

## PEOPLE



**Douglas Hanahan, PhD**, director of the Swiss Institute for Experimental Cancer Research in Lausanne, received the American Association for Cancer Research

(AACR) Award for Lifetime Achievement in Cancer Research in April at the organization's Annual Meeting in San Diego, CA. The award honors his pioneering and lasting contributions to the cancer research community, such as the development of one of the first transgenic mouse models of cancer. In addition, Hanahan has made groundbreaking contributions to the understanding of autoimmunity and tumor microenvironment, and helped establish the field of tumor angiogenesis.



**Webster K. Cavenee, PhD**, director of the Ludwig Institute for Cancer Research in San Diego and distinguished professor at the University of

California, San Diego, received the AACR Margaret Foti Award for Leadership and Extraordinary Achievements in Cancer Research. Cavenee's pioneering work in retinoblastoma provided indisputable evidence for the existence of tumor suppressor genes in humans. He has also made key contributions to understanding the biology of glioblastoma multiforme, illuminating the molecular mechanisms that drive the growth, migration, and survival of tumor cells and identifying potential new therapies for the disease.



**Boris Pasche, MD, PhD**, began his new position as director of the Comprehensive Cancer Center at Wake Forest Baptist Medical Center in Winston-Salem, NC,

on March 1. Prior to joining Wake Forest, he was a professor of medicine and served as director of the division of hematology/oncology at the University of Alabama Birmingham. As a researcher, he has focused on the role of the TGF- $\beta$  pathway in cancer development and progression.

## Technique Helps Target microRNA

Researchers at The Scripps Research Institute's (TSRI) Jupiter, FL, campus have successfully used a drug-discovery technique based on human sequence data to identify a lead drug compound that selectively targets RNA associated with cancer.

"For the first time, we've been able to take the products of genetic material and, in a rational way, design small molecules that precisely target a cancer-associated microRNA," says Matthew Disney, PhD, associate professor at TSRI and lead author of the study, reported online in February (*Nat Chem Biol* 2014;10:291-7).

Disney's team developed a technique, dubbed Inforna, to identify therapeutic small molecules based on RNA sequence information. Then, in the current study, they screened millions of potential precursor microRNA-drug interactions and designed 27 compounds that target disease-associated microRNAs.

The most active interaction was between the compound benzimidazole, which has antiparasitic and antifungal properties, and microRNA-96, which represses the forkhead family transcription factor FOXO1, inhibits apoptosis, and is associated with metastatic breast cancer, Disney says. Benzimidazole upregulated FOXO1 in cancer cells and induced apoptosis.

"The selectivity of the small molecule was very surprising to us," says Disney. "Known chemotherapy drugs like cisplatin [Platinol-AQ; Bristol-Myers Squibb] and chlorambucil [Leukeran; Aspen Global] often act indiscriminately on healthy and diseased cells and don't target biomolecules specific to cancer, whereas this molecule appeared to be very selective for a microRNA that is contributing to cancer."

The next step for researchers is testing the efficacy of microRNA-targeting compounds in animal models, Disney says.

The current method of targeting microRNAs is to use oligonucleotides, which generally are not cell permeable and may cause nonspecific immune effects, says Disney. The Inforna technique may allow identification of

small-molecule lead compounds that specifically target disease-associated RNAs without the disadvantages of oligonucleotides.

The Inforna technique has far-reaching implications, Disney says, and could lead to new drugs targeting any disease-associated RNA molecule.

"In the case of a hepatitis or human immunodeficiency virus that's resistant to chemotherapeutics, potentially you could use Inforna to design small molecules that specifically target and modulate mutated viral RNAs to be a potential therapy," he explains.

"We're trying to broadly use this as a technological platform where one could target any RNA from sequence," he continues. "That could allow us to make a chemical probe to help study the function of these RNAs." ■

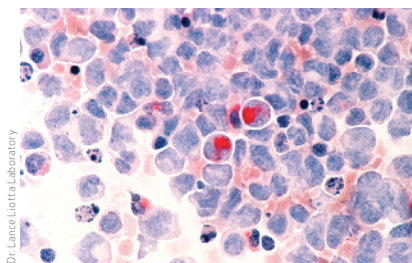
## Researchers Identify Stem Cell Origin of AML

For most patients with acute myeloid leukemia (AML), the disease seems to arise suddenly, with no previous indication, raising questions about its origin and evolution. Researchers have now identified ancestral pre-leukemic hematopoietic stem cells (HSC) that may give rise to the disease.

These ancestral stem cells are present at diagnosis, can survive chemotherapy, and persist in the bone marrow, potentially leading to disease recurrence, according to a report published in February (*Nature* 2014;506:328-33). These observations may lead to the identification of pre-leukemic HSCs in healthy individuals, and the HSCs may be viable targets for intervention.

John E. Dick, PhD, a researcher at the Princess Margaret Cancer Centre in Toronto and the University of Toronto in Canada, and his colleagues sequenced 103 commonly mutated leukemia genes in 83 patients. In roughly 25% of the samples, they identified mutations in the *DNMT3A* gene in the AML cells. The researchers found another well-known leukemia mutation in *NPM1c*, which occurred in 88% of the samples that carried mutations in *DNMT3A*.

However, the analysis turned up an unexpected surprise: T cells in 15 patients also contained the *DNMT3A*



Dr. Leland Lentz, Laboratory

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