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

Alan Ho, MD, PhD, presents results of a trial testing tipifarnib. The agent targets HRAS, long considered undruggable.

for these patients are 13% to 15% for immune checkpoint inhibitors and less than 10% for chemotherapy or cetuximab, Ho said.

All patients experienced adverse events, and more than 10% experienced hematologic side effects, namely anemia, neutropenia, and leukopenia. These were also the most common adverse events of grade 3 or higher.

"We have very compelling antitumor activity in a heavily pretreated cohort of these recurrent metastatic head and neck cancer patients with *HRAS* mutations," Ho said. Next, researchers will test tipifarnib in the pivotal phase II AIM-HN/SEQ-HN trial of *HRAS*-mutant HNSCC. They also plan to explore tipifarnib in combination with other agents, including chemotherapy, immune checkpoint inhibitors, and targeted therapies—particularly in patients with *HRAS* mutations at a VAF of less than 20%.

Targeting the RAS–RAF–MAPK pathway "has been one of the holy grails of cancer, given the high frequency of *RAS* mutations in tumors such as colorectal, pancreas, and melanoma," said William Sellers, MD, of the Broad Institute of Harvard and MIT in Cambridge, MA, who was not involved in the trial. Sellers added that the tipifarnib trial, along with others testing agents that act on the same pathway, "emphasizes the excitement … of what's happening in the cancer field in general, and in particular in the RAS pathway." –*Catherine Caruso* ■

Early Pembrolizumab Ups TNBC Responses

Adding the PD-1 inhibitor pembrolizumab (Keytruda; Merck) to neoadjuvant chemotherapy may improve outcomes in early-stage triple-negative breast cancer (TNBC), researchers reported at the ESMO Congress 2019, September 27–October 1, in Barcelona, Spain. In the phase III KEYNOTE-522 trial, patients treated with the combination had a significantly higher pathologic complete response (pCR) rate and trended toward better event-free survival than those who received chemotherapy alone.

Patients with early-stage TNBC typically receive neoadjuvant chemotherapy, followed by surgery to remove the tumor. However, given the aggressiveness of TNBC, and patients' poor prognosis once it metastasizes, researchers have pushed to develop treatment regimens that might stem the disease at an early stage. "It is well established that patients who achieve a pathological complete response after neoadjuvant chemotherapy have a long-term clinical benefit," said Peter Schmid, MD, PhD, of Barts Cancer Institute at Queen Mary University of London, UK, who presented the results.

When combined with chemotherapy in phase I and II trials, pembrolizumab had promising neoadjuvant activity in early-stage TNBC. In KEYNOTE-522, researchers assigned 1,174 patients with newly diagnosed, early-stage TNBC in a 2:1 ratio to receive neoadjuvant pembrolizumab plus chemotherapy or a placebo plus chemotherapy. After surgery, patients assigned to the combination arm received pembrolizumab, whereas patients assigned to the chemotherapy arm received a placebo.

In an analysis of the first 602 patients, performed after a median follow-up of 15.5 months, 64.8% of those in the pembrolizumab arm experienced a pCR compared with 51.2% of those in the chemotherapy-only group—a statistically significant difference that was seen regardless of nodal stage, tumor size, patient age, chemotherapy regimen, or PD-L1 expression. Among all 1,174 patients, just 7.4% of those treated with pembrolizumab experienced disease recurrence, compared with 11.8% of those who received chemotherapy alone, a trend that has not yet reached statistical significance.

"The safety profile in general is consistent with what we know for single-agent therapy with pembrolizumab and other checkpoint inhibitors, as well as the combination of chemotherapy and checkpoint inhibitors," Schmid said. During neoadjuvant treatment, 76.8% of patients in the combination arm experienced grade 3 or higher adverse events, compared with 72.2% of those in the chemotherapy arm; throughout adjuvant treatment, 5.7% of patients receiving pembrolizumab experienced grade 3 or higher adverse events, compared with 1.9% of patients receiving a placebo. Overall, 42.3% of patients treated with pembrolizumab experienced immune-related side effects—most commonly hypothyroidism or rashes—or infusion reactions, compared with 21.3% of patients in the control arm.

"This is the first phase III neoadjuvant immunotherapy study to report [results in TNBC], so this is very exciting," said Sherene Loi, MD, PhD, of the Peter MacCallum Cancer Centre at the University of Melbourne in Australia, who provided commentary on the trial.

Loi was particularly intrigued by data suggesting that PD-L1 status does not predict whether patients with early-stage TNBC will respond to immunotherapy. "This is somewhat surprising because in the advanced setting, it is only the PD-L1–positive patients that benefit," she said, a result that should be investigated further.

Loi noted that it isn't entirely clear how pCR translates into event-free survival—or how patients who experience immune-related side effects will fare over time. "There is no doubt in my mind that checkpoint blockade will help us treat early-stage triple-negative breast cancer patients better," she said. "However, we need to wait for longer and more mature event-free survival data … to understand the benefit." –*Catherine Caruso* ■

Olaparib to Change Practice in mCRPC

For the first time, a phase III trial has shown that a PARP inhibitor can be effective in patients with metastatic