

A BOOST TO RADIOTHERAPY

Radiation activates tumor-busting immune responses. Can they be amped up to create a new therapy?

Ralph Weichselbaum has long studied how radiotherapy destroys tumors. He has delved into how it disables cancer cells by damaging DNA, studied the molecules it activates, and tested new dosing regimens and combination therapies in patients.

But Weichselbaum, Ludwig Chicago director, was not prepared for what he saw in late 2008: his experiments suggested that high-dose radiation activated the immune system. This finding flew in the face of the traditional view that tumor cells die because of the direct effects of exposure to radiation.

Spurred on by his immunologist colleagues at Ludwig, Weichselbaum adjusted the course of his studies, unraveling the snarl of immune cells and mediators to show how they work together in response to radiotherapy. Earlier this year he published a key study in mice. It shows how to combine an experimental immunotherapy drug with radiation to boost tumor killing in models of colon and breast cancer. He found, further, that the enhanced destruction of tumors by this combination extends beyond the irradiated tumor to tumors implanted outside the field of irradiation.

Weichselbaum's studies at this intersection of radiotherapy and immunotherapy, which have traditionally been separate subfields of clinical

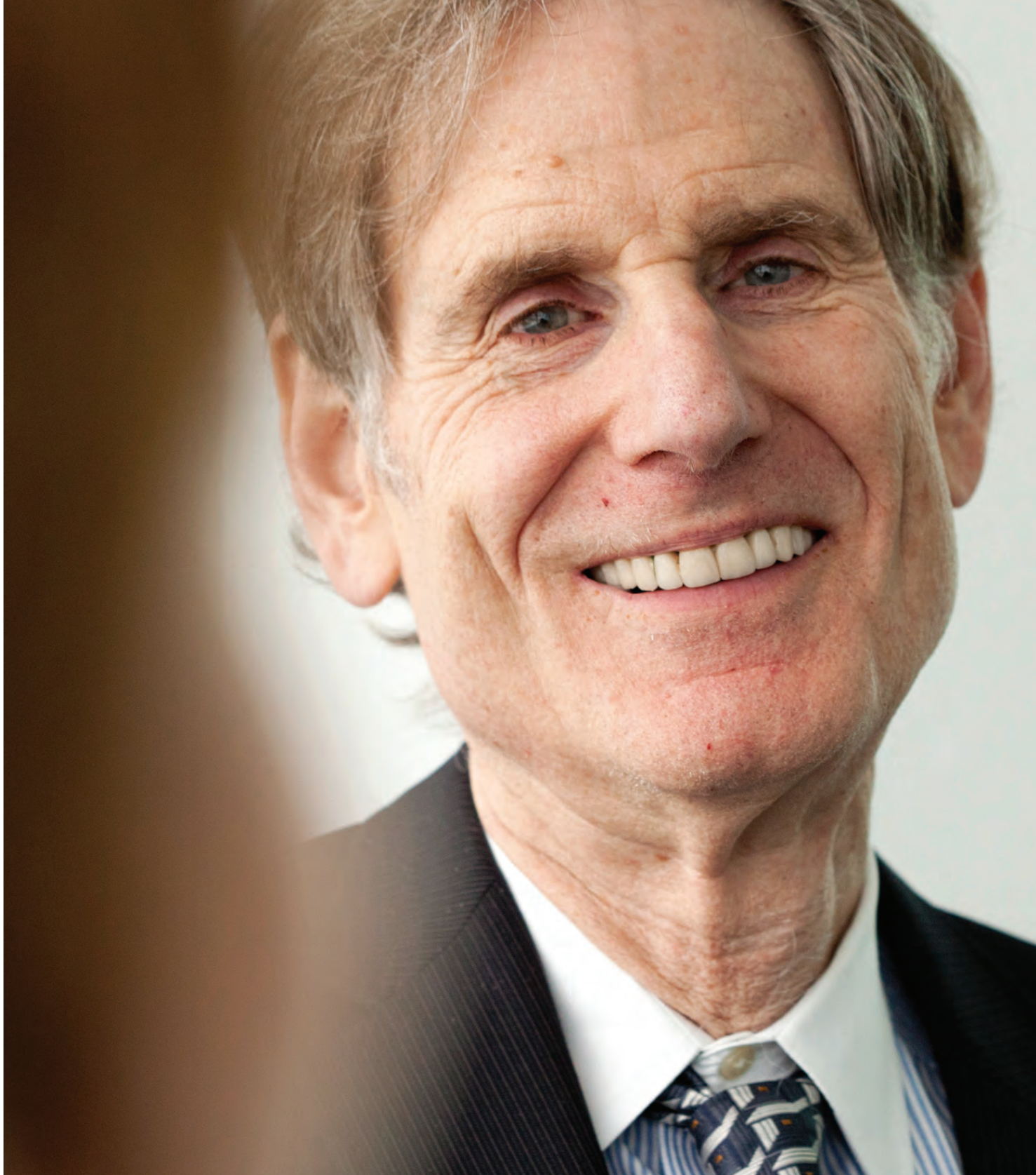
oncology, could lead to new strategies to induce durable antitumor responses in patients with highly resistant cancers.

SUPPORT FROM THE PIONEERS

Weichselbaum started down the path to these studies when he analyzed the results from a group of patients who each had fewer than five metastatic tumors, and on whom he had tested an experimental treatment regimen: the delivery of highly focused, tumor-killing doses of radiation. Such patients normally opt for chemotherapy or palliative treatments, depending on the extent of the metastases. But Weichselbaum found that some of the patients had durable remissions with such "ablative" radiotherapy.

He was pleased that this treatment had an effect, but what really struck him were the results of his patients' blood tests. He noticed that the patients who had the strongest responses also had high numbers of white blood cells. Did the immune response have something to do with their tumor shrinkage?

That question spurred Weichselbaum to go back to the bench, pairing up with fellow Ludwig Chicago scientist and immunology expert Yang-Xin Fu. The researchers treated tumor-bearing mice with high-dose, ablative radiation. To Weichselbaum, who is schooled in the DNA-damaging effects of radiation, the results were



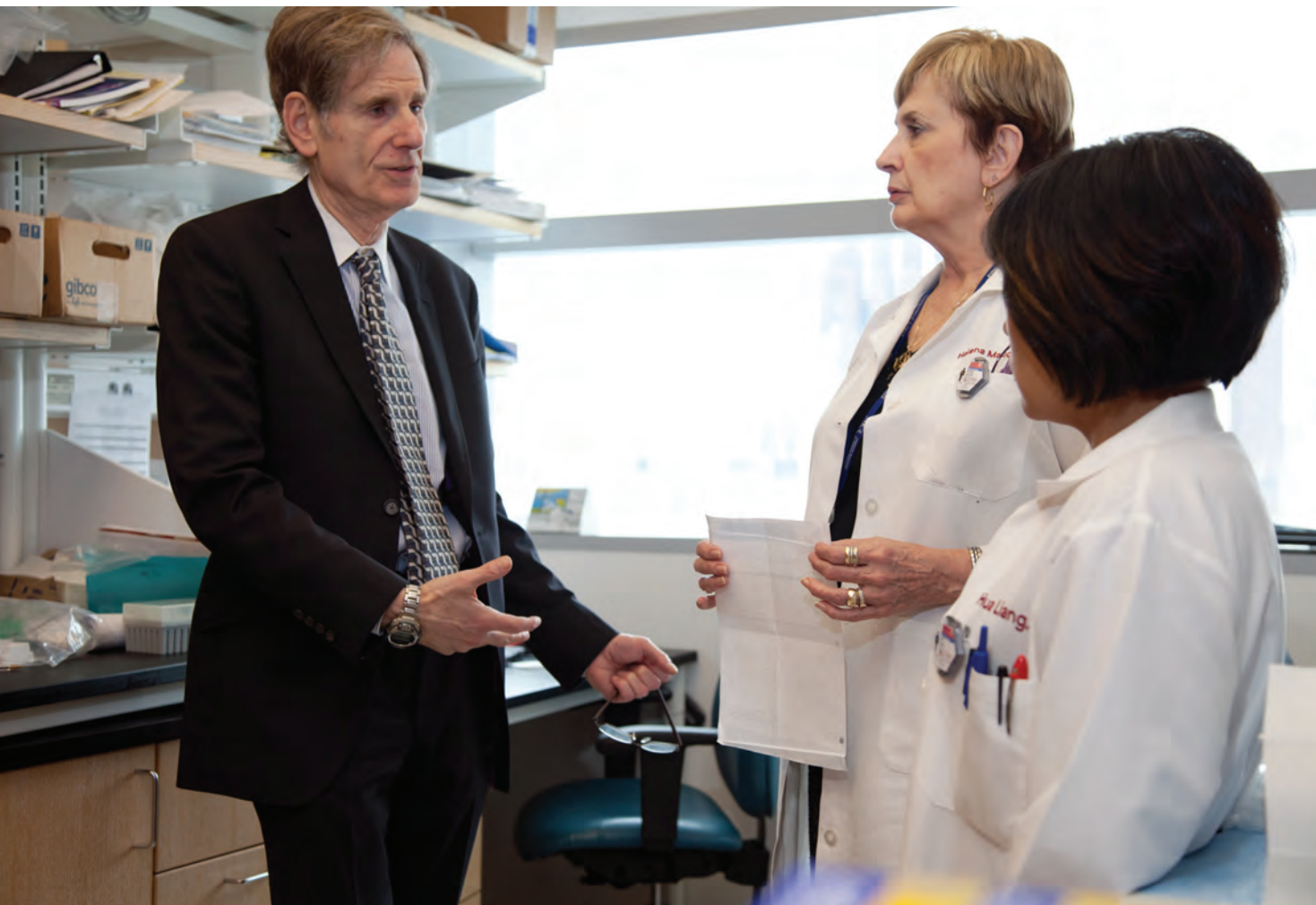
Ralph Weichselbaum, Ludwig Chicago

dumbfounding. The ablative regimen activated T cells of the immune system, and the T cells helped kill both irradiated and metastatic tumors. The effect was not observed with more conventional radiation treatments, such as repeated low-dose “fractionated” radiation.

Previous studies had hinted that some of the antitumor effects of radiation might be

mediated by immune cells. But this was not, at the time, a mainstream view.

One researcher was convinced that Weichselbaum was on to something, however. That was the late Lloyd Old, longstanding scientific director of the Ludwig Institute and a champion of cancer immunotherapy. Weichselbaum spent



many hours discussing his data with Old and other Ludwig colleagues in New York, such as Jedd Wolchok. “They were extremely supportive and forthcoming,” he says. Lloyd, in particular, “was an inspiration to me. Jedd is an extremely patient supporter.”

His New York colleagues convinced him to keep going. He followed up with studies showing that cells damaged by radiation activated specific immune molecules, which in turn powered up cells to attack tumors. Weichselbaum continues to dissect the mechanism behind the effect. He is working on ways to harness the immune system to enhance the effects of radiation—an avenue of research that has been particularly fruitful in 2014.

FINDING THE RIGHT COMBINATION

For the new study, Weichselbaum was eager to test out his ideas using immunotherapy drugs in development. One such drug is an antibody to

PDL-1, which is a ligand for PD-1, a receptor on T cells that suppresses their killing of cancer cells. Blocking the ligand powers up the immune response.

He and his colleagues combined the use of anti-PDL-1 antibodies with high-dose ablative radiation in mice with colon and breast tumors. They found that the combination activated tumor-attacking T cells in the mice while disarming myeloid-derived suppressor cells, which are known to quell the immune response. As a result, tumor growth slowed substantially in the mice exposed to the combination treatment, as compared with those exposed to either treatment alone.

To their surprise, the researchers also saw that the combination therapy quelled metastatic tumors in parts of the body distant from the site of radiation. Though this long-distance effect of radiotherapy—dubbed the abscopal

These studies at the intersection of radiotherapy and immunotherapy could lead to new strategies to induce durable antitumor responses.

effect—has been observed in cancer patients, it is a rare phenomenon.

Weichselbaum thinks he may have hit on a way to enhance the tumor-killing ability of high-dose radiation in patients with multiple metastatic tumors, as occurred with the patients in his original 2008 study. Some of the effect of the combination treatment is systemic, in that the combination of anti-PDL-1 and local radiation shrank tumors on the opposite side of the animals, which were not irradiated and did not respond to anti-PDL-1 alone.

Weichselbaum is now testing the tumor-busting capability of various radiation regimens and experimental drugs in mice to look for the perfect combination.

“Reagents like anti-PDL-1 and other immune modulators are going to be widely used with radiation and chemotherapy,” says

Weichselbaum. And he is prepared to understand how to combine them appropriately.

Weichselbaum misses his conversations with Old, who died in 2011. But he keeps the phone line open to other Ludwig colleagues, as they usher the resurgent field of immunotherapy to the forefront of cancer care.

REFERENCE

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