NEW VISIONS FOR PROGRESS

2013 RESEARCH HIGHLIGHTS

LUDWIG
CANCER
RESEARCH

WELCOME

Edward A. McDermott Jr.
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Any cancer in any patient is, in a sense, a truly unique disease. Yet the majority of cancers have a few things in common. For one thing, most harbor small populations of cells that can colonize other organs—more than 90% of cancer deaths are caused by such metastases. For another, they evolve, and so evade both the immune system's defensive weaponry and the therapies doctors deploy to destroy them. In practical terms, these interconnected capabilities confer on many tumors a lethal resistance to all kinds of intervention, and dealing with them is critical to getting a medical handle on this deadly family of diseases.

As you'll see in this year's report, scientists of Ludwig Cancer Research—encompassing the Ludwig Institute and Ludwig Centers—are leading efforts on four continents to do just that. You will learn how they are probing the mechanisms by which brain, breast and other cancers dodge targeted therapies, and devising drugs and treatment regimens that put the bull's-eye back on resistant cells. You will read about how other Ludwig labs are probing the genetic and biochemical aberrations that transform a standard cancer cell into a mobile "stem" cell that can populate another organ—and how that knowledge is being applied to design new therapies. And you will see how our scientists are decoding the molecular signals that allow cancers to elude immune attack, using what they learn to create candidate immunotherapies or apply such strategies in combination with radiotherapy and other treatments for a wide range of cancers.

Throughout the report, you will also notice how Ludwig actively translates scientific insight into candidate therapies. By supporting the early stages of new drug development, largely through the efforts of a dedicated technology development team, Ludwig ensures that its science ultimately serves the needs of cancer patients.

The quality of that research, whether basic, applied or clinical in focus, owes much to the method by which Ludwig funds its scientists. The founder and namesake of our organization, the late Daniel K. Ludwig, believed that the best way to solve a difficult problem is to find the best minds available and set them free to solve it. By recruiting top researchers and granting them long-term support and freedom to pursue their most daring ideas at a pace amenable to rigorous science, Ludwig encourages research of a quality and ambition essential to solving a puzzle as complex as cancer. The net result, as you will discover in this report, is a flood of groundbreaking science and potentially transformative ideas for new cancer therapies.

We trust that you will find the stories in this report as encouraging as they are engaging, and that you will emerge from its perusal sharing our firm belief that we are making steady—and steadily swifter—progress toward the goal of conquering cancer.

Sincerely,

Ed and David

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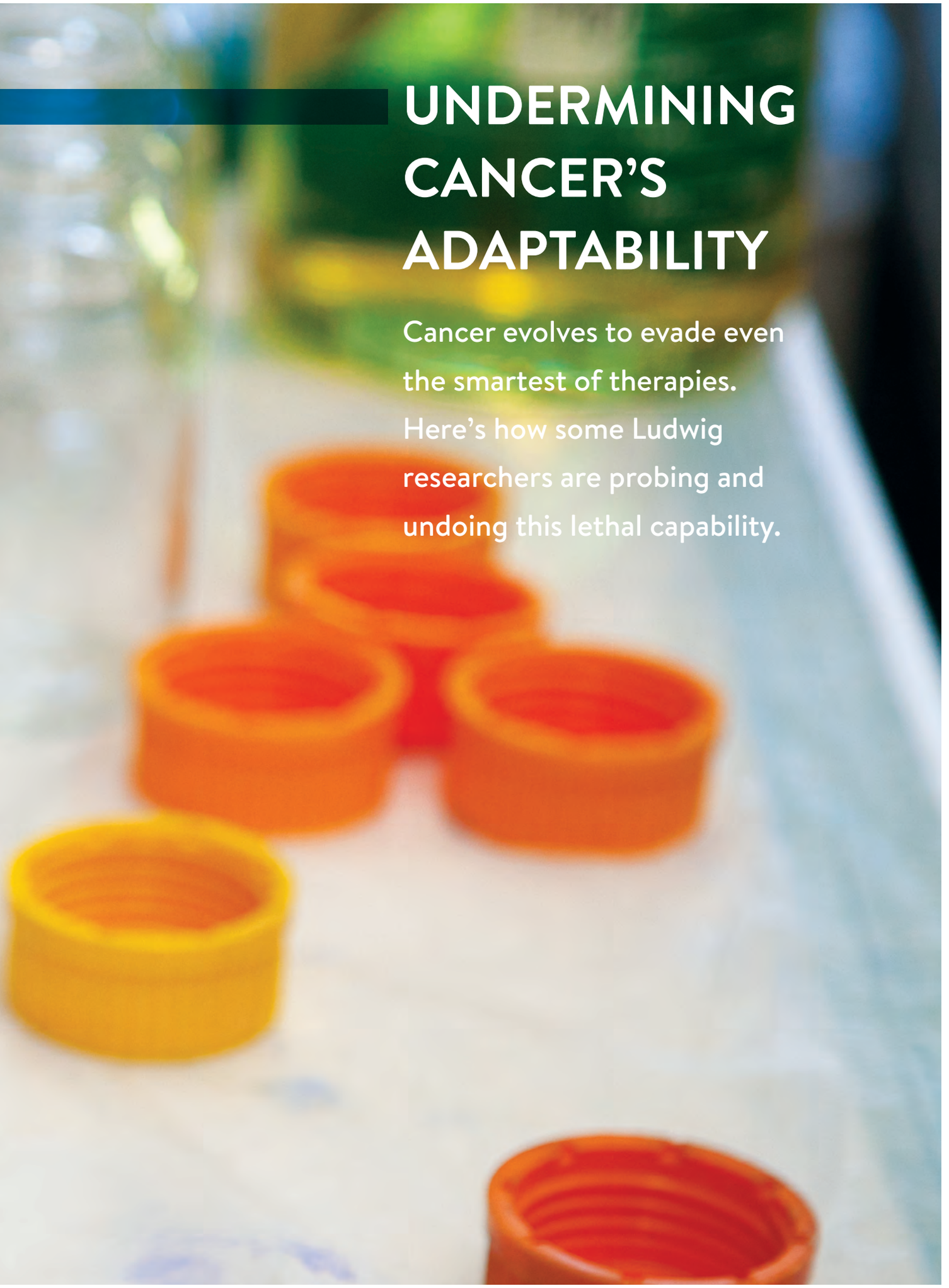


UNDERMINING CANCER'S ADAPTABILITY

Cancer evolves to evade even the smartest of therapies. Here's how some Ludwig researchers are probing and undoing this lethal capability.

A BRAIN CANCER'S DISAPPEARING DNA

Learning how a deadly tumor evades a targeted therapy suggests how it might be defeated

Cancer cells are as complex as they are cunning. To grasp their inner workings and the multifaceted malignancies they form, it is best to examine them from a variety of angles. Working together at Ludwig San Diego, Frank Furnari, Paul Mischel and Web Cavenee provide just that sort of sophisticated perspective. Each looks at tumors in a different way. Each has a distinct expertise. Each is equally intent on tackling one of the most stubborn tumors known to modern medicine: glioblastoma multiforme (GBM), a common brain cancer that leaves most newly diagnosed patients with less than two years to live.

GBM is something of a Hydra, the mythological many-headed beast who grows two new heads each time one is cut off. Conventional chemotherapy barely singes this monster. Zap it with radiation, and it grows back quickly, only now resistant to radiation. As for targeted therapies—the reputed 'smart bombs' in the oncologic arsenal: "The field has really struck out in the first clinical trials evaluating targeted drugs for glioblastoma," admits Mischel. GBM tumors have evaded single-agent, targeted therapies, particularly those delivered at suboptimal doses, by developing many drug resistance mechanisms that ensure clinical failure.

How does GBM resist the shrewdest attempts to kill it? Cavenee, director of Ludwig San Diego, believes the question is far too complex for any individual researcher to handle. "The synergy between our groups," he explains, "is personal and scientific."

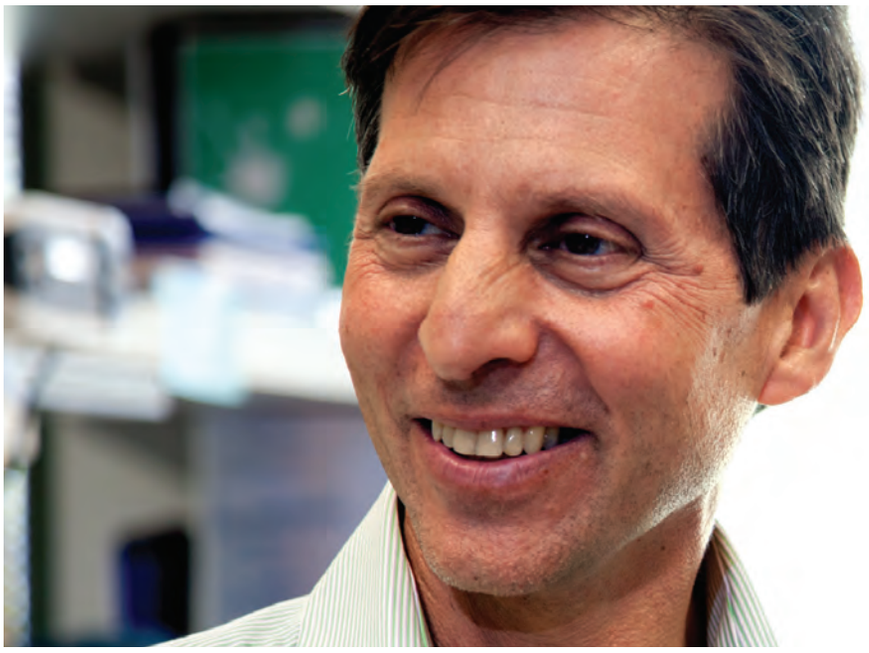
It is also paying off. Early this year, for example, the trio reported how a rogue piece of circular DNA helps GBM counteract targeted therapies, and added a layer of stunning complexity to standard models of how cancer cells resist therapy. These and other findings by the team may have set the stage for new treatment strategies not only for people with GBM but also for those with other types of cancer. "These studies will make a difference for patients in a real, substantive way," says Mischel.

SNEAKY CIRCULAR DNA

At first glance, GBM would seem an ideal candidate for targeted therapies. Most GBM tumors carry a well-known drug target, a hyperactive form of the epidermal growth factor receptor (EGFR). This protein sits on the surface of cells and drives their proliferation. Drugs called EGFR inhibitors, such as erlotinib, gefitinib and lapatinib, can shut down tumor growth and show efficacy against certain lung and breast cancers. But EGFR inhibitors have failed dismally against GBM, despite the prevalence of EGFR amplifications and mutations in GBM. The Ludwig San Diego researchers wanted to know why.

Frank Furnari, Ludwig San Diego

Web Cavenee, Ludwig San Diego



Paul Mischel, Ludwig San Diego

“The synergy between our groups is personal and scientific.”

WEB CAVENEE

Previous studies have shown that the gene encoding EGFR resides in a peculiar place in GBM cells—on a circular piece of DNA, separate from the chromosomal DNA that normally encodes a cell’s genes. When the researchers applied EGFR inhibitors to GBM cells in a petri dish, they found that the cells didn’t just disable expression of the gene to gain resistance. Instead, the circular DNA itself vanished. “Nobody had ever described that before,” says Furnari, referring to the disappearing act pulled off by the circular DNA. “When we saw that, we were off to the races.”

Mischel had been perfecting techniques to isolate single tumor cells and manipulate them individually. Furnari has a background in virology, and is very good at examining tiny bits of DNA in human cells. Together they examined the DNA of hundreds of individual cells taken directly from GBM patients. The team confirmed that the circular DNA’s disappearing act was no laboratory artifact: it happened in experiments performed on actual tumors taken from patients who were treated with an EGFR inhibitor. Equally surprising was their discovery that taking the drug away led to the swift reappearance of the DNA.

“This is like a game of hide-and-seek,” says Mischel. “It’s a stunningly adaptive mechanism.”

That molecular game may have implications for cancer treatment. “The findings suggest a very

“This is like a game of hide-and-seek. It’s a stunningly adaptive mechanism.”

PAUL MISCHEL

different dosing strategy,” says Cavenee. Cancer patients are generally treated with a moderate but sustained regimen of EGFR inhibitors. Instead, the researchers propose pulsing patients with a high dose of EGFR inhibitors to more effectively kill cancerous cells, followed by a drug holiday—a pause in the regimen—when tumors become resistant. This would permit re-emergence of the DNA encoding the target EGFR, which could then be hit once again with the EGFR-targeting therapy.

The team is now investigating whether this mechanism of hide-and-seek occurs in other types of tumors as well. “We have to look deeper,” says Cavenee. “Is this a widespread mechanism in cancer?” A glimmer of support comes from a recent study by George Demetri, director of Ludwig Harvard, and his colleagues. The work hints that gastrointestinal stromal tumor patients who have become resistant to targeted therapy with kinase inhibitors can become resensitized to the same drugs after introduction of an alternative inhibitor or even after a drug holiday. This may work even better if higher doses of the drug are pulsed periodically, as both dose and schedule appear to be important variables.

BENCH TO BEDSIDE AND BACK AGAIN

The researchers have also identified another way that GBM evades EGFR inhibitors and related drugs. They have shown that GBM cells crank up production of a molecule called PML in response to such drugs. PML obstructs the activity of the drugs. They are now gearing up to launch a clinical trial in collaboration with Ludwig’s clinical trials management group. It will test whether the combination of two drugs—arsenic trioxide, which inhibits PML, and TOR kinase inhibitors, which blunt downstream EGFR signaling—does a better job of stalling GBM.

“We use the data from the trials together with the biology we uncover in the lab to design the next iteration of clinical trials that will make a difference,” says Mischel. “That is the cornerstone of our collaborative approach.”

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A WINDOW INTO GIST'S RESISTANCE

A rational approach to drug design and development yields life-saving results

George Demetri has a knack for finding new cancer drugs.

Over the last ten years he has helped develop several drugs that hit a key family of molecular targets, receptor tyrosine kinases (RTKs). Though the drugs have helped patients worldwide, Ludwig Harvard Director Demetri has been frustrated by their lack of long-term effectiveness for most individuals. Ludwig Harvard's research focuses on understanding and overcoming resistance to these therapies, which target signal transduction pathways, as well as others. By elucidating how resistance is induced by structural changes in the targets of the first two agents he helped to develop, imatinib and sunitinib, Demetri and his colleagues identified a promising compound that hits the same molecular target, but in a different manner—one that might circumvent resistance.

That experimental drug, regorafenib, was owned by the pharmaceutical company Bayer. But the company was evaluating its efficacy as a treatment for colorectal cancer without a clear focus on its mechanism of action across many kinases. Demetri approached the company about collaborating to develop the drug with an eye on how it affects the two kinases that directly drive gastrointestinal stromal tumors (GISTs). He and his team had long studied these deadly tumors. "I said, this thing you have on the shelf looks pretty good," he recalls.

Demetri has not been disappointed. He swiftly obtained the agent in 2010, completed studies in mice and, by the end of 2011, finished testing it in patients with GIST. Within three years—a sprint in the slow-moving world of drug-testing—the US Food and Drug Administration (FDA) approved regorafenib as a proven therapy for GIST resistant to imatinib and sunitinib. The approval came on the heels of a successful phase 3 clinical study, published in 2013 in *The Lancet*.

Behind this success is a research enterprise built for speed and efficiency and focused on applying the best science to real-world clinical problems.

"We have a lot of scientific ammunition behind us," says Demetri. His team harnesses a suite of carefully developed cell-based and human-in-mouse "avatar" xenograft models that accurately predict eventual outcomes in patients. They also routinely assess the molecular profile of a patient's tumor to determine which cellular factors have gone awry. This approach, which is now becoming more common, helps tailor the scientific understanding of a cancer and its treatment to each individual patient.

George Demetri, Ludwig Harvard

Demetri's rational approach to drug design and development is making a difference in the lives of patients. With access to imatinib, sunitinib and regorafenib, patients diagnosed with GISTs today can expect to survive, on average, for five years or more, in contrast to the prognosis of less than a year of survival that was typical 14 years ago, before any of these drugs were available. Additionally, nearly one-quarter of patients with advanced metastatic GISTs can survive for more than a decade on targeted therapy.

Demetri is now rallying his lab's considerable resources to test new RTK inhibitors and combinations, and to develop drugs that kill cancer cells by hitting other targets. The studies have the potential to extend life in patients with GIST and benefit patients with other tumors.

DRUGS IN A BASKET

Receptor tyrosine kinase inhibitors choke off tumors by shutting down molecules that prompt cells to survive and proliferate. But as cancer cells evolve to evade treatment with successive

A CHINK IN BREAST CANCER'S ARMOR

Tamoxifen is a mainstay of treatment for many women with breast cancer, but when the drug stops working, tumors can progress rapidly. In a recent study that could lead to new options for such patients, Ludwig Chicago Director Geoffrey Greene and his colleagues discovered why some of the most advanced cases of breast cancer become resistant to this drug.

Tamoxifen binds the estrogen receptor, and in so doing blocks its activity, choking off the ability of estrogen to fuel tumor growth.

Many late-stage, metastatic tumors contain the estrogen receptor but fail to respond to tamoxifen. Greene asked why by closely looking at a battery of 36 such tumors.

He and his colleagues found that about one-quarter of the tumors contained mutations that made the receptor hyperactive. The hyperactive receptors drove tumor cell proliferation even in the absence of estrogen.

In cell culture experiments, the researchers found that it took extremely high doses of tamoxifen—doses too toxic for patients—to shut down metastatic tumors containing the mutations. The findings suggest that compounds that block the estrogen receptor more potently, gram for gram, than tamoxifen may keep breast cancer at bay for longer. The findings were bolstered by similar findings last year by other groups.

"Drug companies and researchers are now actively developing and testing next-generation compounds," says Greene,

George Demetri and Joan Brugge, Ludwig Harvard

"The next step is all about discovering and developing the right combinations for the right patients."

GEORGE DEMETRI

RTK inhibitors, much as bacteria do in response to antibiotics, patients can run out of options.

To circumvent such resistance, Demetri is working on ways to simultaneously hit tumors with drugs that kill cancer cells in different or complementary ways. Even endlessly adaptable cancer cells would be hard pressed to escape all these drugs at once, he reasons. "The next step is all about discovering and developing the right combinations for the right patients," he says.

Demetri is developing a new class of agents to target a protein called MDM2, which helps drive cancer cell proliferation by inhibiting the tumor suppressor protein p53. Compounds that silence MDM2 "wake up" p53, which can then do its work to eliminate cancer cells.

Demetri's group is now testing such agents in patients selected based on the molecular profile of their tumors, particularly the levels of MDM2 in cancer cells along with those of a normal p53 gene. They are initially applying the strategy to address cancers of fat known as well-differentiated or de-differentiated liposarcomas, which harbor amplifications of the MDM2 gene. But Demetri says that patients with many other

whose collaborators in the study included José Baselga and Sarat Chandarlapaty at Memorial Sloan Kettering Cancer Center in New York. Baselga is also a member of Ludwig's Scientific Advisory Committee.

Greene brings decades of experience to the project. His team, for instance, helped determine, at the atomic scale, how tamoxifen binds to the estrogen receptor. This research propelled the development of other hormone-blocking drugs. Yet, even in a terrain so familiar to Greene, cancer biology serves up its surprises. "This was an unexpected result," he says of the team's recent discovery, "and it is making quite an impact on our field."

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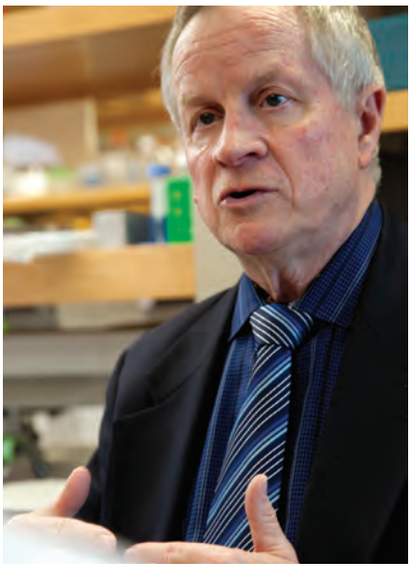

Geoffrey Greene, Ludwig Chicago

types of tumors may also benefit from this strategy, especially if it is used as a sensitizer in combination with another drug to induce synergistic anticancer effects.

About ten years ago, Demetri was one of the first to author a pathway-oriented "basket" clinical trial based on such molecular profiling. When used judiciously, with appropriately chosen targets and patients, this approach can efficiently establish the effectiveness of one therapy against several unrelated forms of cancer that share a particular molecular characteristic. Demetri's application of this basket trial methodology led to the simultaneous FDA approval of imatinib for five different forms of cancer in 2006. Since then, many other research groups have adopted this approach.

Meanwhile, Demetri's team is developing new kinase inhibitors. They include pazopanib, the first FDA-approved therapy for soft-tissue sarcomas other than GISTs since the early 1980s. "We are now understanding resistance at a very deep level," he says, "and with the expansion of Ludwig Harvard, Joan Brugge and I plan to engage the Harvard community in a scientific 'social networking' experiment to bring together even more creative solutions to the problems of drug resistance in cancer." Demetri is hopeful that in the next ten years his quest to develop new targeted cancer drugs will yield an even better record, and, most important, even better outcomes for patients facing many different forms of cancer.

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RECRUITING THE IMMUNE RESPONSE

The only thing as cunning and adaptable as a malignant tumor is the body's own immune system. Here's how some Ludwig scientists are harnessing that response to conquer cancer.

UNLEASHING CELLULAR SOLDIERS

Switching on tumor-targeting T cells and turning off their suppressive siblings to kill cancers

As a clinical oncologist, Jedd Wolchok routinely sees patients with advanced melanoma, an aggressive and often lethal cancer. But Wolchok is also an accomplished researcher. Some of his patients are alive thanks mainly to drugs and therapeutic strategies he has helped develop. They include a recent headline-grabbing, two-drug combination tested against advanced melanoma in a phase 1 clinical trial. But even that relatively potent regimen, which is now being assessed against a variety of cancers in large trials, worked only in some of the patients.

To help the others, Wolchok, who leads Ludwig MSK's Collaborative Laboratory, is probing further into his particular field of research—immunotherapy, which harnesses the immune system to attack tumors. In that effort, he must work closely with basic researchers who specialize in immunology.

He doesn't have to go too far to do that. A small stretch of carpet separates Wolchok's office from that of Alexander Rudensky, director of the Ludwig MSK Center and one of the world's leading immunologists. "We seek each other out," says Wolchok of his collaboration with Rudensky. "We have a very nice confluence of complementary interests, from the level of basic science extending to the early stages of clinical investigation."

In 2013, some of the most promising new therapeutic strategies grew out of this meeting of minds.

TARGETING T CELLS

Rudensky's research focuses on the regulatory T cell, a key agent of the immune system that puts the brakes on immune responses before they do too much collateral damage to healthy tissue. But regulatory T cells also tend to infiltrate tumors, where they perversely quell critical antitumor responses.

In a recent study, Rudensky took a close look at these cells in breast cancer. "This is a type of cancer that has long been thought not to be amenable to immunological means of treatment," he notes. Rudensky and his colleagues asked what would happen when they eliminated regulatory T cells from such tumors: Would other immune cells launch an attack?

That, in fact, is precisely what happens—at least in mice. When the researchers transiently removed regulatory T cells through gene manipulation, they found that tumor cells succumbed quickly to immune attack, and the progression of even well-established and metastatic tumors was slowed.

What's more, when they also treated the regulatory T cell–depleted mice with radiation,

Jedd Wolchok, left, and Alexander Rudensky, Ludwig MSK

the animals suppressed their tumors even more efficiently, and lived considerably longer.

"We were surprised by the magnitude of the effect," says Rudensky, who credits Wolchok with sparking his interest in clinically relevant research. "Without Jedd, I don't think we would have gone into this."

The researchers have shown that an antibody that binds a molecule known as GITR on regulatory T cells can shut down their suppressive activity. They are now testing it in a phase 1 clinical trial in patients with many different types of cancer. This trial is overseen by Ludwig's clinical trials management team and is being conducted in collaboration with Ludwig's longstanding partner, the Cancer Research Institute, and the two institutions' joint CVC Trials Network.

KILLER COMBINATION

In addition to paving the way for a new type of immunotherapy, Rudensky's findings on radiation and T cell ablation illustrate the value of combining distinct types of cancer therapy. And that is a salient theme of Wolchok's work.

In the phase 1 melanoma trial completed last year, Wolchok combined two immunotherapies: ipilimumab, which has been used since 2011 to treat melanoma, and an experimental drug,

"We were very pleased by the speed and sheer depth of the response in so many patients."

JEDD WOLCHOK

nivolumab. Each drug targets a specific molecule on the surface of immune cells that functions as a 'checkpoint' to dampen their activity. Blocking each of these checkpoints with antibody drugs lifts the brakes on the cellular immune response.

When melanoma patients receive ipilimumab alone, about 20% achieve long-term remission extending over three years, which is a notable achievement. The median survival time for this disease before this and other modern medicines became available was just seven months. Wolchok's study suggests that combining it with nivolumab has the potential to dramatically improve outcomes. His small trial found that a concurrent regimen of the two drugs significantly shrank tumors in 21 of 52 patients, with 90% of those who responded to the therapy continuing to benefit after more than a year of follow-up.

"We were very pleased by the speed and sheer depth of the response in so many patients," says Wolchok.

The findings helped convince *Science*, a prestigious journal, to choose cancer immunotherapy as its "breakthrough of the year." Several pharmaceutical firms are vigorously pursuing agents with activity similar to that of nivolumab. They and a host of smaller biotechnology firms in the immunotherapy field are also looking closely at combined immunotherapies of this kind as a new approach to cancer therapy.

FAST FORWARD

Wolchok and others are now testing the combination of ipilimumab and nivolumab in larger clinical trials for melanoma and a variety of other cancers. "It is important to recognize that none of this would have been possible without many decades of basic science," says Rudensky.

Wolchok notes that Ludwig's translational support is allowing his team to move its basic research findings quickly into early clinical trials. Just as invaluable, he notes, is the instant access to other top-notch Ludwig researchers, like Rudensky, who are just a stone's throw from his laboratory.

"It is a pleasure to have such remarkable expertise right next door," says Wolchok. "This collaboration will endure and I believe it will ultimately be of benefit to people diagnosed with a wide variety of cancers."

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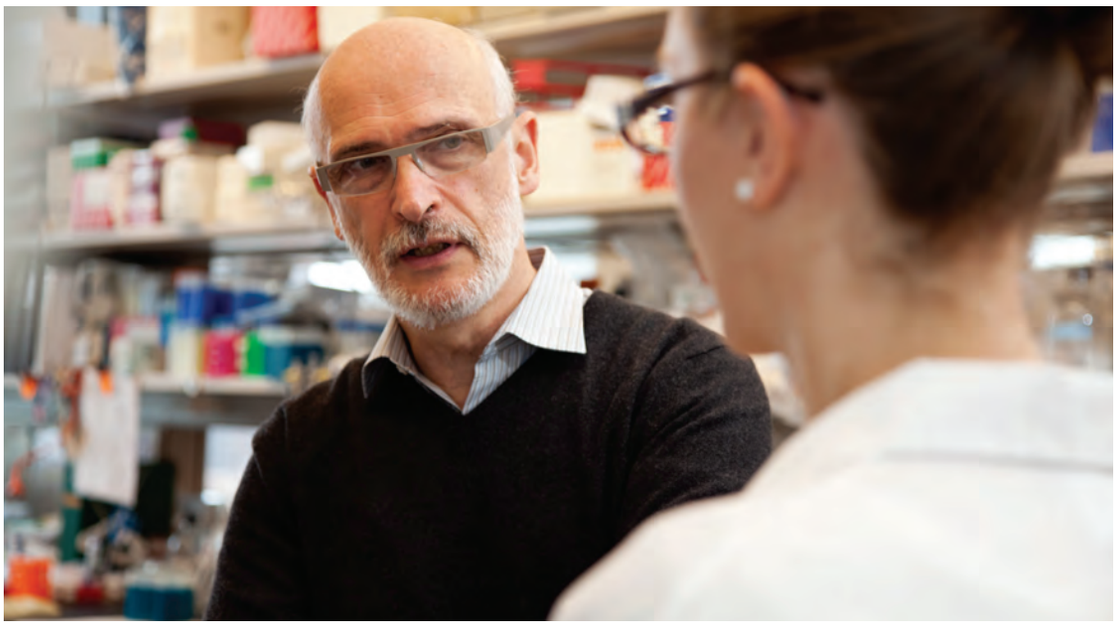

KEEPING PEACE IN THE GUT

Inspired by his collaboration with Ludwig clinical investigator Jedd Wolchok, Alexander Rudensky seeks out opportunities to move his research on the basic biology of immunity closer to the clinic. In a recent study, he examined how a cell that tames the immune response—the regulatory T cell—operates in the gut of mice, and he is now teasing out the implications for colon cancer.

The gut is home to trillions of commensal bacteria, many of which help us digest food. Regulatory T cells help shield these microbes from destruction by the immune system and protect the intestine from inflammation and damage. But how the bacteria communicate with T cells has been unclear.

In a new study, Ludwig MSK Director Rudensky and his colleagues identified a key role for metabolites produced by these bacteria, in particular the fatty acid butyrate, which is produced when bacteria digest dietary fiber. They found that applying the metabolites to mice that lacked microbes could bump up the production of regulatory T cells and calm immune-mediated inflammation in the gut. The researchers also traced the mechanism behind this effect, for instance showing how butyrate bumps up the production of Foxp3, a key protein that helps turn ordinary T cells into regulatory T cells. “Metabolites produced by commensal microorganisms serve as a means of communication with the immune system of the host,” Rudensky says.

Rudensky published his discovery in December, 2013, and is now exploring its implications for colon cancer, which can be fueled by gut inflammation. He is testing various metabolites in preclinical mouse models of colon cancer, and investigating whether he can alter the course of disease by applying butyrate or other microbial molecules. He is also examining how a proper balance of immune cells and microbes in the gut can affect the overall health of the immune system.

Rudensky’s research still has a long way to go before it can reap practical benefit. But he knows he is on the right course. “These metabolites likely have a major effect on colon cancer progression—and probably play a role in other cancers as well.”

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Jonathan Skipper, Ludwig Technology Development

TURNING IDEAS INTO THERAPIES

The source of innovative cancer treatments is the laboratory but their proving ground is the clinic. Linking the two is Ludwig's technology development team.

The team's assignment—translating Ludwig's most promising basic research discoveries into products fit for the clinic—is something few laboratory scientists, even those who have a translational focus, can complete on their own. Researchers often lack the resources and know-how to do that. The tasks required include preclinically evaluating potential drugs and testing them for safety; designing and managing clinical trials; and forging agreements with clinical research partners. "The majority of our work takes place behind the scenes," says Jonathan Skipper, who heads the technology development team. "Most people don't have any true sense of the extent of the work involved."

Many researchers at Ludwig, including Alexander Rudensky and Jedd Wolchok of Ludwig MSK, have teamed up with the technology development group. In just one ongoing project with Ludwig MSK, the group is helping to test a new immunotherapy agent. It is an antibody that binds glucocorticoid-induced tumor necrosis factor receptor (GITR), a molecular target on key immune cells called regulatory T cells. Skipper's team worked with the Ludwig MSK researchers to develop the clinical trial protocol and navigated paperwork to ensure the study's compliance with the requirements of the US Food and Drug Administration and institutional review boards. It also established agreements with clinical trial sites at other institutions and with GITR Inc., the company supplying the investigational drug.

Only after all this was done could the team turn to the task of implementing and managing the conduct of the clinical trial. The trial, which is testing the GITR antibody in patients with many different types of cancer, is now underway,

only months after the publication of the basic research study in mice that sparked the idea.

By shouldering all of these tasks, Skipper's team enables the Ludwig MSK researchers to evaluate their research findings in the clinic.

Lining up drug company support can be a tough, lengthy process and Skipper's team keeps the Ludwig MSK researchers nimble by helping them retain control over critical decisions, such as clinical trial design and correlative research studies. "The support gives us the ability to catalyze the translation of important laboratory findings into clinical trials," Rudensky says.

To navigate the route from benchtop to bedside, Skipper has built a multidisciplinary team of experts with backgrounds in framing partnership contracts and agreements on intellectual property. The team also includes regulatory and clinical trials experts who understand how to design and run trials.

In addition, Skipper oversees the small molecule discovery group at Ludwig San Diego, led by Andy Shiau, which provides researchers with tools and compounds for studies that may eventually lead to the design and generation of new drugs suitable for clinical evaluation.

"Having all this provided by a nonprofit research organization like Ludwig is a major investment in translational cancer research and is pretty unusual," says Skipper. "Many institutions encourage scientists to take discoveries to the clinic; few enable it like Ludwig Cancer Research."

Web Cavenee, director of Ludwig San Diego, has also recently tapped Skipper's team. Together, they are preparing for a clinical trial combining two antitumor agents. They are investigating whether they can use the experimental combined therapy to shrink glioblastoma multiforme, a deadly brain cancer—an outcome Cavenee's team recently demonstrated in mice. "They have taken a big load off our shoulders," Cavenee says of the technology development team.

Andy Shiau, of Ludwig's Small Molecule Discovery Group

"Many institutions encourage scientists to take discoveries to the clinic; few enable it like Ludwig Cancer Research."

JONATHAN SKIPPER

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.

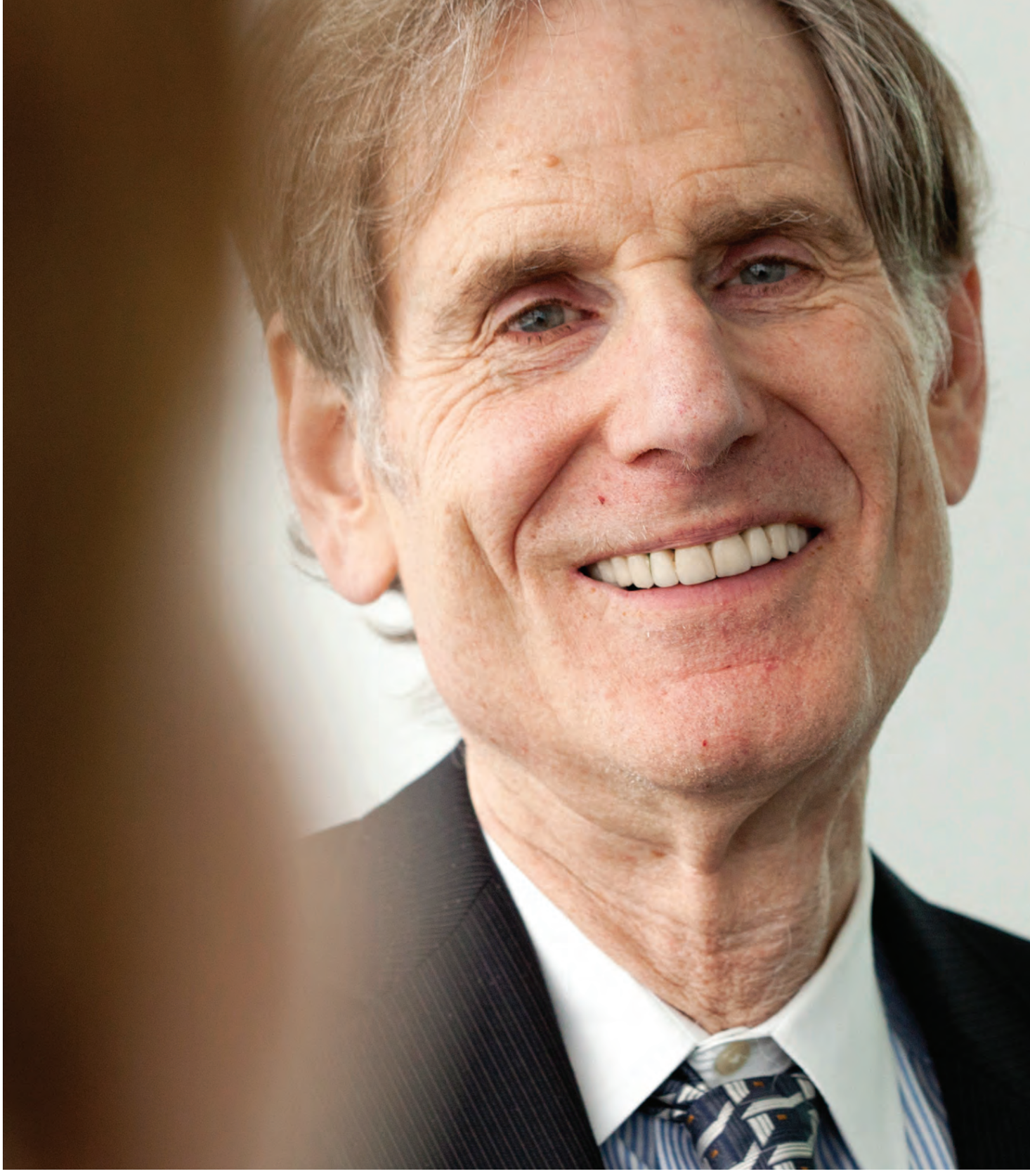
Weichselbaum's studies at this intersection of radiotherapy and immunotherapy, which have traditionally been separate subfields of clinical oncology, could lead to new strategies to induce durable antitumor responses in patients with highly resistant cancers.

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

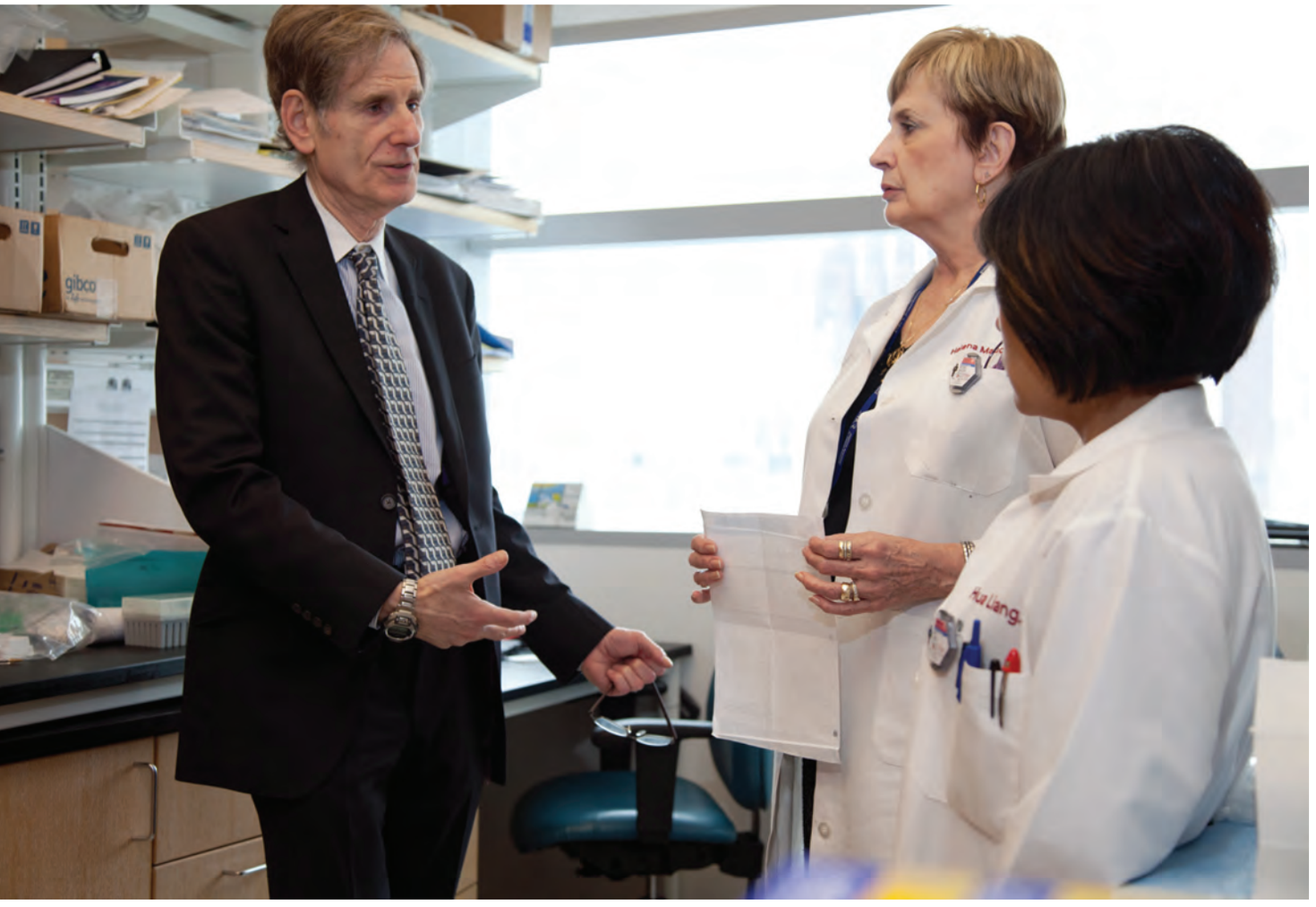


Ralph Weichselbaum, Ludwig Chicago

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.

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SERVING UP CANCER CELLS

An antibody that counters cancer's "don't eat me" signal is all set to be tested as a therapy

Irving Weissman is wary of the pitfalls of drug development.

Over decades of research, the Ludwig Stanford director has launched three biotechnology companies, and has set up many partnerships with large pharmaceutical firms. These are often the only ways to move products through the expensive clinical trial process. The experience has changed Weissman's mind about how best to get major discoveries to the clinic. All too often, he says, promising therapies are shelved at early stages because of business decisions. And he is determined not to let that happen to his latest endeavor. Weissman and his colleagues aim to hold onto this latest project longer, proving its worth before seeking the appropriate venue for clinical and commercial application.

Weissman's team has developed a therapeutic antibody against a key protein found on the surface of essentially all tumor cells, CD47, and is preparing it for human studies. After years of labor, including readying paperwork and lining up patients, human studies are set to begin this summer at Stanford. The researchers will examine the safety and appropriate dosage of the antibody therapy against a variety of solid tumors. This will be followed by a similar trial for acute myeloid leukemia centered at the University of Oxford. If all goes as planned and hoped, the antibody will be tested against a broad spectrum of cancers in more advanced trials.

In addition to tapping Weissman's extensive experience in launching biotech firms, the project bridges his three primary domains of scientific expertise: stem cells, cancer and immunology. Last year his team also made strides with basic research studies that could refine the therapeutic targeting of CD47 and create opportunities for new therapeutic candidates down the line.

ROAD TO IMMUNOTHERAPY

CD47 first caught Weissman's interest when his team found that it coated the surface of cells they had been studying for years, stem cells in the blood and bone marrow that give rise to leukemia. Intrigued, the researchers investigated how widespread the phenomenon might be. "We found that it is highly expressed in every type of cancer we examined," says Weissman.

CD47, it turns out, is critical to tumor survival. It tells macrophages, immune cells that patrol the body and engulf diseased cells, to cease and desist. "Every cancer cell seems to transmit this 'don't eat me' signal to help it avoid elimination by macrophages," Weissman says.

Weissman and his colleagues have tested their antibody against CD47 in immune-deficient

Irving Weissman, Ludwig Stanford

mice bearing transplanted tumors taken directly from patients, and found that it blocks the "don't eat me" signal. As a result, macrophages consume cancer cells, dramatically reducing tumor size. What's more, the anti-CD47 antibodies synergize with therapeutic antibodies such as rituximab, which is used to treat certain blood cancers. This synergy, the team found, leads to the complete elimination of most human tumors in these mice, and the elimination of all metastatic tumors evaluated so far.

HONING THE APPROACH

Meanwhile, Weissman and his team have gone back to the bench to take a closer look at how the anti-CD47 antibody operates. In July 2013, his team showed in mice that the antibody not only prompts macrophages to eat tumors, but also activates killer T cells. Their studies revealed that these immune cells, which can attack cancer cells, prevent human tumors from taking hold when implanted into mice. The new findings have led to a planned scientific collaboration with Alexander Rudensky and Jedd Wolchock of Ludwig MSK, who are also running immunotherapy trials.

Together, the researchers plan to monitor the immune responses of patients in the upcoming clinical trial. They will investigate whether the patients' T cells are activated by anti-CD47 antibodies, as they are in mice. The scientists are also planning animal studies to examine whether anti-CD47 antibody treatment can be powered up by drugs that activate T cells—such as murine versions of the experimental drug nivolumab, one of several "immune checkpoint blockers" that modulate the immune response.

In 2013, Weissman's team also found an alternative way to target CD47, using a small protein molecule based on a natural binding partner for CD47 on macrophages. The new protein synergized strongly with rituximab and other tumor-targeting antibody therapies, enhancing their tumor-busting capability in experiments in mice. "This new agent is about

a year and a half from moving into clinical trials," says Weissman. "But it could be an alternative first-line therapy, and certainly has potential as a backup therapy if resistance evolves to the CD47 antibody."

IN THE HOUSE

Weissman leads a group of Ludwig-funded principal investigators at Stanford with a wide range of expertise. "Weissman has made an antibody himself, and it is now poised for evaluation in clinical trials without the help of a commercial entity," says Jonathan Skipper, who leads Ludwig's technology development program. "That is a major accomplishment."

If the phase 1 trials show that the antibody is safe, and if the experiments show synergy of anti-CD47 treatments with immune checkpoint blockade antibodies, Weissman plans to carry out preclinical tests to optimize the combination and test its safety. If these are successful, he hopes to launch clinical trials to test whether the optimized combination has synergistic effects on tumors. He has already begun discussions with Skipper's team, which will bring expertise in immunotherapy to guide the trials.

Weissman is confident that his team's work on CD47 will, with Ludwig's support, be judged worthy (or not) of further investment on the basis of its scientific merit, independent of commercial considerations. "If all of this works out," he says, "we can move forward with this whole package of immunotherapies in a way that will be of maximum benefit for patients."

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AIMING AT THE SOURCE

Most cancers are lethal only because they spread. Here's how some Ludwig scientists are investigating cancer's mobility and devising strategies to stem the tide of malignancy.

TARGETING THE SEEDS OF METASTASES

A better understanding of cancer stem cells opens the door to designing more effective therapies

A tumor is a constantly changing thing. Within its constituent cells, DNA shatters and mutations accumulate. The cells themselves shift shape and change state—migrating or staying put, resisting cancer treatment or succumbing to it.

Robert Weinberg has long investigated how such transformations occur. Director of Ludwig MIT, Weinberg was one the first researchers to identify key genes—tumor suppressors and activators—that control cancer development.

Lately, one peculiar but powerful type of cellular shape-shifting has captured his interest. Five years ago, he and his colleagues showed how less aggressive breast cancer cells can morph into cancer stem cells that can spawn new tumors, including metastases.

"This area of study has profound implications for translational medicine and the treatment of tumors," says Weinberg.

PLASTIC CANCER CELLS

Until recently, researchers presumed that cancer stem cells operate unidirectionally—that these quiet, slow-growing cells give rise to the more rapidly growing cells that make up the bulk of a tumor. But recent studies have challenged that notion, showing that in some tumor types the opposite can occur: non-stem cells can become cancer stem cells.

Weinberg and his colleagues took a close look at this reverse conversion in breast cancer. They found that the process is driven by a gene called *ZEB1*, and that it occurs most often in more lethal types of breast cancer. In the cells of such tumors, the *ZEB1* gene is poised to be activated by a simple molecular nudge—such as exposure to TGF-β, a molecule often present in tumors. "If you treat non-stem cells with TGF-β, then *ZEB1* springs into action," explains Weinberg. More benign breast cancer cells, in contrast, fail to respond to TGF-β by activating *ZEB1* expression, entering into a cancer stem cell state and becoming aggressive.

Weinberg thinks that the mechanism may account for the aggressiveness of some tumor types, notably breast cancers. He proposes that before primary tumor cells migrate to new locations in the body, they can switch on ZEB1 and turn into cancer stem cells that seed metastatic tumors.

HITTING THE STEM CELL

Several research groups are developing experimental drugs to specifically target stem cells. Weinberg is working on such agents with Verastem, a biotechnology company he cofounded, testing agents that kill cancer stem cells or disable them by prompting them to turn into non-stem cells.

Robert Weinberg, Ludwig MIT

The new findings suggest that researchers have to go one step further to kill aggressive tumors: they also need to target non-stem cells that can change into cancer stem cells, or prevent their formation. Weinberg is hopeful that in the next few years his laboratory will generate experimental agents that can do these things.

Research such as this may one day lead to treatments that block metastasis and enable durable control of cancer, says Weinberg. “Patients rarely die from their primary tumors. They almost always die from their metastatic tumors.”

That reasoning has driven Weinberg to make the study of metastasis the central focus of Ludwig MIT. His own group is now building on the ZEB1 study to investigate whether a similar mechanism generates stem cells in other tumor types and to uncover other processes that propel metastases.

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LURING MELANOMA CELLS TO THEIR DEATH

An experimental strategy pushes drug-resistant stem cells into a susceptible state—and kills them

It all began with a white mouse. Ludwig Oxford scientist Colin Goding first heard about the creature in 1992, through the scientific grapevine. The mouse that so piqued his curiosity carried a disruption in a long-sought gene that controlled the production of melanocytes, pigmented cells of the skin.

Goding, who was using cells grown in culture to study the control of cellular pigmentation, had already identified a key DNA sequence pattern he called the M-box. He predicted that this M-box was bound by a master regulator in pigment cells. When he heard about the mutant mouse, he knew immediately that its disrupted gene encoded that missing regulator.

Now, more than 20 years later, Goding's research on the gene, called MITF, is paying off with a potential treatment for melanoma, a skin cancer that is easily treated if caught early but swiftly lethal once it has metastasized. Goding's approach involves a two-drug combination: one drug tweaks tumor cells so they produce the protein encoded by the MITF gene, and the second selectively kills cells expressing high levels of that protein. Last year Goding and his Ludwig colleagues showed that this combination beats back melanoma in mice, and they are now conducting preclinical studies toward its future assessment in patients.

FROM STEM CELL TO DEAD CELL

Melanoma tumors, like those of most cancers, comprise a variety of cells. The bulk of the primary melanoma tumor contains pigmented cells, some of which proliferate rapidly. These cells generally express the MITF gene. But most melanomas also contain some deadly unpigmented cells lacking MITF that tend to be highly resistant to therapy because they do not divide very frequently. Like stem cells, these unpigmented cells can seed new tumors elsewhere in the body.

Metastatic tumors account for the poor prognosis of melanoma. Recent advances in harnessing the immune response to treat melanoma—in which Ludwig has played a leading role—have significantly improved prospects for patients. Still, there remains a serious need for new strategies to control this cancer.

In their new study, Goding and his colleagues reasoned that there might be a way to prompt the stem cell–like components of melanoma tumors to become susceptible to therapy. After testing various agents, the researchers found that methotrexate, a drug that has long been used in the clinic to treat some cancers and autoimmune diseases, prompted those cells to express MITF, produce pigment and proliferate. Methotrexate had this effect on the cells in both laboratory cultures and animal models.

Colin Goding, Ludwig Oxford

Next, the researchers asked how they could selectively disable the MITF-expressing cells. To do this, Goding and his colleagues designed a drug that was activated by a protein whose expression is ramped up in MITF-expressing melanocytes. When activated, the drug, called TMECG, killed tumor cells. “The drug combination works beautifully in mouse models,” says Goding.

MOVING IN ON MELANOMA

This two-step approach has several potential advantages as a therapy. By transforming the stem cell–like cells into proliferating, pigmented cells, the researchers eliminate the source of metastases. And by killing off the tumor with a drug that is activated only in pigmented, MITF-expressing cells, they effectively target the drug to melanoma cells. “This drug combination is very specific to pigmented cells,” says Goding. “You would not expect to see any side effects.”

Moreover, the new combination also works in tumor cells that have become resistant to targeted therapies, such as inhibitors of the protein BRAF.

Goding is now laying the groundwork for potential clinical trials, and he is already working with colleagues to perform toxicology tests on his new drug candidate. The utility of the new strategy will, of course, be proved only through such trials. What requires no further proof is that it pays to keep an ear close to the scientific grapevine.

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