The Albert and Mary Lasker Foundation

William Kaelin, Peter Ratcliffe, and Gregg Semenza (from left to right) at the Lasker Awards ceremony in September.

disease, characterized by tumors that are rich in newly formed blood vessels. He found that cells lacking VHL protein ramped up erythropoietin production and generated high levels of VEGF even when oxygen levels were high.

Intact VHL, Ratcliffe and Kaelin found, is required for HIF1α degradation under high-oxygen conditions: Prolyl hydroxylases add a hydroxyl group to HIF1α, making it recognizable to VHL, part of a ubiquitin ligase. But because prolyl hydroxylases require oxygen to complete their task, HIF1α remains functional under hypoxia, traveling to a cell's nucleus and activating genes that set off a chain of signals that sustains tumors.

By better understanding the biology of HIF and how cells adapt to the availability of oxygen, these studies helped lay the foundation for developing VEGF inhibitors to decrease the formation of blood vessels that feed cancer, said Kaelin. These drugs include bevacizumab (Avastin; Genentech) and pazopanib (Votrient; GlaxoSmithKline). He noted that HIF inhibitors, which could be an option for patients who don't respond to standard therapies, are under development.

"The goal of the Lasker Awards is not only to celebrate these great scientists," said Lasker Foundation President Claire Pomeroy, "but also to draw public attention to the importance of sustained investment and societal commitment to medical research." *–Suzanne Rose* ■

PD-1, CTLA-4 Point to Drug Response

Immune checkpoint blockers pose a vexing problem: They don't work in many eligible patients. However, according to a recent study in melanoma, patients whose tumors have an abundant population of CD8+ cytotoxic T cells expressing both PD-1 and CTLA-4 are more likely to respond to these drugs (J Clin Invest 2016;126:3447–52).

Normally CD8+ T cells express little PD-1. However, persistent antigen stimulation drives up PD-1 expression in tumor-associated T cells. Continuous signaling through PD-1 can leave T cells "exhausted" and unable to function. Anti–PD-1 therapies expose tumors to immune attack by blocking interactions between PD-1 and its ligands expressed in the tumor microenvironment.

Oncologists can gauge whether patients are good candidates for anti–PD-1 therapy by assessing their tumors' PD-1 and PD-L1 expression levels through immunohistochemistry. The trouble is that histology is sometimes subjective: A protein's expression may be judged "high" by one pathologist and "medium" by another. "It can come down to an opinion," says study leader Michael Rosenblum, MD, PhD, of the University of California, San Francisco. Furthermore, histology analyzes only a thin section of the tumor. Flow cytometry is more objective, quantitative, and comprehensive.

Rosenblum's team performed flow cytometry on fresh metastatic melanoma samples from 20 patients, assessing the relative quantities of tumor-infiltrating effector, regulatory, and cytotoxic T cells, as well as PD-1, PD-L1, CTLA-4, and MHC class II expression in these subsets. The patients were then started on the PD-1 inhibitors pembrolizumab (Keytruda; Merck) or nivolumab (Opdivo; Bristol-Myers Squibb). Two years later, the researchers correlated the patients' tumor immune profiles with their clinical responses. In this discovery cohort, the combination of PD-1 and CTLA-4 emerged as the best predictor of response. Patients whose tumors had at least 20% of CD8+ T cells expressing these two markers had a median progression-free survival of 31.6 months, versus 9.6 months for patients with less than 20% of this subtype among their tumor CD8+ cells.

The predictive value of PD-1 and CTLA-4 held up in a separate validation cohort of 20 more patients with melanoma. If less than 20% of their tumor's CD8+ cells expressed these two markers, the patient "had no chance of responding" to monotherapy with pembrolizumab or nivolumab, says Rosenblum. Meanwhile, individuals "had about an 80% chance of responding" if at least 30% of their tumor-infiltrating CD8+ cells were positive for both markers. As such, patients whose PD-1 and CTLA-4 levels fall below 30% could be given pembrolizumab plus ipilimumab (Yervoy; Bristol-Myers Squibb) "right off the bat," Rosenblum adds. "The risk–benefit there probably favors double therapy."

In functional assays, this PD-1– and CTLA-4–high population behaved like "partially exhausted" T cells that can produce some cytokines but not others. The researchers verified that these T cells could not produce TNFα and IL2 and that checkpoint blockade successfully reactivated the cells.

The findings "have the potential to be very useful," says Roy Herbst, MD, PhD, of Yale School of Medicine in New Haven, CT, who previously reported that CTLA-4 mRNA expression in tumors predicted response to PD-L1 blockade. However, he adds, it's not always possible to obtain fresh tumor tissue—a requirement for flow cytometry—and the technique demands a high level of expertise. *–Esther Landhuis* ■

Pinpointing a Factor in Myeloma Bone Disease

Osteolytic lesions—soft spots in weakened, damaged bones—are a common occurrence in multiple myeloma. Patients with this hematologic malignancy often suffer chronic bone pain and are at high risk for fractures. Recent research from The University of Texas MD Anderson Cancer Center in Houston implicates the enzyme thymidine phosphorylase (TP) and suggests that inhibiting TP may be a viable therapeutic option for myeloma-induced bone disease (Sci Transl Med 2016;8:353ra113).

The lifelong process of bone remodeling involves a balance between two partners: osteoclasts, which govern bone resorption, or breakdown, and the release of minerals such as calcium to the blood; and osteoblasts, which