

The background of the entire page is a close-up photograph of laboratory equipment. On the left, a portion of a green microplate is visible. In the center and right, several clear plastic test tubes with blue and green caps are shown. The test tubes have volume markings in milliliters (mL). One tube in the foreground has markings for 35, 40, 45, and 50 mL. Another tube to its right has a marking for 1 mL. The tubes contain liquids of various colors, including green and yellow. The overall lighting is bright, creating a professional and scientific atmosphere.

# LUDWIG CANCER RESEARCH

2017  
RESEARCH HIGHLIGHTS

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LIFE-CHANGING SCIENCE



# WELCOME

No scientific discovery is made in a vacuum. Behind every publication in a peer-reviewed journal lies a story, each with its own genesis, causal arc and cast of leading characters. The theme that binds them all is that intellectual itch—curiosity—that has always propelled science. But scientific stories, especially those of biomedical research, can also generate new technologies, sometimes even transformative ones that save lives.

This is certainly true for cancer research. So in this Research Highlights Report, we have sought to showcase a sampling of the life-changing science published by the scientists of Ludwig Cancer Research in 2016. We could not, however, resist the opportunity to also profile the scientists themselves. This is why you will learn in these pages not only about the discoveries but also about the discoverers and their personal journeys. You will probably notice that one thing all the stories illustrate, and amply, is the centrality of human interaction—mentorship, chance encounters, collaboration—to the progress of science.

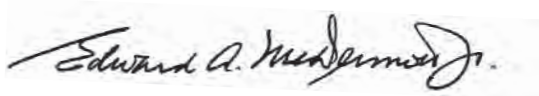
Since its founding, Ludwig has recognized these essential human elements of the scientific endeavor: teamwork and the passions that drive researchers to do what they do. It has thus encouraged collaboration between its scientists, while giving them the space and time they need to pursue their fascinations and refine their ideas to better serve biomedical science, and Ludwig's mission. The approach works. It allowed our scientists in Europe and the US to help lay the foundations for one of the most exciting developments in cancer research today—the rise of immunotherapy. It has also allowed them to contribute significantly to a richer understanding of basic cancer biology.

But we are not resting on our laurels. You will learn in this report how our researchers are changing the uses of radiotherapy and the future of bone marrow transplantation, altering how we understand tumor evolution and the cancer cell's adaptability, and expanding our knowledge of DNA repair. You'll find out how they elucidated the mechanism by which a drug coaxes tumor-tolerant immune cells to turn against cancer cells, and engineered bacteria into invasive, drug-pulsing destroyers of tumors. And you will read about how Ludwig's Lausanne Branch has launched a pioneering and scientifically ambitious program to revolutionize the design, development, delivery and evaluation of personalized immunotherapies for cancer patients.


We hope you find the reading engaging, informative and, above all, enjoyable.

Sincerely,

Ed and Chi



**Edward A. McDermott Jr.**  
President and Chief  
Executive Officer



**Chi Van Dang**  
Scientific Director

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# MAKING DISCOVERIES



Paul

Mischel

Photo by Stewart Marciano

# CANCER'S SUBVERSIVE INQUISITOR

Paul Mischel's long exploration of the cancer cell's adaptability led him to one startling discovery about cancer genes and another about a brain tumor's dependency on stolen cholesterol.

About a week after Paul Mischel arrived at Ludwig San Diego in 2012, Andy Shiao and Tim Gahman of Ludwig's Small Molecule Discovery Program stopped by his office bearing gifts. Two gifts, to be precise.

One was a brain-shaped lollipop, the other a vial of LXR-623, an experimental drug once fielded in clinical trials for heart disease but dropped because people on it tended, of all things, to lose track of time. "They're fantastic colleagues," Mischel says of Shiao and Gahman, who had worked on cholesterol drugs in the private sector before joining Ludwig. "They had scanned the literature carefully and recognized this critical opportunity in a molecule that wasn't even meant to treat cancer."

In 2016, Mischel and a colleague at The Scripps Research Institute published a study they'd led that validated Shiao and Gahman's instincts. The researchers reported in *Cancer Cell* that LXR-623 crosses the blood-brain barrier—the achievement symbolized by the lollipop, and manifested in the loss of time—where it selectively kills cells of the aggressive and preternaturally drug-resistant brain cancer glioblastoma multiforme (GBM). Their paper describes how the drug sabotages a key metabolic adaptation of GBM cells, and shows that therapies that target novel vulnerabilities in cancer cells might be found outside the traditional cancer drug pipeline.

Mischel was far from done for the year. Working with colleagues at the University of California, San Diego, he also completed a long-running study on an entirely different phenomenon. The paper, published in *Nature* in early 2017, upended a fundamental assumption of cancer biology. It reported that, across a broad spectrum of tumor types, cancer genes are primarily located not on chromosomes, as had long been assumed, but on circular fragments of extrachromosomal DNA (ecDNA). The distinction is not academic. Mischel and his colleagues found that oncogenes located on ecDNA drive tumor evolution and drug resistance far more potently than their chromosomal counterparts. Their discovery fundamentally alters how researchers will now regard tumor evolution and has implications for the development of cancer therapies.

## METABOLIC DEXTERITY

When Mischel, trained as a clinical pathologist and then as a scientist, set up his first laboratory at UCLA in 2001, he turned his attention to dissecting the signaling pathways that drive GBM, working with Charles Sawyers, who is today at Memorial Sloan Kettering in New York. Together, the researchers uncovered some key molecular tricks GBM cells employ to resist therapy. Yet, though the research was rewarding and productive, Mischel saw challenges ahead. "It was almost like we were chasing our



Photo by Stewart Marciano

tails: We were always going to be one step behind cancer's ability to adapt and develop resistance to therapy."

The problem, he grew convinced, needed to be considered from a number of different angles, with an eye to how the GBM cell adapts to both its particular environment—the brain—and to therapy. One approach to discovering new vulnerabilities that fascinated Mischel was cellular metabolism.

"One of the most important things mutations in GBM do is change how the tumor takes up and utilizes nutrients," he says. "If we could define those changes, we might begin to understand and identify new vulnerabilities in GBM tumors."

Over the past several years, Mischel and his colleagues have shown how the signals transmitted by EGF receptor vIII (EGFRvIII), a mutant cell-surface protein that often drives the fierce proliferation of GBM cells, is linked to their metabolic control systems. His team has elucidated how its signals cascade through the GBM cell, coordinated by protein complexes known as mTORC 1 and 2, to not only fuel growth but alter the import and processing of vital nutrients that support

such growth as well. In 2015, he worked with Ludwig San Diego's Bing Ren to detail the molecular cascades by which EGFRvIII alters the chemical, or "epigenetic," modification and reading of the GBM genome to reprogram cellular metabolism.

Work previously done in Mischel's lab at UCLA had revealed that GBM tumors are exceptionally rich in cholesterol, even by the standards of the brain, which holds 20% of the body's total. Those studies also revealed that EGFRvIII was responsible for GBM's cholesterol glut, and that tumor cells import (rather than produce) vast quantities of the molecule. Indeed, blocking cholesterol import proved especially lethal to GBM cells. Why this was the case, however, remained unclear.

Mischel and his team decided to take a deeper dive into that dependency in a collaboration with the laboratory of Benjamin Cravatt of The Scripps Research Institute.

### BAD CHOLESTEROL

When normal cells have enough cholesterol, they start pumping out the excess and convert some of it into molecules known as oxysterols. These molecules activate a receptor in the cell's nucleus called the liver X receptor (LXR), which turns on the genes that coordinate that process.

In 2016, Mischel, Cravatt and their colleagues reported in their *Cancer Cell* paper that GBM cells are extremely dependent on imported cholesterol because they don't make their own. They also showed that GBM cells shut down the production of oxysterols to keep the cholesterol coming. LXR-623, which short-circuits that mechanism by independently activating LXR, not only penetrates the GBM tumor but selectively kills cancer cells.

"The brain's local environment creates a uniquely rich soil for GBM tumors and the cancer cells behave like parasites to take



Photo by Stewart Marciano

advantage of it,” says Mischel. “This is a real example of the tumor adapting to scavenge resources. But it also creates a vulnerability because they switch off the stop mechanism for cholesterol import and fail to produce their own stock of the molecule. This creates a metabolic codependency, making the GBM cells vulnerable to drugs that turn that switch back on.”

Mischel and his colleagues examined LXR-623’s effect on GBM tumors taken from patients and implanted in mice. The drug, they showed, significantly slowed the growth of the tumors and prolonged the survival of treated mice. It did so in every GBM tumor examined and even with other types of tumors that had metastasized to the brain.

The drug’s ability to cross the blood-brain barrier excites Mischel because few drugs can do that very well. This failure causes inadequate dosing, which in turn drives GBM’s drug resistance.

“The brain’s local environment creates a uniquely rich soil for GBM tumors and the cancer cells behave like parasites to take advantage of it.”

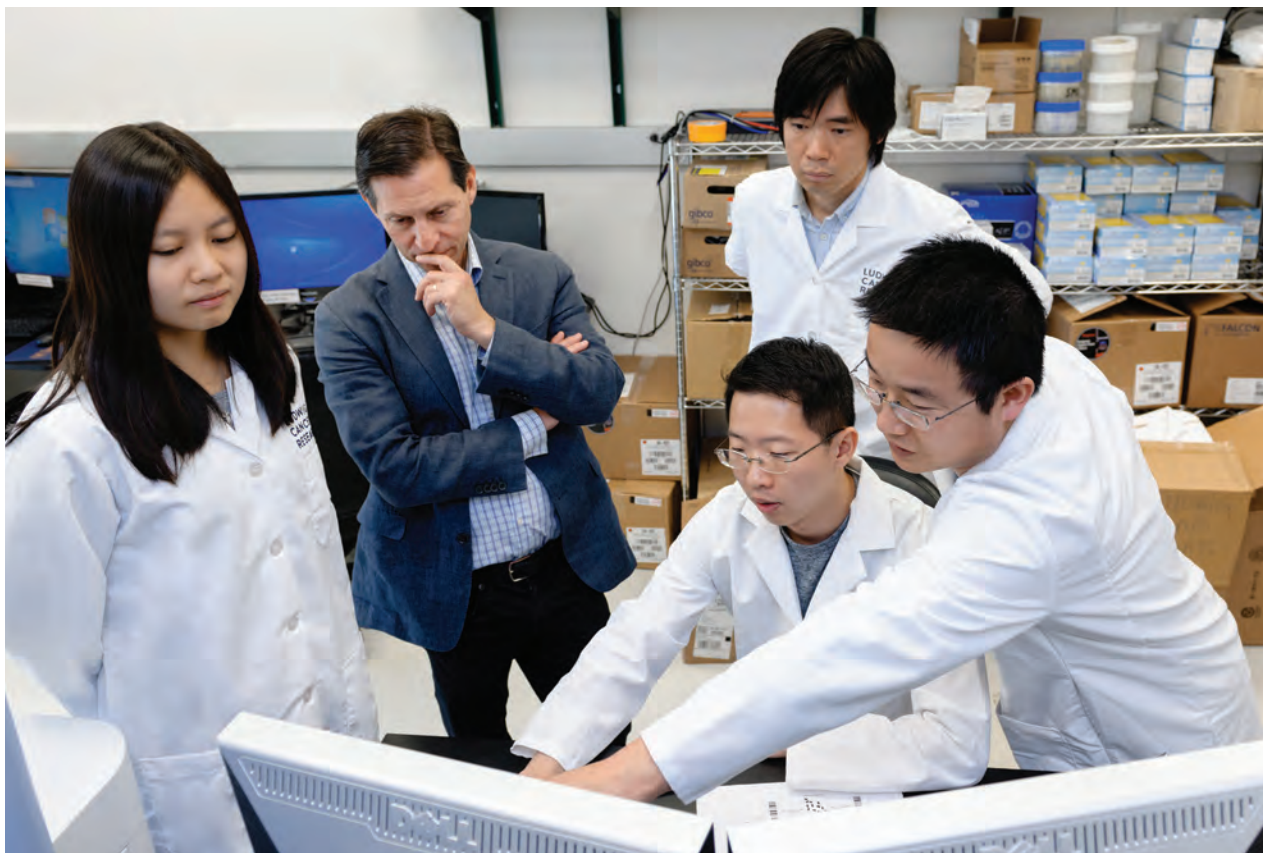


Photo by Stewart Marciano

“The important thing here is that by targeting different aspects of a tumor’s adaptations, rather than just its growth, we might be able to take advantage of drugs coming from a variety of pipelines,” says Mischel. “These drugs can have far more favorable pharmacological properties.”

#### BROADER ADAPTATIONS

Along with their studies of cancer metabolism, Mischel and his team have continued a parallel and sometimes overlapping line of investigation into the tumor’s many mechanisms of drug resistance. In early 2016, for example, they co-authored a paper in *Cancer Cell* with James Heath of the California Institute of Technology in which the researchers analyzed responses to therapy in individual GBM cells. They showed that the cells begin adapting their internal signaling networks to resist therapy within as little as three days of its initiation.

Such adaptations have long fascinated

Mischel. In the early years of this decade, he and his colleagues at Ludwig San Diego, Frank Furnari and Web Cavenue, were looking at how GBM tumors evolve against drugs that block EGF receptor signaling when they noticed something startling. In a paper published in 2014 in *Science*, they reported that GBM cells expressing EGFRvIII stored genes for the mutant receptor not only on their chromosomes but on circular elements of DNA, or ecDNA, as well. Strangely, when exposed to EGFR-targeting drugs, the tumors seemed to “hide” their ecDNA; when the treatment was stopped, the ecDNA would come screaming back to drive growth.

#### LOCATION, LOCATION, LOCATION

Conversations with other researchers who had also noticed ecDNA in cancer cells turned Mischel’s interest in the phenomenon into a minor obsession. But when he scoured the scientific literature, he found that while ecDNA had been seen in tumor cells decades ago, it had long been assumed to be rare

and inconsequential. Cancer biologists had focused almost exclusively on which genes promote cancer, not where in the nucleus those genes are located. Genomics technologies had at the same time evolved along lines that favored the former type of analysis. As a consequence, nobody had really looked into the matter seriously.

Mischel decided to start looking. Led by post-doc Kristen Turner, Mischel's team applied classical cell genetics techniques and integrated them with cutting edge genomics to get a grasp of how common ecDNA might be across 17 distinct types of cancers. They found ecDNA in 40% of tumor cell lines and in nearly 90% of patient-derived models of brain tumors, but very rarely in normal cells.

"Once we saw how big an issue this was, we started thinking about the fundamental question of why," says Mischel. "Why would this actually happen? What's the benefit to a tumor of having an oncogene on ecDNA as opposed to a chromosome?"

Trouble was, given the paucity of research into ecDNA, there were no biological models in which to conduct the necessary experiments. So Mischel began working with Vineet Bafna—a computational biologist at UC San Diego introduced to him by Bing Ren—to build mathematical models of the influence ecDNA would have on tumor evolution. The researchers then vetted those predictions against the results of experiments conducted on tumor samples from patients.

They found that cancer genes are far more likely to occur on ecDNA than on chromosomes. ecDNA apparently allowed tumors to more rapidly achieve and maintain high levels of such genes. Further, ecDNA is parceled out randomly to daughter cells when a tumor cell divides, and the researchers showed that the greater the variation in their number, the more diverse the cells in a tumor.

“There’s increasing evidence that cancers have a burst of genome instability, where they go from having a gradual, stepwise accumulation of mutations to all hell breaking loose ...”

"This is likely to be of great importance to the genesis of cancers, or at the very least to the changes that occur as cancers go from early stage to highly drug-resistant, late stage tumors," says Mischel. "There's increasing evidence that cancers have a burst of genome instability, where they go from having a gradual, stepwise accumulation of mutations to all hell breaking loose in their genomes."

EcDNA, Mischel observes, might be an important driver of that transformation, and he hopes next to explore the mechanisms by which it is generated. Unraveling those processes could expose new vulnerabilities in a variety of cancers—and throw open an entirely new approach to cancer drug development. ■



George

Coukos

# LUDWIG LAUSANNE: IMMUNOTHERAPY'S HI-TIDE

George Coukos is all set to make Ludwig Lausanne a global pioneer in the development, delivery and evaluation of personalized, cell-based immunotherapies.

It was with some hesitation that George Coukos first responded in 2011 to an invitation to consider moving to Lausanne. On offer was the directorship of both a revamped Lausanne Branch of the Ludwig Institute for Cancer Research and a proposed Department of Oncology at Centre Hospitalier Universitaire Vaudois (CHUV) of the University of Lausanne (UNIL). Trouble was, he was quite happy at the University of Pennsylvania, where he had established the Ovarian Cancer Research Center—a prototype for linking basic, translational and clinical research in cancer immunotherapy. He was also a tenured professor and clinician at the prestigious university, with guaranteed tuition for his children, a dream house and no intention of ever leaving the United States.

On the other hand, as he learned more about the opportunity, it became increasingly clear that if he wanted to build a truly pioneering program for developing advanced immunotherapies, Lausanne was just the place for it. Coukos would find in CHUV a sophisticated hospital and at UNIL and beyond a vast pool of researchers who would be eager to participate in any such effort. Further, Lausanne is home to the Swiss Federal Institute of Technology (EPFL) and the Swiss Institute of Bioinformatics (SIB). “These are two ingredients essential to the development of advanced T cell therapies, and they’re extraordinarily difficult to come

by,” says Coukos. “Here, I had them within reach, 25 minutes from the Ludwig Branch, available and eager to collaborate.”

So it was that after several discussions with Ludwig’s leadership and five trips to Lausanne in which he met with the leadership of UNIL, CHUV, and the Cantonment to ensure he’d have the financial and institutional support he’d need, Coukos was sold. His colleagues at Penn were astonished. “They tried very hard to persuade me not to leave,” recalls Coukos. “‘George,’ they said, ‘this is career suicide, what you’re trying to do. You’ll never be able to get it up and running in time.’ But here we are, five years later, and we have built it all.”

What Coukos and his colleagues have built is a rationally assembled, integrated system for swiftly devising, creating and testing personalized immunotherapies for individual cancer patients. It has two core components. One is a network of translational research labs, housed primarily at Ludwig Lausanne, named the Human Integrated Tumor Immunotherapy Discovery & Development Engine, or Hi-TiDe. The other is the clinical arm of the endeavor, the Centre for Experimental Therapeutics (CTE), which is at CHUV. “The Hi-TiDe is responsible for the discovery and the development of new immunotherapies, and the CTE is responsible for the clinical

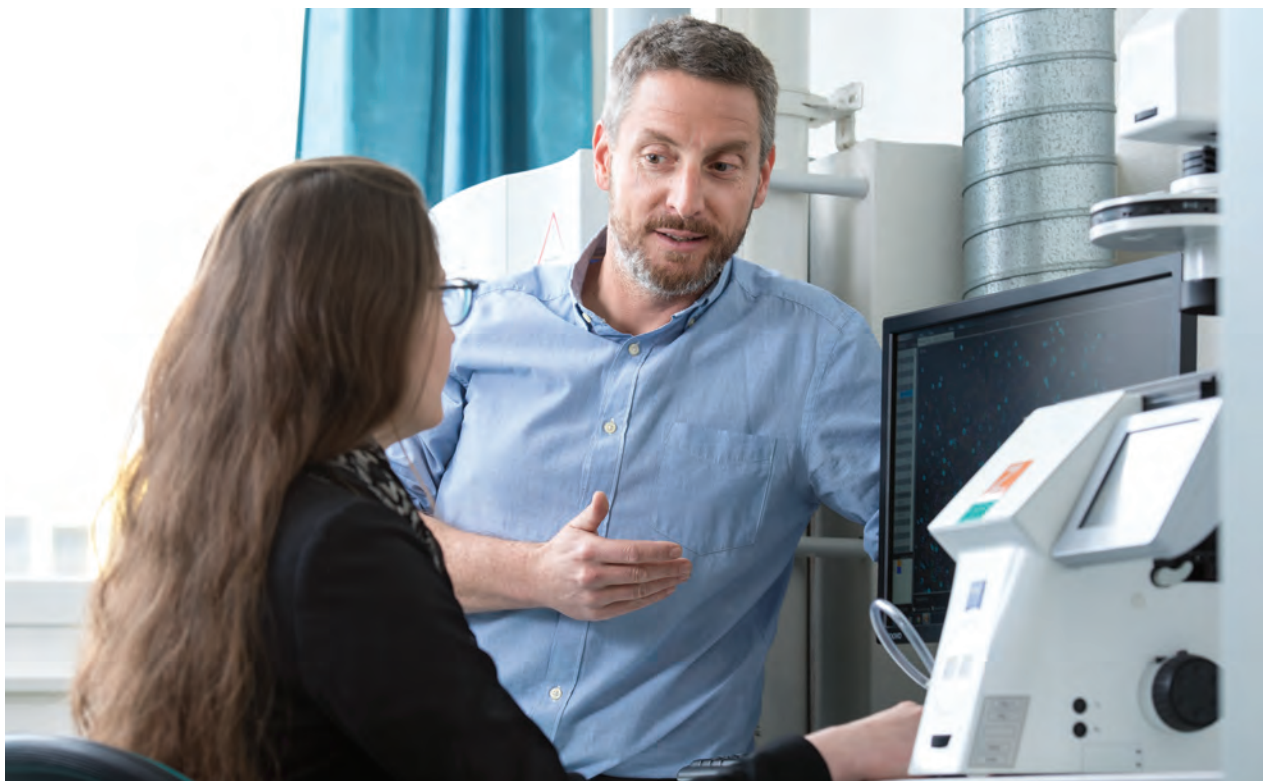


Photo by Eric Deroze

Alexandre Harari

operations that bring them to the bedside,” says Coukos.

The two units are now working in sync to launch two clinical trials of advanced immunotherapies, one that will test individualized cancer vaccines for ovarian cancer, and another that will evaluate a personalized, adoptive T cell therapy for solid tumors. “We want to transform immunotherapy, particularly as it relates to T cell therapy, and believe strongly that Lausanne can be one of the world’s pioneers in that arena,” says Coukos.

### THE CHALLENGE

What makes immunotherapies so exciting to oncologists is that they train the body’s versatile defense systems—its immune cells—to detect and destroy cancer cells. Yet even the most advanced immunotherapies in use today fail to work in many patients, and fewer still are curative.

There are many reasons for this. One

is the enormous variability of cancer cells, which evolve and diversify as they proliferate. Every cancer in every patient is in some ways a unique disease, with its own set of characteristics, defenses and identifying molecular markers—or antigens. Some common cancer antigens exist and researchers continue to try to develop general cancer vaccines on their basis. More often, however, every tumor is characterized by its own distinctive antigens.

Cells known as tumor infiltrating lymphocytes (TILs) must recognize these antigens and launch an attack. But telltale antigens might be hard to find. If found, the immune cells must overcome a second major obstacle: tumors usually evolve intricate defenses to snuff out such attack. Some of those defenses can now be countered by novel drugs—like checkpoint inhibitors, a handful of which dismantle one of the brakes cancer cells engage on threatening killer T cells. But tumors often have many such defenses in play.

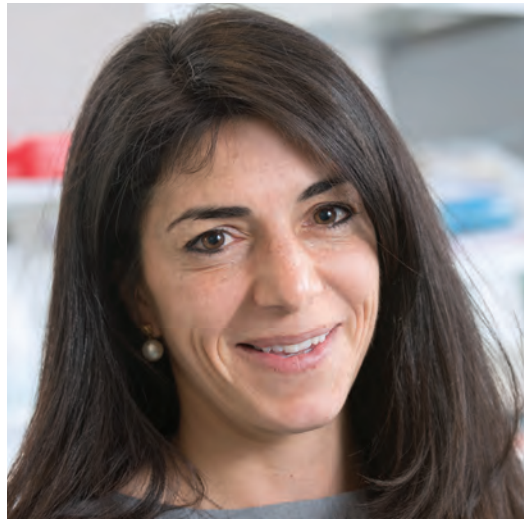
Adoptive T cell therapies offer an alternate route to stimulating immune attack. In these so far experimental therapies, a variety of TILs are extracted from a patient, selected for their cancer-detecting chops and then grown in the lab before they're reinfused into the patient. Alternatively, T cells can be engineered to carry cancer-detecting antibody "warheads" before they are amplified and re-infused. The latter experimental treatments are known as chimeric antigen-receptor (CAR) T cell therapies.

The Ludwig Lausanne effort aims to streamline and accelerate the delivery of these therapies—and personalized cancer vaccines—to patients. "We are uniquely placed to translate advanced scientific hypotheses to the clinic," says Coukos. "We have secured the infrastructure to do so, which is not trivial because it requires deep scientific, technical and clinical expertise and integration, and it requires some very significant investments. All of these are now in place."

### Hi-TIDe's FLOW

The Lausanne Branch, says Coukos, is devised to serve science in the most unrestricted and creative way without losing its emphasis on more goal-oriented translational research. "To do this, we've recruited top scientists who will be free and resourced to pursue discovery and knowledge," he says. But they do so in an environment that also provides deep resources and mechanisms for the clinical translation of their best ideas. They work very collaboratively, and in pursuit of a common goal—developing personalized immunotherapies and testing them in the clinic. That goal has lured leading researchers to the center.

Alexandre Harari, for example, had by 2012 established his reputation as an expert in the assessment of immune responses to HIV infection and tuberculosis and was ready to leave his post at CHUV and start up his own



Lana Kandalaft

Photo by Eric Deroze

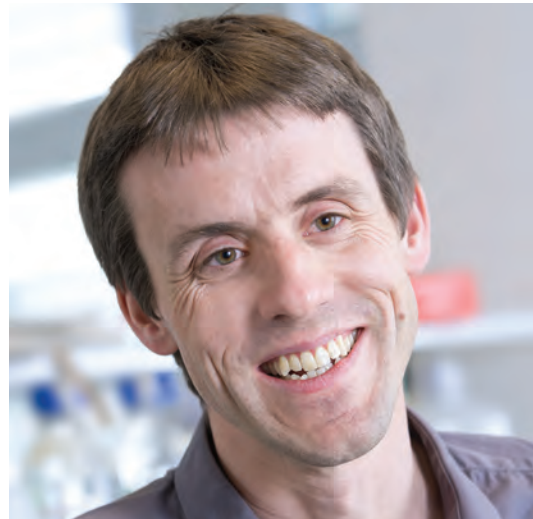
lab. He had even pulled together the support he'd need to make that happen. Then he met Coukos, who described what he had in mind for Ludwig Lausanne. "After half an hour with George, I was like a groupie," recalls Harari, who is today a team leader of the antigen discovery unit of the Hi-TIDe and head of the Immune Monitoring Core Facility at the CTE. "And then I did something extremely counterintuitive for a researcher: I returned my grants, and my fellowships, and I started in this new field of cancer research in which I had never worked before."

Similarly, Ludwig Lausanne's Lana Kandalaft moved from the University of Pennsylvania to head the CTE. The unit, based at the CHUV's Department of Oncology, which Coukos directs, will run the upcoming clinical trials of personalized immunotherapies. It will also provide tissue samples for the design of those therapies, manufacture the cell-based treatments in line with good manufacturing practices, and monitor the anti-tumor immune responses of patients. Its facilities have been inspected and approved by Swiss authorities.

Tumor samples from patients enrolled by the CTE will make their way to the Hi-TIDe's antigen discovery unit, which is led by Harari and Michal Bassani-Sternberg, who joined



Michal Bassani-Sternberg



David Gfeller

the Hi-TiDe from the Max Planck Institute. Working in the laboratory of Matthias Mann at the Planck Institute, Bassani-Sternberg pioneered methods to identify tumor antigens using mass spectroscopy coupled with sophisticated computational analysis. Like Harari, she was drawn to Ludwig Lausanne by the unique opportunity it offered to translate her scientific innovations to the clinic. She has teamed up with bioinformatics and structural computational groups at the SIB and Ludwig's own David Gfeller to identify antigens presented by tumors and pick out the ones most likely to excite a T cell response.

Her team looks for both known cancer antigens—such as melan-A, or the cancer testis antigens—and those that are unique to the patient's cancer. “The advantage of this technology is that we can really apply it to the individual,” says Bassani-Sternberg. “Off-the-shelf vaccines [against a known cancer antigen] may not be the best option for an individual patient.”

Bassani-Sternberg's list of personalized antigens then moves along to Harari, who finds out which of them actually might be useful. “There are distinct ‘flavors’ among the T cells that recognize these antigens, and we are establishing a unique strategy to

quickly identify the most clinically relevant ones,” says Harari. Those cells can be grown in large volumes for adoptive T cell therapy. Their T cell receptor (TCR) genes will also be cloned to furnish data for scientific and computational analysis and, later, T cell engineering.

“The aim is to transfuse patients with T cells expressing the right TCRs,” says Harari. “This can be done by many labs in a few months, but we are trying to optimize steps so that we can do it within a few weeks of the patient arriving at the hospital.” To that end, Harari has teamed up with advanced fluidic and imaging bioengineers from EPFL's Institute of Bioengineering in Lausanne to develop new technologies.

#### THE ARMORY

If the T cells are to be modified, this will be done at the Hi-TiDe's immune-engineering group, which is led by Melita Irving, an expert on T cell engineering, and Steven Dunn, who leads the Ludwig Antibody Core facility (LAbCore) of the Branch. Irving uses gene-engineering tools to equip T cells with natural or synthetic receptors that can improve their targeting of tumors. Engineered T cells can then be expanded and reinfused into the patient. Or they can be co-engineered to express a variety of molecules that are



Melita Irving



Steven Dunn

Photos by Eric Deroze

secreted in tumors to destroy cancer cells, or to counter the tumor's inhibition of the immune response.

"Engineered T cells can be used as miniature drug factories right in the tumor bed," says Irving. "We are extremely excited about the opportunity to use such cells in cancer patients. In the future, CAR T-cells could be customized based on the properties of a patient's tumor for truly personalized T-cell immunotherapy."

If Irving's task is to engineer the T cell, Dunn's is to identify and develop new antibodies that may be used for such engineering. At the heart of his antibody factory is a "library" of some 20 billion antibody fragments that fit in a 1.5 mL tube. To isolate a binding antibody, his team sticks antigens of interest on beads and drops them into the library, where antibodies can latch on to them. After a few cycles of this, a number of antibodies that bind firmly to an antigen remain on the beads, and can be cloned, engineered further and characterized.

Of course, finding a useful antibody is like finding the needle in a haystack—far more complex than merely deploying a screen. "It's not a push button procedure," says Dunn. "There are decisions to be made every step

of the way. It's all data driven and no two projects are ever the same. That's what gives me the buzz, actually."

On the Hi-TiDe front, he says, the technology is very well suited to T cell engineering. "We see this platform as being particularly well adapted to providing warheads for CAR T cells," says Dunn. It's relatively straightforward, he explains, to find and move along an antibody gene for this purpose, since it skips the more technically fraught and time-consuming business of developing a purified protein drug that can survive the manufacturing process. "What we're working toward here is a rationally designed CAR factory."

### MOBILIZING BASICS

A more long-term effort of the Hi-TiDe involves a deeper exploration of the function, and malfunction, of immune cells that are found in tumors. That effort, a program in systems immunology, is led by Marie-Agnès Doucey and Sylvie Rusakiewicz, and involves, among other things, probing how T cells are dysregulated in tumors. Such studies will guide interventions to overcome tumor defenses and open new therapeutic opportunities. "The integration of that knowledge will fuel ideas to move into T cell engineering down the line and suggest



Marie-Agnès Doucey



Sylvie Rusakiewicz

pharmaceutical interventions that could improve the efficacy of T cell therapies,” says Coukos.

But studying human TILs in their native microenvironment—and creating the experimental conditions required to learn how to engineer them into living drugs—requires the development of surrogate systems that reproduce the tumor microenvironment in the culture dish. It also requires sophisticated technology that permits a deep yet swift and high-volume analysis of small numbers of cells. Doucey and Rusakiewicz are developing optimized culture systems to do just that, studying human tumors using a systems approach that captures their extreme heterogeneity and complexity.

Other investigators at Ludwig Lausanne feed into the Hi-TiDe, especially at this level. Coukos says that scientists recruited to lead independent groups at the Branch have the luxury of being unrestricted in their research, and are relatively free to pursue curiosity-driven inquiries. But the researchers themselves, he says, have been recruited to Lausanne because their work might be of relevance to the long-term translational goals of the Branch. Now, he notes, when their discoveries look like they might be

relevant to cancer immunotherapy, they have a direct line to the translational conduit of the Hi-TiDe.

Ludwig Lausanne investigator Ping-Chih Ho has, for example, helped pioneer the study of how immune cells are manipulated by metabolic cues in the tumor. His previous work at Yale showed that cancer cells induce immune dysfunction inside some tumors in part by hogging up glucose, a nutrient essential to killer T cell activity. Ho says that specific subtypes of T cells are manipulated in unique ways in different tumor and tissue types, and his lab is trying to pin down those mechanisms and their consequences to inform targeted therapies.

“You could engineer T cells to be resistant to specific metabolic tumor defenses and reinfuse them into patients,” he says. “We’re also hoping to find drugs that will rejuvenate anti-tumor T cell activity and synergize with T cell therapies or checkpoint blockade.” Such strategies are a natural fit for the systems immunology and T cell engineering teams within the Hi-TiDe.

Johanna Joyce joined the Ludwig Lausanne Branch from Memorial Sloan Kettering



Ping-Chih Ho



Johanna Joyce

Photos by Eric Deroze

Cancer Center in New York, where she led a world-class laboratory focused on tumor macrophage biology. Her cutting edge research on brain tumors and brain metastases will inform key solutions for the development of T cell therapies for such tumors, which are extremely difficult to treat.

Though the Hi-TiDe team leaders tend to be more goal oriented in their studies, they are all accomplished in their fields and many are collaborating with other groups on an array of basic research projects. Bassani-Sternberg, for example, is involved in a collaboration with the Branch's computational biologists David Gfeller and Vincent Zoete. Together, they're exploring how an ocean of mass spectrometry data on the antigens presented to immune cells may be used to better predict such antigens in any patient. She is also investigating why some tumors present more immune-stimulating antigens than others and testing ways to boost the repertoire of such antigens within tumors.

Dunn and his team, meanwhile, are eager to apply their antibody and phage display engineering platform to aid projects that might yield interesting therapeutic approaches or fill an unmet need for a critical

reagent. It is, in fact, already collaborating on a couple of antibody projects with other Ludwig labs. "The idea is that we will not only supply George's translational pipeline in Lausanne but will also have a contributing capacity for the global laboratories of Ludwig," he says.

As for Coukos, an authority on ovarian cancer and a leading researcher in the field of immunotherapy, the coalescing Lausanne Branch is the realization of a dream. "I've been studying the tumor microenvironment and immune suppression for eighteen years," he says, "and we now have the opportunity to find solutions to some of the biggest challenges to cancer therapy posed by these factors. The resources here really enable me to do things that I could not do before."

His integrated Hi-TiDe team is ready to launch trials of the first therapies in patients by the end of the year. "This is just the beginning of a long and exciting journey" says Coukos. "We have set up the infrastructure to bring highly sophisticated therapies to the bedside, and now we are ready to start testing some important hypotheses on how best to reprogram the immune system to fight and eradicate cancer." ■



Richard

Kolodner

Photo by Stewart Marciano

# THE MUTATOR HUNTER

Richard Kolodner has made landmark discoveries on DNA repair and its link to cancer. Now he has unearthed a passel of genes that stabilize the genome, and are often defective in tumors.

There are many reasons to become a scientist, and not doing what your dad does is probably as good as any. Just ask Ludwig San Diego Director Richard Kolodner, who hopscotched from city to city in his childhood as his father, a gifted mathematician, took jobs at institutes and universities across the US. “I became interested in science in part because I didn’t want to be a mathematician,” he says, chuckling.

Mathematics’ loss, it turns out, was a big win for biology. Over the last four decades, Kolodner has methodically probed the molecular mechanisms by which living things—from plants to yeast to humans—guard the integrity of their genetic information, making landmark discoveries in plant, microbial and cancer genetics. In 2016, he added another chapter to his storied career with a paper in *Nature Communications* describing the results of a study he led with Ludwig San Diego’s Christopher Putnam and Ludwig alum Sandro de Souza, a professor of Bioinformatics at the Federal University of Rio Grande do Norte in Brazil. Kolodner and his colleagues describe in their paper how they developed and applied a novel method to suss out the full spectrum of genetic pathways that ensure the stability of the genome. When compromised, these pathways cause massive genomic

rearrangements that can fuel a wide variety of malignancies.

## DNA DETECTIVE

After finishing high school in Pittsburgh, Pennsylvania, where his father was then chair of the mathematics department at Carnegie Mellon, Kolodner joined a bachelor’s program in Biological Sciences at the University of California, Irvine, and then the Biological Sciences graduate program there, completing his bachelor’s and PhD in a little over 6 years. Characterizing the DNA of chloroplasts, the bean-like organelle in which plant cells turn sunlight into food, Kolodner helped pioneer plant molecular biology as a graduate student. In 1976, he began a post-doctoral fellowship in Charles Richardson’s lab at Harvard Medical School, learning how to purify viral proteins and studying DNA replication in the T7 bacteriophage, a virus that infects bacteria.

Hired to the medical school’s faculty following his post-doc, Kolodner started a lab at the Dana-Farber Cancer Institute and began exploring bacterial recombination—a bacterial version of sex that generates genetic diversity. He also started looking into a phenomenon that would occupy him for the next few decades: how a couple (or a few) erroneously paired bases in



Photo by Stewart Marciano

replicating DNA are repaired by cells to prevent mutations. This work led to the development of some of the earliest assays for bacterial mismatch repair (MMR), many of which are still in use today.

By the mid-1980s, Kolodner had shown that yeast too can detect and fix mismatched bases in their DNA and had identified mutations in the known yeast mismatch repair gene, PMS1. This set off a search in his lab for additional yeast MMR genes, resulting in the identification of the MSH1 and MSH2 genes, among others. Kolodner noticed that the effects of MSH1 mutations resembled some features of cellular defects in human genetic diseases known as mitochondrial myopathies. The observation set off a new hunt in Kolodner's lab for the human homologues of yeast MMR genes.

By late 1993, Kolodner and his lab were in a race to identify the human MMR gene responsible for a relatively common form of inherited colon cancer known today as Lynch syndrome. They were uniquely suited to the task. Researchers, including a team lead by Ludwig Johns Hopkins Co-director Bert Vogelstein, had reported that summer the presence of mutations in the Lynch genome that looked an awful lot like the mutations Kolodner had seen in yeast with defective MMR genes.

Within six months, Kolodner and his collaborators had cloned the human MSH2 gene and established that an inherited mutation of the gene caused Lynch syndrome in a patient. It was the first inherited gene defect shown to be associated with cancer. By March of the following year, Kolodner and another colleague had identified a second human MMR gene that causes Lynch syndrome, known as MLH1.

As Kolodner characterized his new genes over the next few years, he developed



Photo by Stewart Marciano

diagnostic tests that were used for years to diagnose Lynch syndrome. He and his colleagues also showed how MMR genes could play a key role in the genesis of spontaneous colon cancers, which account for the vast majority of such cancers. “We showed,” says Kolodner, “the gene for MLH1 is methylated and silenced—so it is not expressed—in non-inherited colon cancers.” The methods used to detect such silencing, which were also developed in Kolodner’s lab, remain in use today.

#### A NEW MUTATOR

In 1974, researchers put forward a “mutator phenotype hypothesis,” which held that cancer genomes must have high rates of mutation to account for all the changes to tumor suppressor genes and oncogenes that drive the progression of cancer. “Our detection of defects in MMR genes,” says Kolodner, “was among the first elements of proof for that idea because you had a gene defect that caused high

“It was my view that genome rearrangements in cancers might also reflect a mutator phenotype, which is to say they are caused by defects in genes unknown.”



Photo by Stewart Marcano

mutation rates, and those mutations drove the development of cancer.”

The approach Kolodner took to find MSH2 is characteristic of his research. In searching for an answer to any new question, his lab tends to begin with yeast, performing genetic experiments on them that are technically cumbersome or impossible in mammalian cells. How things work in yeast often reflects what goes on in human cells, especially in the genetics and biochemistry fundamental to cellular life.

“MMR defects cause a particular class of mutations,” says Kolodner. “Mostly single base changes, and insertions and deletions of one or a few DNA bases. But in cancer there are more drastic genetic alterations that for all practical purposes are also mutations.”

These include events in which entire chunks of chromosomes are rearranged,

deleted or chopped off and glued to other chromosomes, causing massive genetic disruption. More advanced and drug resistant cancers, in particular, are prone to such aberrations.

“It was my view that genome rearrangements in cancers might also reflect a mutator phenotype, which is to say they are caused by defects in genes unknown,” says Kolodner. He got a chance to test this idea when experiments done in his lab revealed mutations in yeast that appeared to cause large genome rearrangements of the kind seen in cancer.

### MUTATORS IN SCADS

These, Kolodner figured, might be the genome instability suppressing genes (GIS) that, when mutated, cause gross chromosomal rearrangements, known in the shorthand as GCRs. Kolodner’s team—including Ludwig San Diego associate investigator Christopher Putnam, postdoc

Anjana Srivatsan and Sandro de Souza, who received Ludwig funding for the work—devised an ambitious approach to finding the GIS genes. They combined methods from yeast genetics and bioinformatics to identify GIS genes—finding them first in yeast and then applying what they learned to human cancers.

The researchers first used assays and technologies from Kolodner's lab to screen thousands of mutant yeast strains for genes that suppress GCRs. They identified 182 GIS genes, 98 of which had not been noted before. They also uncovered more than 400 previously unknown cooperating genome instability suppressing genes (cGIS), which only affect genome stability when combined with other mutations. Only a few dozen such genes had been described before.

To see if these genes had counterparts implicated in human cancers, the team searched The Cancer Genome Atlas (TCGA)—which contains genomic data from thousands of patients—for genes similar to those they had found in yeast. They also added to this list human genes that are not found in yeast but that participate in the same biochemical pathways and protein complexes as the analogous yeast GIS genes. They then looked for defects in these genes in the TCGA in each of three cancers: ovarian cancer, colorectal cancer and acute myeloid leukemia (AML).

The leukemia served as a control because it is a cancer that has a relatively stable genome. The other two, however, have extremely unstable genomes. The researchers found that 93% of ovarian cancers and 66% of colorectal cancers had genetic defects affecting one or more of the predicted GIS genes. The AML, as they expected, had no such defective genes.

Kolodner now has an embarrassment of

“The problem is this is a huge project. We simply couldn't do all the interesting experiments that can be done, so we're focusing on a few things.”

genetic riches to mine as he moves forward. “The problem is this is a huge project,” he says. “We simply couldn't do all the interesting experiments that can be done, so we're focusing on a few things.”

That includes tumor suppressor genes they've identified in their analysis. They're also expanding their analysis to uncover GIS defects in other types of cancer, and mutating the GIS genes they've identified to see if they can't induce genome instability in human cells. Kolodner is now working with the Ludwig's Small Molecule Discovery Program to see if their discoveries might be exploited to develop new cancer diagnostics and therapies. ■





# MOVING DISCOVERIES

Photo by Eric Deroze



Sangeeta  
Bhatia

Photo by Flynn Larsen

# THE MULTIMODAL INVENTOR

Sangeeta Bhatia has harnessed an enduring fascination with getting synthetic things to infiltrate and talk to tissues to devise new approaches to diagnosing and treating cancer.

Ludwig MIT investigator Sangeeta Bhatia was only in high school when she decided to become a bioengineer. But it wasn't until her junior year at Brown University, during an internship in the laboratory of the prominent tissue engineer Patrick Aebischer, that she figured out what exactly she would do with that expertise.

Bhatia was trying to accelerate nerve regeneration by guiding growing nerves to muscles with an electromagnetic field induced by piezoelectric materials, which generate a current when deformed. "I was fascinated by the work," she recalls. "It was the perfect marriage of engineering and cell biology, and it was applied science, but it had some pretty fundamental interdisciplinary pieces. I realized I was interested in getting materials to talk to cells, and to do it in a way that would help patients."

And that is precisely what Bhatia—bioengineer, inventor, physician, cancer researcher, entrepreneur—has been doing in one way or another ever since, contributing significantly to fields ranging from infectious disease to tissue engineering to cancer research and care. In that last category, Bhatia published a study in *Nano Letters* in 2016 describing injectable nanosensors for profiling colon tumors that are activated by targeted magnetic fields and provide a read-out in a simple urine test. In another

paper, published in *Nature*, her team and their longtime collaborators at the University of California, San Diego, reported how they engineered bacteria that, when fed to mice, made their way to liver tumors and produced three distinct molecules in consistently timed pulses to help destroy the malignancies.

## DOING IT ALL

Bhatia's parents immigrated out of what is now Pakistan during the 1947 partition of India and met in Mumbai. Her father had just received his engineering degree, and her mother was among the first women in India to obtain an MBA. The couple immigrated once again in the 1960s, this time to the US, where Bhatia's father, a budding entrepreneur, had been accepted into an MBA program. They eventually moved to Boston, where they started a business together importing metallurgical components, boat parts and the like. "I was born in Brigham and Women's Hospital, which is kind of funny because I'm on the faculty there now," says Bhatia. "I've come full circle."

After obtaining her engineering degree at Brown and taking a gap year doing drug formulations at a pharmaceutical company, Bhatia got her PhD from the Harvard-MIT Health Sciences and Technology (HST) program, where she now teaches. "I remember I had to sit my dad down and break it to him that I was going to graduate school,"



Photo by Flynn Larsen

she recalls. “He was, like, ‘oh, ok, when are you going to start a company?’ ” He would not be disappointed. Over the years, Bhatia has put her name on more than two score patents, and collectively, she and her trainees have launched ten startup companies.

The HST program required its engineering students to take a full year of classes at Harvard Medical School. Bhatia, who says she “fell in love with the human body”, decided to stick around for a second year. Meanwhile, her PhD training was proceeding apace in the laboratory of Mehmet Toner, a biomedical engineer at Massachusetts General Hospital who was trying to do for liver disease what dialysis had done for ailing kidneys.

After obtaining her PhD, pioneering the use of microchip fabrication tools to grow liver tissue on a chip, Bhatia took a faculty position at the University of California, San Diego, completing her medical schooling as she set up her new lab (her MD is from Harvard). Her schedule was grueling, but she was

having fun. “Within a year I realized this was the perfect place for me,” she says. “I loved academia, loved idea creation and training young minds.”

### MATERIAL CONCERNS

Bhatia pressed ahead with her work on liver tissue engineering at UCSD. “That had been my window into how cells communicate with materials,” she says. “We were going to use these tiny tools to make materials that pattern and organize cells and interact with them.” But the field was changing. Around the turn of the century, it became possible to make remarkably small and smart materials. “I got really excited about moving from the microscale, where we could build tissues, to the nanoscale, where we could make materials that could enter tissues,” she says. Bhatia started a group in her lab to investigate nanotechnology applications for cancer, and began a collaboration with the cancer researcher Erkki Ruoslahti of the University of California, Santa Barbara, who she says shepherded her into tumor biology.

The pair worked together to devise targeted nano-probes for medical imaging.

Bhatia also got promoted and had the first of her two daughters in San Diego. In 2005, looking to live closer to family, she and her husband Jagesh Shah, who was at the time affiliated with the laboratory of Ludwig San Diego's Don Cleveland, moved to the Boston area. (Shah, an electrical engineer by training, is an associate professor of systems biology at Harvard.)

Bhatia's tissue engineering has since progressed from success to success. Her lab's human "microlivers"—miniature representatives of the organ suited to basic scientific and pharmacologic research—have been put to work to explore the pathology of malaria and Hepatitis C, and implanted successfully in mice. A biotech company launched by Bhatia already sells the technology to scores of pharmaceutical companies, which use it to analyze the metabolic processing and toxicity of experimental drugs.

Her lab at the Ludwig Center at MIT has, meanwhile, branched out in multiple directions. Her graduate students are all engineers because, she says, she understands how to direct their doctoral training. "But the postdocs are very diverse, and deliberately so," she says. "We have chemists, physicists, allergists, developmental biologists, and we have some engineers." The engineers are warned they'll have to get their hands dirty. "It's great if you can derive elegant systems of equations on the board," she explains. "But if you come to our lab, you should know that we're going to push everything *in vivo*. You have to be willing to apply that thinking in a translational way."

### GLOWING SUCCESSES

That principle has paid dividends for both Bhatia's lab and biomedicine. When Bhatia first got excited by nanomaterials as a tool for tumor imaging in the year 2000, her lab

**"I got really excited about moving from the microscale, where we could build tissues, to the nanoscale, where we could make materials that could enter tissues."**

worked on targeting nanomaterials called quantum dots to tumors. When exposed to UV light, the quantum dots glow in different colors depending on their size.

By the early years of this decade, her lab was trying to make nanoparticles that, instead of just revealing tumors, would reveal something about them as well. One approach was to use small protein molecules that are specifically snipped by a class of enzymes known as matrix metalloproteinases (MMPs), which are expressed in distinct patterns in different stages and types of tumors. The pattern of snipping would then serve as a signature of a tumor's type or stage.

"One of the students noticed serendipitously that whenever we administered these materials to a tumor-bearing mouse, there

was an organ lighting up in the abdomen of these animals,” recalls Bhatia. The organ in question was the bladder, indicating that the snipped protein fragments were being cleared from the body via the urine. In 2014, Bhatia’s team harnessed that insight to create a paper-strip urine test for tumors.

That achievement opened up other opportunities as well. “We wanted to see whether we could profile the proteolytic environment of tumors, recognizing that there’s more than one protease expressed as the tumors progress through different stages,” says Bhatia. That would require isolating the signal from the chosen tumor alone. The trouble was that MMPs are also found in the bloodstream, and their activity would cloud signals from the test.

Working with the laboratory of MIT colleague Polina Anikeeva, Bhatia’s team devised a method to control the activation of their sensors in space and time. To do so, as they reported in *Nano Letters* in 2016, the researchers encapsulated their nanosensors in a heat-sensitive coating along with small magnetic particles. When a focused magnetic field was then aimed at the tumor, the particles heated up and the coat melted away, exposing the nanosensors to MMPs solely within the tumor. The researchers showed that the test allowed them to distinguish between two different types of colon tumors in mice using a paper strip test devised to detect specific MMP signatures.

## BUGGING CANCER

In 2011, on a social visit back to San Diego, Bhatia found herself discussing how bacteria might be engineered to report on and treat tumors with an old friend, the synthetic biologist Jeff Hasty, whose own lab was moving in that direction. “There are many bacteria living in and on our body,” says Bhatia. “You can take native strains like *Escherichia coli* that exist in the gut, or the oral, genetically engineered probiotic versions of them, and engineer them further

to report on a tumor, or deliver therapeutic cargo.”

Soon, Hasty and Bhatia were collaborating on a project to that end. It was primarily led by Tal Danino, a graduate student in Hasty’s lab who moved over as a postdoc to Bhatia’s group as the work evolved.

In 2015, Bhatia, Hasty and their team described in *Science Translational Medicine* how they had engineered a widely used probiotic, *E. coli* Nissle 1917, to report on the presence of liver tumors. Fed to mice with intact immune systems, the bacteria traveled from the stomach to the liver through a major blood vessel and selectively accumulated in liver malignancies. Once there, they secreted an enzyme that, when exposed to its injectable target, generated a luminescent chemical detectable by both imaging and urine tests.

“The cool thing about that study was that we discovered, using immune-competent mice, something that we hadn’t previously appreciated so acutely,” says Bhatia. “If you give bacteria systemically, they are privileged in the tumor, where the immune system is suppressed.” When they traveled to other parts of the body, it appeared, the immune system would simply clear them away.

This meant that with the right dose and route of administration, bacteria would infect tumors but spare healthy tissues. And that, in turn, suggested they’d make great vehicles for the delivery of therapies. “If they grew selectively in the tumor,” says Bhatia, “they’d selectively kill tumor cells.”

Building on that insight, the researchers devised an elegant system for not only delivering multiple anti-tumor payloads in bacteria, but also getting those bacteria to deliver them in regularly timed pulses. First, they engineered the bacteria to express a protein that prompts them to self-destruct when their population reaches



Photo by Flynn Larsen

a certain density. They also programmed the bacteria—a variety of *Salmonella*—to produce one of three different anti-tumor agents: one that stimulates an immune response, one that pops cancer cells open, and a third that prompts them to commit suicide.

As the team reported in their *Nature* paper in 2016, the system worked like a dream in their animal models. Fed to mice bearing colon cancer metastases in their livers, the *Salmonella* traveled like the *E. coli* through the portal vein and thrived within the metastatic tumors. When their cancerous housing got a bit too crowded, the bacteria self-destructed on cue—releasing their anti-tumor agents into the heart of the malignancy. But a few remained to rebuild the bacterial colony, reinitiating the cycle of growth and self-destruction. The researchers found that though the combination arrested tumor growth

moderately, it did so more dramatically when it was combined with a standard chemotherapy.

Bhatia and her colleagues have spun off their nanosensors as a biotech startup that hopes to have its product in clinical trials by next year. As for the bacterial work, Bhatia says her collaborators are thinking about translating that research as well. For now, she's mainly intrigued by the trafficking of the bacteria within the body, especially since their migration seemed to be augmented by chemotherapy.

“The bugs had to cross the gut, get into the portal circulation and travel into the liver and then set up shop there,” says Bhatia. “It’s important to understand the fundamentals of how that happened to determine which patients this will be most relevant in.”

It’s a fair bet she’ll let us know soon. 📌

A portrait of an older man with grey hair, smiling, wearing a dark pinstripe suit, a white shirt, and a blue and white striped tie with a geometric pattern. The background is a plain, light grey.

Ralph

Weichselbaum

# 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 Marciano

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- $\alpha$ ) 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

“Sometimes, when you have a hammer, everything looks like a nail. But I’ve been exploring how radiation can be more than just a local treatment, and it really looks like it can be more.”

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.

# 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- $\beta$ . 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." ■



Judith

Shizuru

# THE TRANSPLANT SORCERER

Judith Shizuru has long dreamt of using stem cells to perform—and transform—bone marrow transplantation. She recently took a big step toward that goal.

Back in the early 1990s, when Judith Shizuru was still doing double duty as a postdoctoral researcher and a medical student at Stanford, she would often chat with Irv Weissman about making graft vs. host disease (GVHD) a worry of the past. A potentially lethal complication of bone marrow transplantation, GVHD occurs when mature immune cells from a donor—which flood in with the blood-making stem cells in the foreign marrow—attack the tissues of the patient receiving the transplant. “We’d be saying, ‘well, if you could just transplant pure stem cells, which are immunologically naïve, you won’t get GVHD,’ ” Shizuru recalls.

These were not idle fantasies. Weissman, who is today director of the Ludwig Center at Stanford, had by 1991 isolated the hematopoietic stem cells (HSCs) they were talking about—the source of all types of blood cells. Yet, as they knew, that wouldn’t be enough. At the other end of the transplantation process, the existing stem cells in the patient’s bone marrow would still need to be vacated to allow the new ones from the donor to take root. This is achieved even today by subjecting recipients to a grueling, and sometimes lethal, regimen of chemotherapy and radiation.

In 2016, Shizuru hit a golden milestone in her quest to transform bone marrow transplantation. In a study published in

*Science Translational Medicine*, Shizuru and her team reported that they had, using no chemotherapy or radiation, prepared mice for bone marrow transplantation and successfully completed the procedure with reasonable success using purified hematopoietic stem cells.

“It’s been a long time getting to the point where we think we’re going to be able to translate this concept into the clinic,” says Shizuru. If their approach indeed translates, it has the potential to radically alter the prospects of people undergoing transplants of all sorts and patients with disorders ranging from autoimmune disease to cancer.

## BEGINNINGS

Shizuru grew up in Mountain View, California, a third-generation Japanese American and the fourth of five children. Her parents had both been interned in the Midwest during World War II and resettled in California. Shizuru was a good student, thanks in part to the tutelage of her siblings, and was accepted to Northwestern University.

She soon transferred, with a scholarship, to Bennington College in Vermont, where she could get the liberal arts education she wanted. Shizuru thrived at the school. “I grew up very blue collar, but in the Bay Area,” says Shizuru. “My father was a postal worker, so we couldn’t actually afford music lessons. But

“Stem cell transplantation is like the Holy Grail. It redefines the universe of self and non-self in the body and it’s a potential treatment for a variety of autoimmune diseases.”

at Bennington playing music was encouraged. They gave me a violin and I had a wonderful violin teacher. So in the time I was there I learned to play, and had the joy of playing Bach, Mozart and more.”

When she moved back to Mountain View after college, Shizuru took a job as a lab technician in a transplantation laboratory at Stanford University Medical School, where she’d worked as a secretary during long winter breaks from Bennington. Her boss urged her to join the graduate school and introduced her to her first mentor, who was working on the transplantation of pancreatic islet cells as a treatment for diabetes.

When that mentor left Stanford, Shizuru joined the laboratory of the acclaimed clinical immunologist Garry Fathman, who

supervised her graduate studies. Shizuru continued her postdoctoral research on islet cell transplantation at Stanford as a postdoc, and soon forged a working relationship with a group of leading women at the Juvenile Diabetes Research Foundation (JDRF). They not only sponsored her research but also encouraged her to pursue a medical degree. Shizuru took their advice. With support from the JDRF and plenty of hands-on help from her long-time friend and lab assistant, Cariel Taylor, Shizuru conducted her postdoctoral studies while completing medical school at Stanford, followed by a residency at the University of California, San Francisco.

It was in medical school, says Shizuru, that she became convinced that the path to inducing immunologic tolerance of transplanted tissue—so that recipients do not reject their new organs—went through stem cell research. “Stem cell transplantation is like the Holy Grail,” says Shizuru. “It redefines the universe of self and non-self in the body and it’s a potential treatment for a variety of autoimmune diseases.”

Her research at Ludwig Stanford is still dedicated to the basic immunology of bone marrow and HSC transplantation, and the application of that research to medicine.

#### ROUTE TO STEM

Shizuru’s long collaboration with Weissman—whom she has described as “the Picasso of biomedical research”—dates back to the early 1990s. So she was one of the first to find out when a graduate student in his lab figured out which antibodies could be used to safely deplete HSCs from the bone marrow of immune-compromised mice. Shizuru leapt at the opportunity to translate the discovery for clinical application.

Stem cells in bone marrow sit in specialized physical niches, and for a new stem cell to take hold, the old one has to be nudged out. “It’s like musical chairs: the seats are occupied,” Shizuru explains. “You have to get

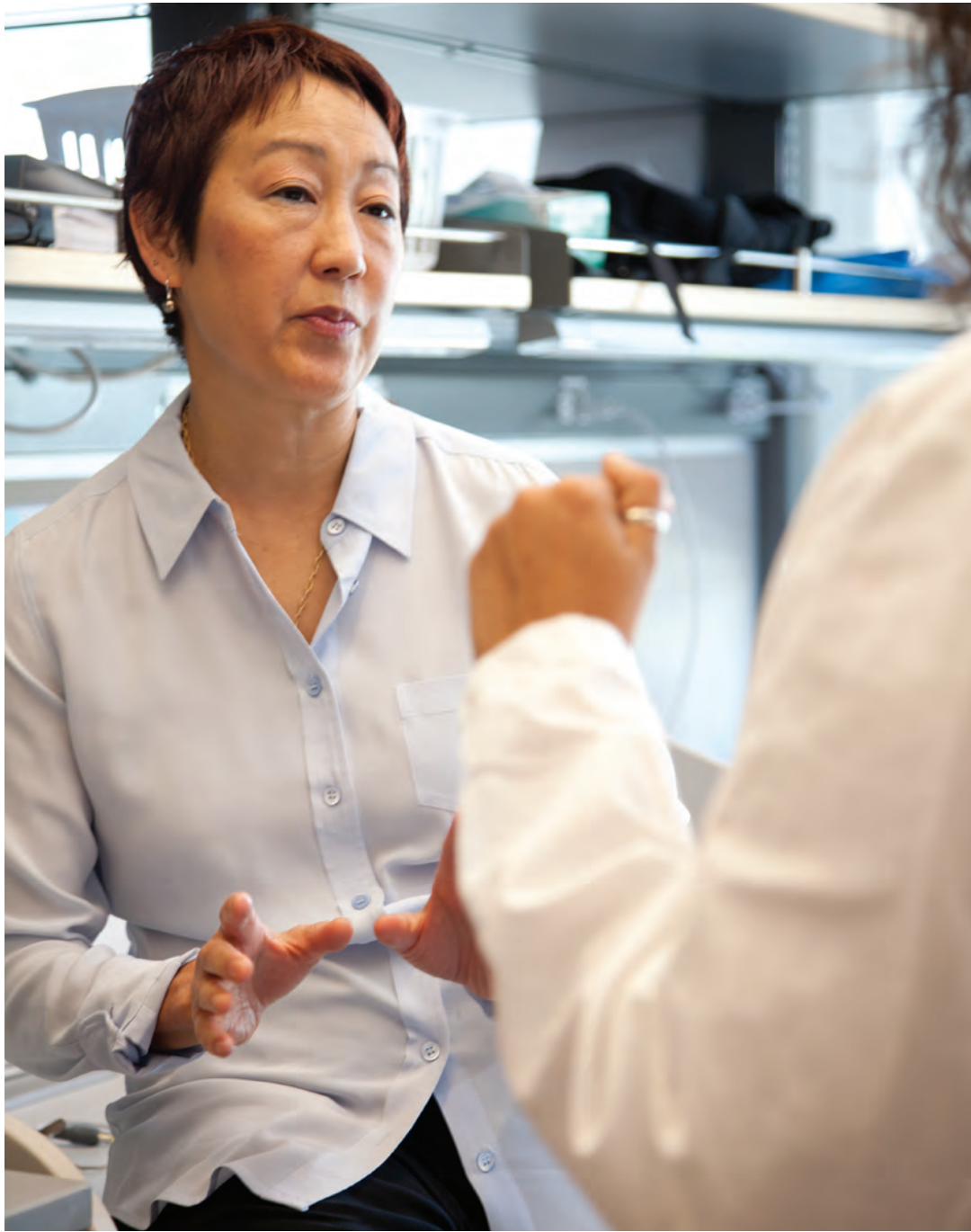


Photo by Flynn Larsen

the host stem cells out so the donor cells can take.”

This need is known simply as “making space” and there are currently only two ways to do it: chemotherapy and radiation, and both are DNA-damaging. Such measures are dangerous, which is why bone marrow transplantation carries a roughly 20% risk of killing the patient. “If there were a way

to get rid of the host stem cells safely, that would make the whole procedure safer,” says Shizuru.

The work on c-Kit followed two parallel paths. One was to see whether antibodies to human c-Kit could be used to prepare patients with severe combined immune deficiency (SCID) for HSC transplantation. Known popularly as the “bubble boy disease”,

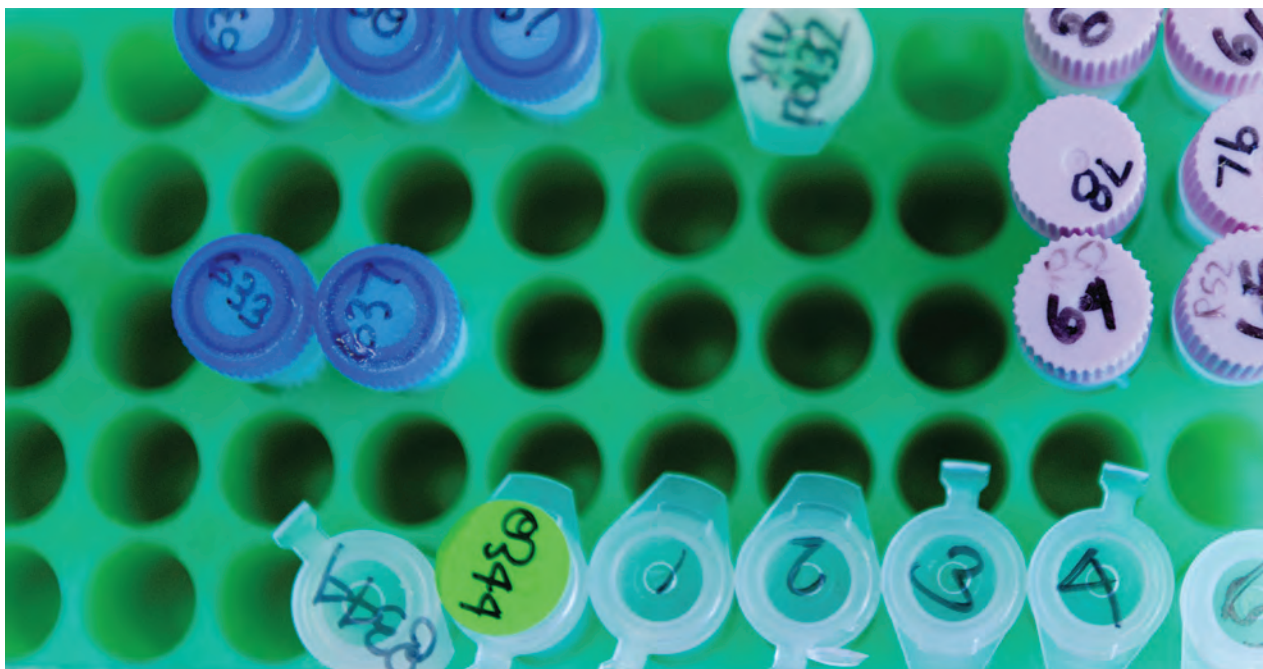


Photo by Stewart Marciano

SCID is a rare congenital disorder that leaves patients without a functioning immune system. This means that SCID patients, from an immunological perspective, reflect the conditions of the mouse experiments that initially suggested c-Kit antibodies could be used to make space for new stem cells. But first Shizuru's team needed to find human c-Kit antibodies suitable for clinical use.

A Google search revealed that the biotech Amgen already had a human c-Kit antibody, and a former postdoc of Shizuru's was on the team developing it as a treatment for a lung disease. Amgen agreed to begin a collaboration with her lab focused on transplantation. After showing that the human c-Kit depleted HSCs in mice with human immune systems and in a large animal model (monkeys), Shizuru's team obtained permission from the US Food and Drug Administration to start a clinical trial for children with SCID. It is now recruiting patients.

### STEMMING REJECTION

But could c-Kit antibodies be used to prepare people with functional immune systems for bone marrow transplantation? This was

the focus of a second path of research undertaken primarily by postdoc Akanksha Chhabra in Shizuru's lab in collaboration with MD/PhD candidates Aaron Ring and Kipp Weiskopf, both of whom have since completed their training at Weissman's lab and moved on.

Turned out c-Kit antibodies alone worked only tepidly in mice with competent immune systems. This is because T cells interfere with both the making of space by host HSCs and the engraftment of the new ones. Weissman's team, however, had a potentially useful antibody, one that is now being tested in clinical trials as a cancer therapy. The antibody targets a cell-surface protein named CD47 that is expressed by HSCs as well as cancer cells. CD47 transmits a "don't eat me" signal to the immune system's macrophages, and blocking it invites macrophages to gobble up targeted cells.

Shizuru and her team wondered whether they could clear up space in immune-competent mice if they used anti-c-Kit antibodies to tag HSCs and then hit them with anti-CD47 antibodies.

As they reported in *Science Translational Medicine* in 2016, their hunch was right: the combined treatment led to a greater than 10,000-fold reduction in the number of HSCs in the mice. “It was spectacular,” Shizuru recalls. “It was the kind of data you get to see just once in a lifetime.” But it still wasn’t enough. “To me, as a transplant physician, this doesn’t matter if you don’t get engraftment,” explains Shizuru.

To get that, the researchers would have to deal with the T cells in the host that were hampering engraftment. Chhabra accomplished that by adding a couple of antibodies to the mix that selectively target the two problematic types of T cells. The researchers then purified HSCs from the donor, leaving behind the donor’s T cells as well, and tried out the transplantation.

Not all of the host’s HSCs were replaced by the donor’s, but the procedure worked better than expected, and it was utterly devoid of the toxic therapies that have long made bone marrow transplantation an option of last resort. “This was the proof of concept that you can use an all-antibody approach to get engraftment of stem cells,” says Shizuru.

Further, Shizuru points out, the levels of stem cell engraftment achieved could be sufficient to treat genetic diseases like sickle cell anemia and SCID, in which even a partial restoration of functional blood-based cells can significantly improve a patient’s condition. In the longer term, the procedure could have important implications for the treatment of a broad variety of cancers, since first line therapies can devastate the immune system.

Ludwig is currently supporting the Shizuru lab’s exploration of their HSC transplantation approach to treat myelodysplastic syndrome, a blood disease that can progress to malignancy. Meanwhile, Shizuru and her team are

“It was spectacular. It was the kind of data you get to see just once in a lifetime. To me, as a transplant physician, this doesn’t matter if you don’t get engraftment.”

trying to figure out ways to target c-Kit alone to accomplish HSC transplantation across unrelated animals. “We’re trying immunotoxins linked to the antibodies and exploring other approaches to deplete c-Kit expressing stem cells,” she says.

“A few years ago I told my lab that if in my lifetime I can get the mouse c-Kit antibody alone to work in a normal immune-sufficient mouse, I can die a happy woman,” says Shizuru. “But we were able to accomplish this goal in just a few years, using a combination of anti-cKit and anti-CD47 antibodies. So now I’m going to have to raise the bar and tell them: ‘if in my lifetime we can replace toxic drugs and radiation and still get pure stem cells to engraft in people, I will die a very, very happy woman.’ ” 📌



Taha

Merghoub

## THE IMMUNOTRANSFORMERS

Partners in science Jedd Wolchok and Taha Merghoub solved a pharmacologic puzzle, to boost a cancer immunotherapy.

Ludwig MSK's Jedd Wolchok was at a conference in 2014 when he bumped into Vito Palombella, whose lab bench Wolchok had inherited when he was working toward his doctorate as an MD/PhD student in the 1990s at New York University. Palombella was at the time chief scientific officer at a small biotechnology company named Infinity Pharmaceuticals, and he told Wolchok about



# Jedd Wolchok

Photo by Flynn Larsen

an experimental drug that he thought might interest him. The molecule, IPI-549, targets an enzyme critical to a class of immune cells frequently recruited by tumors to squelch a potentially lethal immune attack. “It fit exactly into one of the lines of research in our lab—devising new ways to target these cells, which can be an obstacle to cancer immunotherapy,” says Wolchok.

That encounter culminated in a Ludwig study whose results were published in *Nature* in 2016. It established that those suppressive cells, known as myeloid derived suppressor cells (MDSCs), directly mediate resistance to the effects of the immunotherapy known as checkpoint blockade in a variety of tumors. The paper also demonstrated that blocking PI3K- $\gamma$ , an enzyme expressed by

“Science is a full-time job and requires total commitment. Not being able to clone a human, the best solution is to have two people who scientifically see the world the same way.”

tumor-associated MDSCs and targeted by IPI-549, restores the effectiveness of the therapy. Their finding shows how selectively disrupting the noncancerous constituents of the tumor’s microenvironment, which are manipulated in a variety of ways to prevent immune attack, can boost the effects of immunotherapy. The study also opens a new door to the personalization of checkpoint blockade therapy, and to expanding its applicability to cancer types that have so far proved resistant to the treatment.

#### A CONSEQUENTIAL COFFEE BREAK

When Wolchok got back to New York, where he directs the Ludwig Collaborative Laboratory at Memorial Sloan Kettering Cancer Center, he shared what he had learned with lab co-director Taha Merghoub.

The two decided the opportunity was worth a closer look. For all the excitement around immunotherapy, not all cancer patients respond to these treatments, which stimulate the immune system’s innate ability to kill cancer cells. Only about 40% of melanoma patients who take checkpoint blockade therapies known as PD-1 inhibitors to treat advanced melanoma, for example, see their tumors regress. Other malignancies, like breast cancer, have so far proved largely resistant to immunotherapy.

The problem in many cases is that most malignant tumors deploy a variety of defenses against immune attack. These range from biochemical tricks—depriving the foot soldiers of the immune system of vital nutrients—to manipulating the immune cells themselves, recruiting and turning them into enablers and allies of malignant growth.

Wolchok and Merghoub were particularly interested in undoing the latter type of cancerous defense and had considerable experience in probing the phenomenon. They contacted Palombella and arranged to meet up to share their ideas during the October 2014 Hallmarks of Cancer symposium (which stems from the legendary paper of the same title coauthored by Ludwig MIT Director Bob Weinberg).

During a break at the symposium, Wolchok and Merghoub met with Karen McGovern, a senior scientist at Infinity, to go over the data collected in IPI-549’s preclinical development. Infinity had done preliminary work showing that their drug could target a pathway important to the generation of MDSCs. The targeting, however, didn’t appear to have the desired effect in the tumor models being used. Wolchok and Merghoub picked up on the problem almost instantly. “When we saw the data, we had an ‘Aha!’ moment,” recalls Merghoub. “We were like, ‘Ok, you’re dealing with the wrong tumor type here. The target you need isn’t present in these tumors.’ ”



Photo by Flynn Larsen

The models Infinity was using, the Ludwig MSK researchers explained, are not typically infiltrated by MDSCs. “You could have tested this drug on five different tumor types and if none of them had MDSCs, you would have concluded that the drug is inactive,” says Wolchok. The Ludwig researchers mapped out the experiments they’d need to do to explore the immunological mechanisms of IPI-549’s effects—and help Infinity sort out its problem. Eager to tap their expertise, Infinity agreed to support studies they would lead at the Ludwig Collaborative Laboratory at MSK.

### THE RESEARCHERS

The company could not have found better researchers to solve their problem. Wolchok, a clinical oncologist and leading authority on immunotherapy, has played a central role in the development of checkpoint blockade and a variety of other immunotherapies currently in clinical trials. Merghoub, an Algerian and

the son of a Swiss-trained physician, grew up in a small town, deep in the Sahara, about 500 miles from the coast. After completing his undergraduate studies in genetics in Algiers and a PhD in France, where he studied the genetics of sickle cell anemia and thalassemia, he came to the US for his postdoctoral studies.

The two initially met in Alan Houghton’s laboratory at MSK in 2002, where Wolchok had once done a college internship and returned to conduct postdoctoral research with his mentor while completing his oncology fellowship. Merghoub had joined the lab after a postdoctoral stint studying gene regulation in a form of leukemia in the MSK laboratory of Pier Paolo Pandolfi, who is now an investigator at Ludwig Harvard. When Houghton’s neurological disorder—he has ALS—made it difficult for him to manage the day to day operations of his lab, Wolchok and Merghoub accepted responsibility



Photo by Stewart Marcano

for continuing the lab's operations and, eventually, oversaw its transition into the Ludwig Collaborative Laboratory.

Today they co-direct the lab's scientific investigations. The arrangement has worked out well for both. It has allowed Wolchok, a practicing clinical oncologist, to keep a foot in both the clinical and the scientific world without neglecting either. Merghoub, meanwhile, is able not only to pursue his scientific studies but to see a good share of his discoveries translated to the clinic, given the translational bent of the lab and its ties to clinical trial networks.

"Science is a full-time job and requires total commitment," Wolchok says. "Not being able to clone a human, the best solution is to have two people who scientifically see the world the same way, share a vision for the

laboratory and have a track record of working together."

The pair have led several studies to devise novel immunotherapies for cancers and to explore the immunologic mechanisms of response and resistance to these treatments. For them, IPI-549 was an excellent tool to evaluate a hypothesis explaining why checkpoint blockade fails against a number of tumor types. As important, if that hypothesis passed muster in the laboratory, it could be swiftly put to the test in the clinic.

#### FROM HYDES TO JEKYLLS

The researchers moved quickly to explore the pharmacology of IPI-549 and use it to interrogate tumor immunology. To demonstrate that MDSCs are indeed involved in resistance to checkpoint blockade, they compared two mouse tumor models—one

for breast cancer, which is typically resistant to checkpoint blockade, and another for melanoma, which is not.

They showed first that the breast cancer tumors are full of MDSCs and that their presence correlates tightly with reduced infiltration by the killer T cells, which are unleashed by checkpoint blockade to kill cancer cells. Those that do make it in are relatively defanged and ineffectual. The opposite was true in the melanoma model. Further, when they used a growth factor to boost the number of MDSCs in melanoma, it made these previously responsive tumors impervious to checkpoint blockade.

The researchers then examined the effects of IPI-549 on multiple tumor models, and showed that even treatment with this drug alone slowed the growth of tumors rich in MDSCs. Tumors with few such cells, on the other hand, hardly responded. This established that IPI-549 was not targeting the cancer cells directly but exerting its effects by compromising MDSCs in particular—in other words, by perturbing the tumor’s microenvironment.

The researchers showed that it was doing so by flipping the identity of MDSCs. “By inhibiting PI3K- $\gamma$ , we turned the tumor-associated MDSCs from bad guys into the good guys,” says Merghoub. Instead of suppressing the immune response against tumors, treated immune cells now activated it, prompting killer T cells to turn their molecular weaponry against cancer cells.

As a consequence, IPI-549 dramatically improves responses to checkpoint blockade therapy in tumors that harbor large numbers of MDSCs, but not against those that do not. The effects appear to be multiplicative in animal models. When a combination of checkpoint inhibitors were administered to mice with MDSC-rich tumors, only 20% of the animals underwent complete remission. When the same drugs were administered

“By inhibiting PI3K- $\gamma$ , we turned the tumor-associated MDSCs from bad guys into the good guys.”

with IPI-549, that portion climbed to 80%. Notably, animals whose tumors had regressed completely rejected tumors that were subsequently implanted in them, indicating that they had developed an immunological memory of the cancer that could sustain its durable control.

The implications are exciting for other reasons as well. Several of the most common types of cancers do not respond to checkpoint blockade, and in many cases this may be due to a high infiltration of MDSCs in their tumors. Merghoub and Wolchok’s findings open the door to personalizing checkpoint blockade treatments and could significantly expand the utility of this immunotherapy against a broad variety of tumor types. Best of all, their hypothesis is beginning to be tested now in a clinical trial examining the combined effects of IPI-549 and checkpoint blockade against a variety of solid tumors. ■

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