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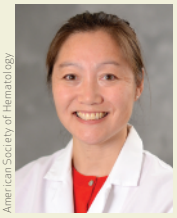
American Society of Hematology

Stephanie Lee, MD, MPH, began a 1-year term as president of the American Society of Hematology (ASH) this month at the organization's 2019 Annual Meeting in Orlando, FL. She is a professor of oncology and medicine at the University of Washington and a member of the Fred Hutchinson Cancer Research Center in Seattle. Lee is also the research director of the Fred Hutchinson Long-Term Follow-Up Program, which tracks patients after bone-marrow or stem-cell transplants. Her research focuses on developing better ways to prevent, diagnose, and treat graft-versus-host disease.


American Society of Hematology

Also at the ASH meeting, **Richard A. Larson, MD,** professor of medicine and director of the Hematologic Malignancies Clinical Research Program at the University of Chicago in Illinois, won the Henry Stratton Medal for Clinical/Translational Research. His work has centered on understanding the genetic basis of leukemia and developing new therapies. As chair of what is now the Alliance for Clinical Trials in Oncology, Larson oversaw numerous leukemia trials. Larson has also served on the editorial boards of several journals.

MCLA-128 Fights *NRG1* Fusion–Positive Cancers

Three patients harboring *NRG1* fusions—two with pancreatic cancer and one with lung cancer—exhibited tumor shrinkage and improvement in symptoms when treated with Merus's bispecific antibody MCLA-128 (zenocutuzumab) in a clinical proof-of-concept study. Researchers reported the results at the 2019 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics in Boston, MA, October 26–30.

NRG1 fusions occur in less than 1% of cancers overall, but they are "enriched in diseases in desperate need of better therapy," such as *KRAS*–wild-type pancreatic ductal adenocarcinomas (PDAC) and invasive mucinous lung adenocarcinomas, said Alison Schram, MD, of Memorial Sloan Kettering Cancer Center (MSKCC) in New York, NY, who presented the findings. Directed against HER2 and HER3, MCLA-128 docks on HER2 and blocks NRG1-fusion binding to HER3, preventing downstream PI3K–AKT–mTOR signaling and inhibiting tumor-cell proliferation. It also engages the immune system by enhancing antibody-dependent cellular cytotoxicity.

Preclinical testing of MCLA-128 demonstrated its effectiveness in ovarian and breast cancer models harboring various NRG1 fusions, including *CLU–NRG1*, *TNFRSF10B–NRG1,* and *DOC4–NRG1* (Cancer Discov 2018;8:686–95).

Schram reported on three men who received MCLA-128 as part of an expanded access protocol. Two of them had *KRAS*–wild-type PDAC and had previously received chemotherapy, but the disease progressed. DNA sequencing revealed that they had *ATP1B1–NRG1* fusions, so they opted for MCLA-128.

The first patient experienced a partial response: Imaging showed a 54% reduction in tumor diameter after 5 months, and levels of CA 19-9, a biomarker for pancreatic cancer, decreased from 262 units/mL to 50 units/mL. (A normal level is less than 40 units/mL.) In addition, Schram noted that he regained weight and had improved quality of life. The second patient experienced stable disease, with a 25% reduction in tumor diameter; his CA 19-9 level dropped from 418 units/mL to 11 units/mL.

"Both patients remain on treatment 7-plus months into therapy and are tolerating it extremely well, with improvement in both disease-related symptoms and resolution of chemotherapy-associated toxicity," reported Schram.

The third patient had been diagnosed with non–small cell lung cancer (NSCLC). He received several chemotherapies and the HER2 inhibitor afatinib (Gilotrif; Boehringer Ingelheim), but the disease progressed. After DNA sequencing uncovered a *CD74–NRG1* fusion, he tried MCLA-128. He experienced a partial response, with a 41% decrease in tumor diameter after 4 months and improvement in brain metastases. He remains on treatment.

Research presented at earlier medical meetings found that less than 5% of 117 patients experienced grade 3 or 4 toxicity. Most side effects were mild, with diarrhea, weakness, fatigue, and nausea being the most common. None of the three patients with *NRG1* fusions treated at MSKCC experienced adverse events greater than grade 2.

The biggest limitation of the MSKCC research is the small number of patients. Although the researchers had identified 29 patients whose tumors carried *NRG1* fusions, several died before therapy could begin, and several more had localized disease and weren't eligible to receive the drug. However, based on their experience treating the three patients, researchers have launched a phase II basket trial of MCLA-128 in patients with *NRG1* fusion–positive PDAC, NSCLC, and other solid tumors. "We feel that this is a novel paradigm for targeting these rare genomic alterations," said Schram.

–Suzanne Rose ■

Trio Wins Nobel for Hypoxia Discoveries

Three scientists—William G. Kaelin Jr., MD, of Dana-Farber/Harvard Cancer Center in Boston, MA; Sir Peter J. Ratcliffe, MD, of the University of Oxford and the Francis Crick Institute in the UK; and Gregg L. Semenza, MD, PhD, of Johns Hopkins University School of Medicine in Baltimore, MD—won this year's Nobel Prize in Physiology or Medicine for their research elucidating how cells sense and adapt to changing oxygen levels—work that not only is fundamental to biology, but also has clinical applications for a range of diseases, including cancer.

"This is really a textbook finding," said Randall Johnson, PhD, of the University of Cambridge in the UK, who is a member of the Nobel Assembly. "This is one of the most basic mechanisms a cell has to adapt to its environment—to be able to counteract whatever oxygen levels it's encountering and … metabolically adjust to them."

William Kaelin Jr., Sir Peter Ratcliffe, and Gregg Semenza (from left to right) won the 2019 Nobel Prize in Physiology or Medicine.

Scientists have long known that hypoxia triggers increased production of erythropoietin, which leads to the formation of more oxygen-toting red blood cells. However, it took the trio of Nobel Laureates, working independently, to untangle the molecular mechanism behind this physiologic response—an effort that also earned them a Lasker Award in 2016 (Cancer Discov 2016;6:1200–1).

Conducting complementary research, the researchers determined that this mechanism centers on the HIF1 protein complex—composed of HIF1α and ARNT/HIF1β—that increases erythropoietin production when it binds to DNA segments near the erythropoietin gene. At normal oxygen levels, hydroxyl groups are added to HIF1α, which allows a complex consisting of the von Hippel-Lindau (VHL) protein, produced by the tumor suppressor *VHL*, to recognize and tag HIF1α with ubiquitin. This tag tells the cell that HIF1α should be broken down, which decreases the amount of HIF available for DNA binding. However, when oxygen levels dip (or when *VHL* is mutated, as in the familial cancer syndrome VHL disease), these hydroxyl groups aren't added to HIF1α, so the VHL complex can't recognize and tag it. This prevents the breakdown of HIF1α, making it available for DNA binding, which increases erythropoietin production and oxygen levels.

"It's sort of like a thermostat, if you will, cells have to adjust," said Kaelin, who studied VHL. "If they're getting too much oxygen or too little oxygen, they have to adjust themselves so that they can tolerate that environment."

"It is a very elegant and unusual mechanism—it is a really basic finding about how biology works," Johnson said.

However, the mechanism has applications beyond basic biology. "Many of the common diseases have derangements in the ability to maintain proper oxygen levels," said Semenza, who discovered HIF1. In cancer, cells rapidly consume oxygen as they divide, yet they can continue dividing in a hypoxic environment by producing more HIFs.

"We find that HIFs play a really critical role in the progression to metastatic disease and the ability of the cancer cells to shield themselves both from the immune system and from therapies," Semenza said.

Consequently, HIFs have become a therapeutic target: Phase II trials are testing a HIF2 antagonist in renal cell carcinoma, which has high HIF2 levels due to a *VHL* mutation. The development of this agent "represents a real leap forward," said Celeste Simon, PhD, of Perelman School of Medicine at the University of Pennsylvania in Philadelphia.

Simon emphasized that research on mechanisms of hypoxia should not stop with HIF. "I think [this award] recognizes a large body of work that has illuminated a highly conserved stress response," she said. "I just hope that it inspires people working in hypoxia to keep looking at … HIF-independent sensors."

For the Nobel Laureates, their work illustrates the importance of basic research. "As with almost any discovery science, the impact of that becomes evident later, and we didn't really foresee the broad reach of this system when we started the work," said Ratcliffe, whose research linked VHL to HIF1α.

"Our story is really one of trying to generate knowledge and to understand how things work," Kaelin said. "If you go deep enough and you understand things well enough, occasionally opportunities for translation and therapeutic application will arise."
–Catherine Caruso ■

Tipifarnib Targets *HRAS*-Mutant Cancers

The experimental farnesyltransferase inhibitor tipifarnib (Kura Oncology) may be effective in treating *HRAS*-mutant head and neck squamous cell carcinoma (HNSCC), according to results presented at the 2019 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics in Boston, MA, October 26–30. These findings suggest that after more than a decade of trying, researchers may have finally developed a drug that targets mutant HRAS within the elusive RAS–RAF–MAPK pathway—and they've done so in a population of patients with few treatment options.

HRAS mutations occur in 5% to 8% of patients with advanced HNSCC. Farnesyltransferase is an enzyme that catalyzes the binding of farnesyl groups to RAS proteins, enabling them to localize to the cell membrane and initiate oncogenic activity. Tipifarnib blocks this activity.

"There have been several lines of preclinical evidence suggesting that while NRAS and KRAS are susceptible to certain biological processes that allow them to circumvent [farnesyltransferase inhibitor] action, indeed *HRAS* mutations are not susceptible to those mechanisms," explained Alan Ho, MD, PhD, of Memorial Sloan Kettering Cancer Center in New York, NY, who presented the findings. This notion was supported by studies of tipifarnib in mouse models of skin and thyroid cancers, which led Ho and his colleagues to test the agent in the clinic.

A phase II trial enrolled patients with HNSCC tumors that had *HRAS* missense mutations at a high variant allele frequency (VAF; at least 35%, or a minimum of 20% if baseline serum albumin was at least 3.5 g/dL). Patients had received a median of two prior therapies: 90.5% had received a platinum agent, 61.9% had received an immune checkpoint inhibitor, and 52.4% had received cetuximab (Erbitux; Eli Lilly).

Overall, tipifarnib elicited partial responses in 10 of 18 evaluable patients and led to stable disease in the others. Four responses lasted more than a year, and six responses lasted at least 6 months. Responders had a median progression-free survival (PFS) of 8.3 months, and those with stable disease had a median PFS of 4.5 months. Notably, with their last therapy prior to joining the tipifarnib trial, patients had a median PFS of 3.2 months, and none had partial responses. Historical response rates