The Albert and Mary Lasker Foundation, is required for HIF1 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;126:4475–52).

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;8:333ra113).

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

*Image by Lasker Learning Center. William Kaelin, Peter Ratcliffe, and Gregg Semenza (from left to right) at the Lasker Awards ceremony in September.*
target worth pursuing clinically,” says Noopur Raje, MD, director of Massachusetts General Hospital’s Center for Multiple Myeloma in Boston. “It’s one more factor among many others, including DKK1, sclerostin, and activin A, which have all been closely studied.”

To Yang, “targeting TP offers a brand-new strategy to treat osteolytic lesions in multiple myeloma,” given that bisphosphonates, the current therapeutic mainstay, offer only moderate palliative effects. When her team tested two TP inhibitors, 7-deazaxanthine and tipiracil hydrochloride, in mice with myeloma-induced bone disease, they reported a significant reduction in osteolytic lesions and an improved balance between bone resorption and formation.

Yang notes that tipiracil hydrochloride is one of two key components of Lonsurf (Taiho Oncology), the other being trifluridine, a nucleoside metabolic inhibitor. The drug is already FDA-approved for metastatic colorectal cancer, and “its potential application in myeloma bone disease will be most intriguing to explore,” she says. Hypomethylating agents are another possibility, she adds.

Next, Yang plans to test TP inhibition in tissue samples from patients with multiple myeloma, and to extend this approach to other bone-metastatic cancers. “A large pool of samples with different degrees of osteolytic lesions will help us pinpoint the effective range of TP inhibition,” she observes. —Alissa Poh

Panel’s “Moonshot” Goals Released

In response to President Obama’s Cancer Moonshot, a Blue Ribbon Panel has released a report outlining 10 recommendations they say will help meet the initiative’s goal: a decade’s worth of progress against cancer in 5 years (available at www.cancer.gov).

The panel, which included nearly 150 scientists, oncologists, patient advocates, and industry leaders, brainstormed in working groups and also considered more than 1,600 ideas from the public. “We were looking at what science was ripe that would make a really big difference,” says co-chair Elizabeth Jaffee, MD, of Johns Hopkins Medical School in Baltimore, MD.

On the research front, the group called for more studies of drug resistance as well as how fusion oncoproteins cause pediatric cancers. They also proposed public–private collaborations to speed the development of new technologies, such as high-resolution tumor imaging and implantable drug-delivery devices.

To improve patient care, the panelists recommended the creation of guidelines on managing treatment-related side effects. They also called for retrospective analyses of banked tissue samples from people who received standard therapy, and the development of an online “atlas” to document tumor evolution: how tumors, surrounding cells, and their immediate environment respond to treatment and changes in immune responses over time. In addition, the group recommended expanding the use of proven strategies to detect cancer early—or prevent it entirely—and building a clinical trials network that would focus on immunotherapy.

Another recommendation called for patients to be key contributors to the Moonshot by joining a nationwide network that would enable them to obtain a genomic profile of their cancer and “preregister” for future trials.

Finally, the report proposed a “national cancer data ecosystem” to build upon and link the cancer data centers already in existence. For example, the American Association for Cancer Research’s (AACR) Project GENIE is connecting genomic data with patient outcomes from multiple institutions to help match future patients with the best treatments for their cancers. Meanwhile, the American Society of Clinical Oncology’s CancerLinQ is collecting and disseminating clinical information.

The NCI, which is spearheading the Moonshot, plans to begin some projects in 2017 to meet these recommendations; others will likely take longer to start, says acting deputy director and panel co-chair Dinah Singer, PhD. Federal funding is key: The NCI received $195 million for Moonshot efforts as part of the 2016 fiscal year budget, which it used to support precision medicine research. Obama has asked for an increase of $680 million to the NCI’s budget next year, plus $75 million for
Pinpointing a Factor in Myeloma Bone Disease


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