are rushing to identify and market the best combinations first.

"Time is of the essence given the number of companies that have independent programs and the indication that immunotherapies are active across a range of tumor types," adds Dranoff.

Like other immune therapies, MK-3475 combats a tumor's ability to evade the immune system. By blocking PD-1, it essentially releases a brake on the immune system, enabling the activation of T-cells to target the cancer.

David Mauro, MD, executive director of clinical oncology at Merck Research Laboratories in Upper Gwynedd, PA, says his company hopes that the testing will help expand MK-3475 into tumors where it hasn't worked as a monotherapy. Merck was less concerned, he says, about finding both parts of the combination in-house.

"What we wanted to do was pull together a portfolio of combinations that made sense regardless of whether they were internal compounds or with other companies," explains Mauro.

Financial terms of the collaboration were not disclosed, but Mauro notes that it was surprisingly easy for the companies to reach mutually acceptable deals. "I've been in the business for a while, and I've never seen companies willing to work together so easily," he says. "There's less the spirit of competitiveness and much greater spirit of collaboration."

Mace Rothenberg, MD, senior vice president of clinical development and medical affairs of Pfizer in New York, NY, says the deal simply made sense.

"We are exploring opportunities to evaluate our assets in combinations where there is strong scientific rationale and in a variety of tumor types," explains Rothenberg. "We are prioritizing these opportunities based on unmet need, insight into cancer genomics, promising preclinical data, and/or early signs of clinical activity." ■

CT Scans Predict Response to Cancer Therapy

Computed tomography (CT) may help researchers predict which patients are likely to respond to treatment and lead to more-effective delivery methods, a recent study has found.

The study, published in the April issue of the *Journal of Clinical Investigation*, tests the hypothesis that the dense stroma surrounding pancreatic tumors prevents effective delivery of chemotherapy into cancer cells, leading to poor clinical outcomes (J Clin Invest 2014;124:1525–36). Investigators enrolled 12 patients with primary pancreatic cancer who received gemcitabine (Gemzar; Eli Lilly) during surgical resection and analyzed their tumors after surgery to assess drug penetration.

"This is the first study in humans where we've been able to measure if chemotherapy given intravenously is actually getting into a pancreatic cancer tumor and performing its function," says Jason Fleming, MD, professor of surgical oncology at The University of Texas MD Anderson Cancer Center in Houston and the study's corresponding author. "We found that delivery of gemcitabine into the tumors was much more variable than previously thought."

By analyzing tumor DNA, the researchers found that the variability was tied to expression of the protein

hENT1, which has been shown to facilitate transport of gemcitabine across the cell membrane. Drug penetration was lowest in patients with dense, fibrotic tumors and low hENT1, and those patients also had the poorest responses to therapy.

The researchers then analyzed CT scans from 110 patients who had previously received presurgical gemcitabine-based chemoradiation. They noted a correlation between the absorption patterns of the dye used in CT scans and clinical outcome, suggesting a possible method for predicting the effectiveness of therapy.

"The IV dye used in CT scans acts as a surrogate for the chemotherapy that you would give intravenously. Knowing this, we could use the CT scan as a predictive study that could tell us which patients would respond poorly to therapy so we could hopefully use other drugs to modify that delivery," explains Fleming. "For example, you could assess the hENT1 expression status and collagen density of the tumor, combined with imaging data, to get a profile of the expected efficacy of IV therapies in an individual patient."

A patient predicted to respond poorly to chemotherapy, based on data from a CT scan and a biopsy, says Fleming, might receive a drug prior to chemotherapy that might alter the tumor's blood vessels [such as the hypertension drug losartan (Cozaar; Merck)] to improve delivery of chemotherapy.

Preliminary data suggest that using imaging to predict responses to therapy may be effective for other types of solid tumors, says Fleming. ■

E-cigarettes Linked to Smoking among Teens

Electronic cigarettes, or e-cigarettes, are often promoted as smoking cessation aids, but among teens they may increase the likelihood of smoking conventional cigarettes, according to a new cross-sectional study reported in March (JAMA Pediatr 2014 Mar 6 [Epub ahead of print]).

E-cigarettes deliver nicotine-containing vapor without many of the toxins found in conventional cigarettes. Their use has climbed rapidly in recent years, particularly among adolescents, according to the National Youth Tobacco Survey, designed by the Centers for Disease Control and Prevention (CDC) to assess smoking behavior among youth. In 2011, 4.7% of high-school students who responded to the survey reported trying e-cigarettes; in 2012, that number rose to 10%.

Lauren Dutra, ScD, and Stanton A. Glantz, PhD, of the Center for Tobacco Research and Education at the University of California, San Francisco, analyzed survey answers from the CDC's national survey of teens who had ever experimented with cigarettes to better understand the connection between e-cigarette use and conventional smoking.

They reported that adolescents who had puffed on an e-cigarette were nearly eight times as likely to smoke conventional cigarettes as peers who had never tried one. In addition, teens who had never used e-cigarettes were three times as likely to have gone a year without smoking conventional cigarettes as those who had.

On the other hand, teenage smokers who used e-cigarettes were one and a half times as likely to intend to quit in the next year, compared with those who didn't use e-cigarettes, suggesting that youth may be trying to quit using these devices. However, the survey did not include data on quit attempts.

Dutra points out that their study is based on data from the 2011 and 2012 surveys, and the e-cigarette landscape has changed dramatically in the last 2 years.

"Many products have popped up since then," Dutra says. These new products, with names like hookah pens or vape pens, are often flavored to taste like fruit or candy and represent manufacturers' attempts to market to kids and teens while steering clear of the term "cigarette." They're also likely causing a further uptick in the market. "I certainly think it's likely that the numbers we saw for e-cigarette use were underestimated," Dutra adds.

Because cross-sectional studies show only a snapshot of behavior at a given time, "we need longitudinal data to see if kids are starting with e-cigarettes and moving on to conventional cigarettes or not," she says. ■

NOTED

- **President Obama released his budget proposal for fiscal year (FY) 2015, which recommends $30.2 billion for the NIH,** a $300 million increase over the current funding level of $29.9 billion; the National Cancer Institute would receive a $2 million increase, bringing its budget to $4.931 billion. Even with the proposed increases, however, these amounts fall short of FY 2012 budgets.
- **Attorneys general from 28 states and territories sent letters to five of America's largest retail chains, encouraging them to stop selling tobacco products in stores that have a pharmacy.** Kroger, Rite Aid, Safeway, Walgreens, and Walmart were asked to consider following the example set by CVS Caremark, which announced in February that it will stop selling tobacco in its stores by October 1.
- **The U.S. District Court for the District of Utah denied a request from Salt Lake City's Myriad Genetics and other patent holders for a preliminary injunction against Ambry Genetics** to prevent it from selling tests to assess *BRCA1* and *BRCA2* mutations. Myriad filed suit against Ambry, of Aliso Viejo, CA, in July 2013, alleging that Ambry's tests infringed on patent claims that were not invalidated when the U.S. Supreme Court ruled in June that genes cannot be patented because they are products of nature. Ambry can continue to offer its *BRCA* tests pending the lawsuit's outcome.
- **The American Society of Clinical Oncology issued a comprehensive report on the cancer-related challenges facing the U.S. medical system.** *The State of Cancer Care in America: 2014* estimates that, due to an aging population, the number of cancer cases will increase by as much as 42% by 2025 while the number of oncologists will likely grow by just 28%, creating a shortage of nearly 1,500 doctors. In addition, the cost of cancer care, the report says, is likely to increase by 40% between 2010 and 2020.
- **The European Parliament approved new rules to ban advertising for e-cigarettes beginning in mid-2016.** E-cigarettes would also be required to carry graphic health warnings on their packaging, limit nicotine content, and be childproof.

For more news on cancer research, visit *Cancer Discovery* online at http://CDnews.aacrjournals.org.