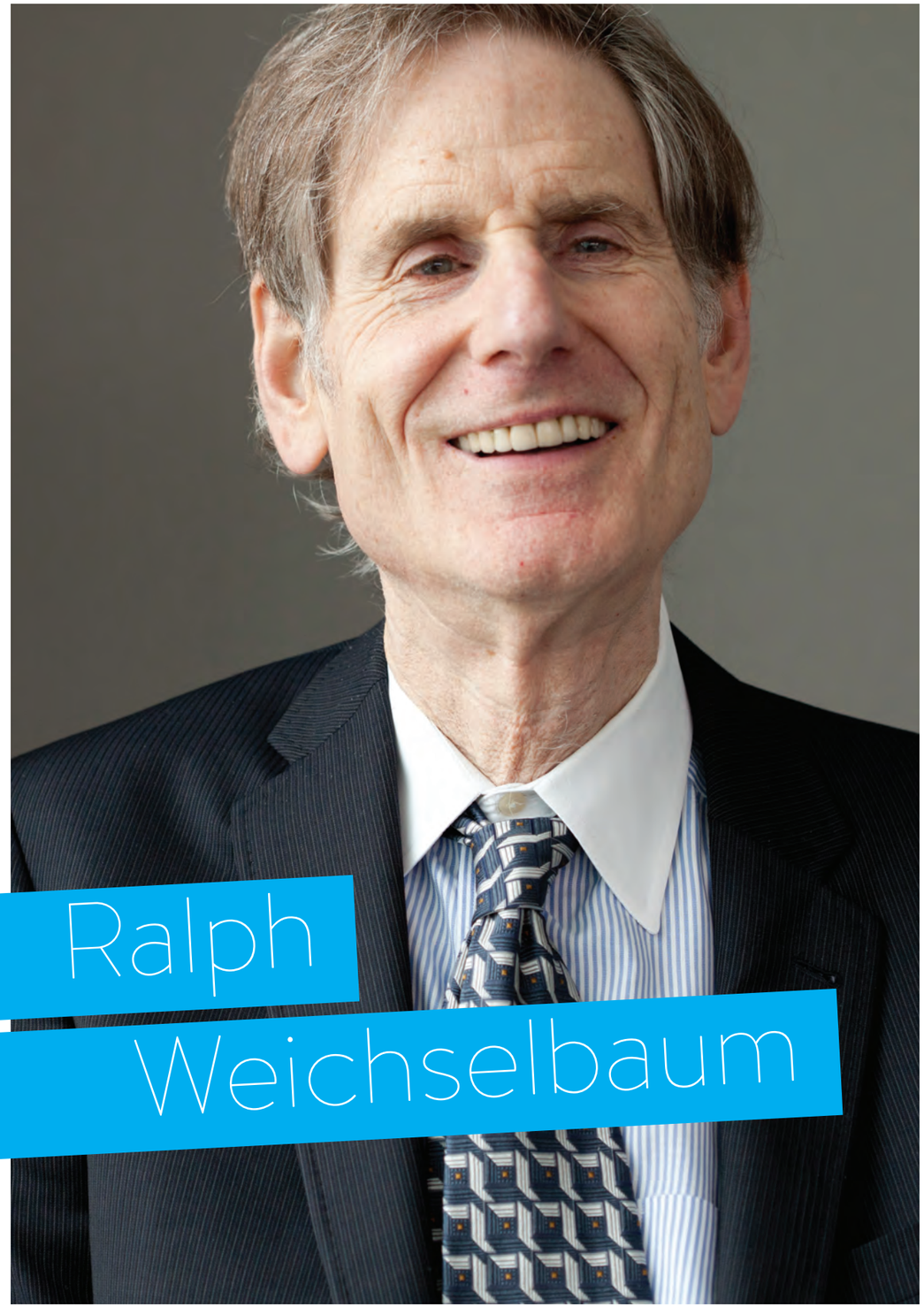

Photo by Flynn Larsen

THE RADIATION REVOLUTIONARY

Ralph Weichselbaum's decades-long quest to expand the uses of radiotherapy has exposed its ties to the immune response and yielded a trove of clues to novel cancer therapies.

For the better part of four decades, Ralph Weichselbaum, co-director of Ludwig Chicago, has focused more than anything else on discovering new ways to wield his weapon of choice—ionizing radiation—against cancer. In this quest, he has dug deep into how cells respond to radiation, exposing links between those responses and the body's innate defenses against infection. He has also explored, first in mice and now in humans, how those links might be exploited for cancer therapy. "Sometimes, when you have a hammer, everything looks like a nail," he says, in his characteristically droll way. "But I've been exploring how radiation can be more than just a local treatment, and it really looks like it can be more."

In his continuing efforts to make that case, he and his colleagues published in 2016 a pair of studies that identified cellular responses to viral infection switched on by radiation, and modeled the use of combination immunotherapies along with radiotherapy to treat pancreatic tumors—which are typically resistant to immunotherapy. Taking a pivot off his bailiwick, Weichselbaum also led an intriguing study on stem-like cells in bladder cancer, illuminating their association with disease progression and creating a possible test to predict treatment outcomes.

STUMBLING INTO A CALLING

Weichselbaum was born in Chicago, where his mother was a homemaker and his father worked as a doctor. His father died when Weichselbaum was in his early teens, which left the family with no income. "It was pretty grim," he says, recalling how he hopped from one awful job to another to shore up the family's finances, including a stint at a meat-packing plant that still makes him shudder. "As I tell my kids, I went from being rich (relatively) to being poor, and being rich is better."

Weichselbaum says he was a middling student, at best. Fortunately, tall and wiry, he was sufficiently talented at basketball to win a scholarship to the University of Wisconsin, Madison—though, he admits, he quit "after getting roasted in a few practices." Still, he somehow retained his scholarship and majored in psychology, with a minor in history, mainly, he says, because he figured both subjects would be a breeze. After college, with the Vietnam War raging and the draft a threat, Weichselbaum thought it prudent to apply to medical school at the University of Illinois.

He was accepted, and was soon surprised to find he had a knack for the subject. "Probably, I always secretly wanted to be a doctor," he says, "but it had always seemed like so much work. I was not the most ambitious person that ever lived. When I think about it now, I'm amazed I ever became a doctor."

Photo by Stewart Marcano

And a good one, at that. Weichselbaum went on to do his residency at the storied Joint Center for Radiation Therapy, which included Brigham and Women's Hospital and the Dana Farber Cancer Center, where he specialized in radiation oncology while starting up a lab at the Harvard School of Public Health. There, he soon met Samuel Hellman, a renowned oncologist and researcher who has long been on the Board of the Ludwig Institute. It was the beginning of a long friendship and a fruitful research collaboration.

"The guy is just brilliant, a monumental talent," says Weichselbaum of his old friend and mentor. "One of the luckiest things I got to do was to work with him. Not only did he shape my ideas, but I'm sure I incorporated some of his ideas in my work."

HOME, AGAIN

In 1984, Weichselbaum returned to Chicago, joining The University of Chicago's Pritzker School of Medicine, where Hellman too took a post a few years later. Through the 1990s, Weichselbaum was engaged in exploring how a protein known as tumor necrosis factor-alpha (TNF-α) sensitizes tumors to radiation, ultimately translating his findings into an experimental gene therapy that was evaluated in clinical trials.

But he was also working closely with Hellman on other matters. Hellman was by the mid-90s engaged in a heated debate with an equally prominent oncologist named Bernard Fisher. Their argument was over whether cancer—in particular, breast cancer—is inevitably a systemic disease by the time it is detected (Fisher's position) or whether it exists in a spectrum of states, from localized to systemic (Hellman's view). The former would imply that cancers should always be treated systemically, while the latter that each case called for a distinct therapeutic approach, including localized, high-intensity radiotherapy.

Weichselbaum agreed with Hellman, and in 1995 the pair published an editorial in the *Journal of Clinical Oncology* positing a potentially curable, early stage of cancer's spread that they called "oligometastasis." The stage was roughly defined as an initial tumor plus one to three or five metastases. They argued that aggressive treatment of oligometastasis with high-dose radiation or surgery, rather than the drawn out low doses which were standard practice, could effect a cure. In some cases this could be achieved without need for systemic therapy.

In the years since, the pair have probed the molecular biology of oligometastasis to better define the state, and been proved largely correct about its treatment by their own and others' studies. It turns out that up to 20% of oligometastatic cancers, especially breast malignancies and certain lung tumors, can be controlled for extended periods, or even cured, by intense, targeted radiotherapy or surgery following the removal of a primary tumor.

TALKING TO KILLER CELLS

While conducting his clinical studies on oligometastasis with Hellman—an uphill struggle against prevailing dogma—Weichselbaum wandered over one day in the mid-2000s to his former Ludwig Chicago colleague, the pathologist Yang-Xin Fu, to request help with some microscopic slides. "He asked me, 'Did you ever think giving tumors these big doses of radiation works because it improves T cell priming?'" Weichselbaum recalls. "I said, 'listen man, if I knew what T cell priming was, I'd tell ya.' "

He would learn soon enough. Though Weichselbaum likes to joke that he's a "Wikipedia immunologist," his subsequent collaboration with Fu elegantly unraveled the interplay of the immune response and radiotherapy. The pair first showed in 2009 that killer T cells, which target cancer cells, are required for high-dose radiation's tumor-killing effects in mice.

By 2014 they had demonstrated that when tumors in mice are hit with intense radiation, treatment with anti-PD-L1 antibodies—an immunotherapy known as checkpoint blockade that unleashes a T cell attack on tumors—extends immune targeting to tumors well outside the field of radiation treatment. The treatment, they showed, also destroys in mice a type of immune cell often recruited by tumors to suppress immune responses.

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The study suggests a strategy for turning “cold” tumors that are resistant to immunotherapy into “hot” ones that might be conquered.

These findings were published in the *Journal of Clinical Investigation* and *Immunity*.

Weichselbaum is now involved in a trial to evaluate stereotactic radiotherapy with checkpoint blockade for cancer treatment, and developing other combinations of high-dose radiation and immunotherapy. In 2016, he and Fu reported in *Oncotarget* a novel strategy for treating pancreatic cancer, which is highly resistant to immunotherapy because its tumors tend to be poorly infiltrated by T cells.

The tumors Weichselbaum and his colleagues used in their study expressed an artificial antigen for which the researchers had a vaccine. “What we found is that when you vaccinate and give the mice PD-L1 antibodies, it makes good T cells but they don’t get into the tumor,” says Weichselbaum. “In this case, when you also use radiation, you turn on chemokines, which are factors that call the activated T cells into the tumor.” With that combination, the researchers showed, the pancreatic tumors regressed, significantly extending the survival of the mice.

Personalized tumor vaccines are only in the early stages of development, so the translation of these findings into a clinical study may take some time. But the study suggests a strategy for turning “cold” tumors that are resistant to immunotherapy into “hot” ones that might be conquered.

THE ALARMS

Weichselbaum has also explored how irradiation—once believed to kill cancer cells solely by destroying their DNA—activates the antitumor immune response. In 2014, for example, he and Fu showed how dendritic cells, among the body’s primary reconnaissance forces, play a central role in the process. They reported in *Immunity* that an innate cellular mechanism for detecting viruses and sounding the alarm, one that is switched on by fragments of double-stranded DNA, fuels the release of an immune factor called IFN-β. This factor then spurs the activation of killer T cells by dendritic cells.

In 2016, Weichselbaum and his Ludwig Chicago colleague Nikolai Khodarev reported in *Oncotarget* that a second cellular virus-detection system also plays an essential role in destroying irradiated cells. This system, mediated by a cellular signaling cascade known as the RIG-like receptor pathway, is activated by small fragments of RNA whose presence in cells also suggests viral infection. The researchers also described a protein in this pathway whose activation induces resistance to radiotherapy. These studies, Weichselbaum hopes, will guide the development of drugs that can improve the effects of both radiotherapy and immunotherapy.

FARTHER AFIELD

Weichselbaum also published in 2016 a study far removed from his typical focus—one exploring the cellular and molecular underpinnings of bladder cancer’s progression. For this study, published in *Nature Scientific Reports*, he partnered with a postdoctoral fellow who was recruited from the laboratory of Ludwig Stanford Director Irv Weissman and joined Weichselbaum’s group for a spell before going into private practice.

Photo by Flynn Larsen

They showed that an excess of typically rare stem-like tumor cells, basal tumor cells (BTCs), in early-stage bladder cancers is associated with poor patient outcomes. In more advanced tumors, however, the presence of BTCs has little prognostic utility. Rather, it is the ability of BTCs from such tumors to take hold and grow when injected into immune-deficient mice that indicates poorer outcomes.

Having devised a method to easily isolate BTCs and grow them outside the tumor, Weichselbaum and his team examined the gene expression patterns in the cells and identified a potentially new biomarker for bladder cancer: CDC25C, a protein that drives cell division. They showed that the protein is associated with a higher risk of death even after wholesale removal of the cancerous bladder.

Notably, this association disappeared in patients who had received chemotherapy. So a test for CDC25C could help determine whether a bladder cancer patient is likely to benefit from chemotherapy, and spare those who aren’t the ordeal of such toxic treatment. Weichselbaum is now trying to raise funds to examine the biomarker in a clinical trial.

He also expects that with the ability to culture BTCs, some good science and a little luck, he should be able to find drug targets specific to these cells. He certainly has the good science covered, and luck is not something he tends to worry about.

“I’m a lucky guy,” Weichselbaum muses, looking back over his mentorship by Hellman and his career. “When they asked Khrushchev how he survived Stalin, Khrushchev said, ‘I drew a lucky lottery ticket.’ That’s how I feel about my life: I drew a lucky number.”