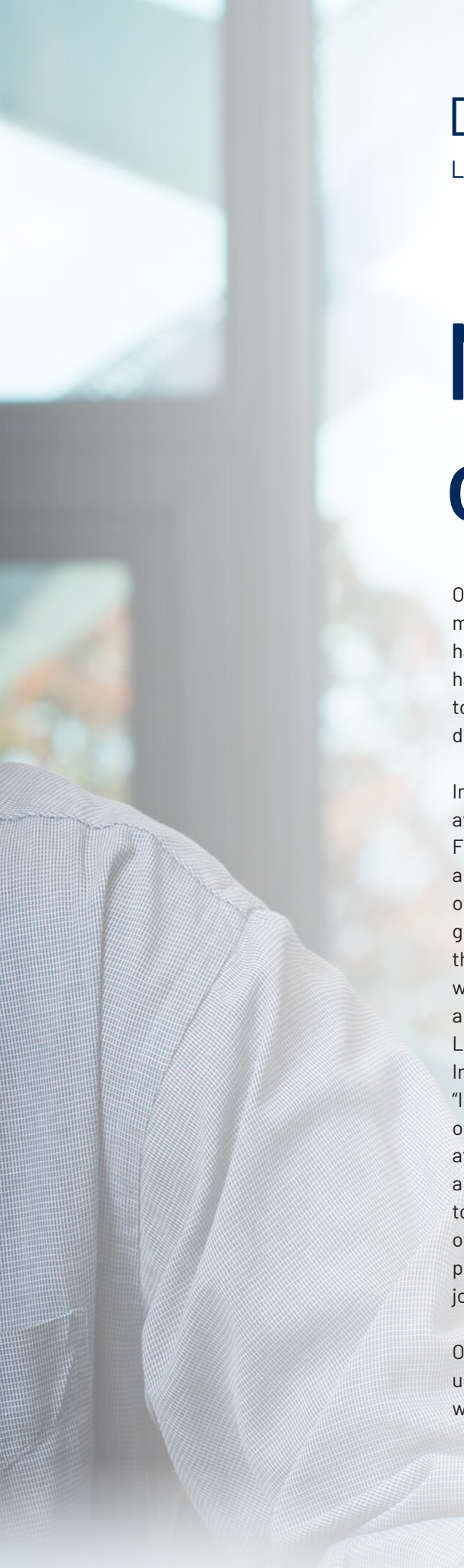

DOUGLAS HANAHAN

LUDWIG LAUSANNE

Modeler of malignancy

One of the most influential papers in modern cancer biology might never have been written if Doug Hanahan had not issued an open invitation to a few colleagues to explore a dormant Hawaiian volcano.

In 1998, Hanahan, then a professor at the University of California, San Francisco (UCSF), was attending a cancer conference on the island of Maui. "I had decided that I was going to play hooky one day from the meeting," says Hanahan, who in January 2020 became a distinguished scholar at the Lausanne Branch of the Ludwig Institute for Cancer Research. "I announced to a small group of scientists in the bar after the afternoon session that I had rented a car and was planning to drive up to Haleakalā because I think it's one of the most amazing places on the planet, and that if anyone wanted to join me, they were welcome."

Only one person took Hanahan up on his offer: Robert Weinberg, who is now the director of the Ludwig Center at MIT. The next day, during the long drive there and back, and while strolling across the moonscape of the crater rim, the conversation turned to one of their mutual interests. "Rather than talking about our families or whatever, we just got into a conversation about the complexities of cancer," Hanahan says.

Over the next several hours, an idea began to crystalize between them: that underlying the bewildering variety of cancers that afflict people are a set of common capabilities that cancer cells and tumors must acquire before they can become deadly. Differing cells in differing tissues might acquire them in different orders, but all tumors must acquire these core biological functions—what Hanahan and Weinberg would call the "hallmarks of cancer"—to become malignant. "We compared it to climbing Mount Everest," Hanahan says. "There are many routes you can take to climb the mountain, but all of them must

Photo by Felix Imhof

"The main lesson from physics that I brought into my PhD research was the notion of problem solving, because throughout your physics training, you're given very difficult problems and you have to figure out how to solve them."

pass through the same heights to reach the top."

Hanahan and Weinberg refined this idea over the next two years, ultimately publishing their meditations on the hallmarks of cancer as a perspective in the millennium issue of the journal *Cell* in January 2000. In that first essay, the pair identified six capabilities acquired by incipient tumors as they develop, step by step, into full-blown malignancies. These included sustaining proliferative signaling, evading growth suppression, resisting cell death, enabling replicative immortality, activating invasion and metastasis and inducing angiogenesis, or blood vessel formation. While each of these phenomena were already known at the time, no one had ever arranged them so coherently. Their synthesis served as an unparalleled conceptual framework for understanding the cellular and molecular underpinnings of cancer.

"Neither of us had any great sense of destiny or thought that this was going to somehow be very impactful. We just thought this was kind of a cool idea and maybe we should throw it out there," Hanahan says. "But within a couple years, it became clear that it was being widely cited. People were really resonating with it."

"I've often wondered whether the hypoxia at 10,000 feet that day had anything to do with it," Hanahan jokes.

In 2011, the pair published an updated version that included two new hallmarks—the reprograming of energy metabolism and evading the immune response. They also further emphasized in that update the importance of the "tumor microenvironment," a unique ecosystem of noncancerous cells and molecular factors that contribute critically to the acquisition of hallmark capabilities. Aside from their outsize influence on the sprawling field of cancer research, the hallmarks described in the two papers also established an enduring infrastructure for Hanahan's program of research as his laboratory moved from UCSF to the EPFL in Lausanne and then to the Lausanne Branch of the Ludwig Institute for Cancer Research. As for the papers themselves—citations of the sequel have now far outpaced even the impressive numbers of the first, which long held the title of *Cell's* most highly cited paper of all time.

COLD SPRING HARBOR

It probably helped that by the time the *Hallmarks of Cancer* was published, Hanahan was already well known as a pioneering molecular biologist with several

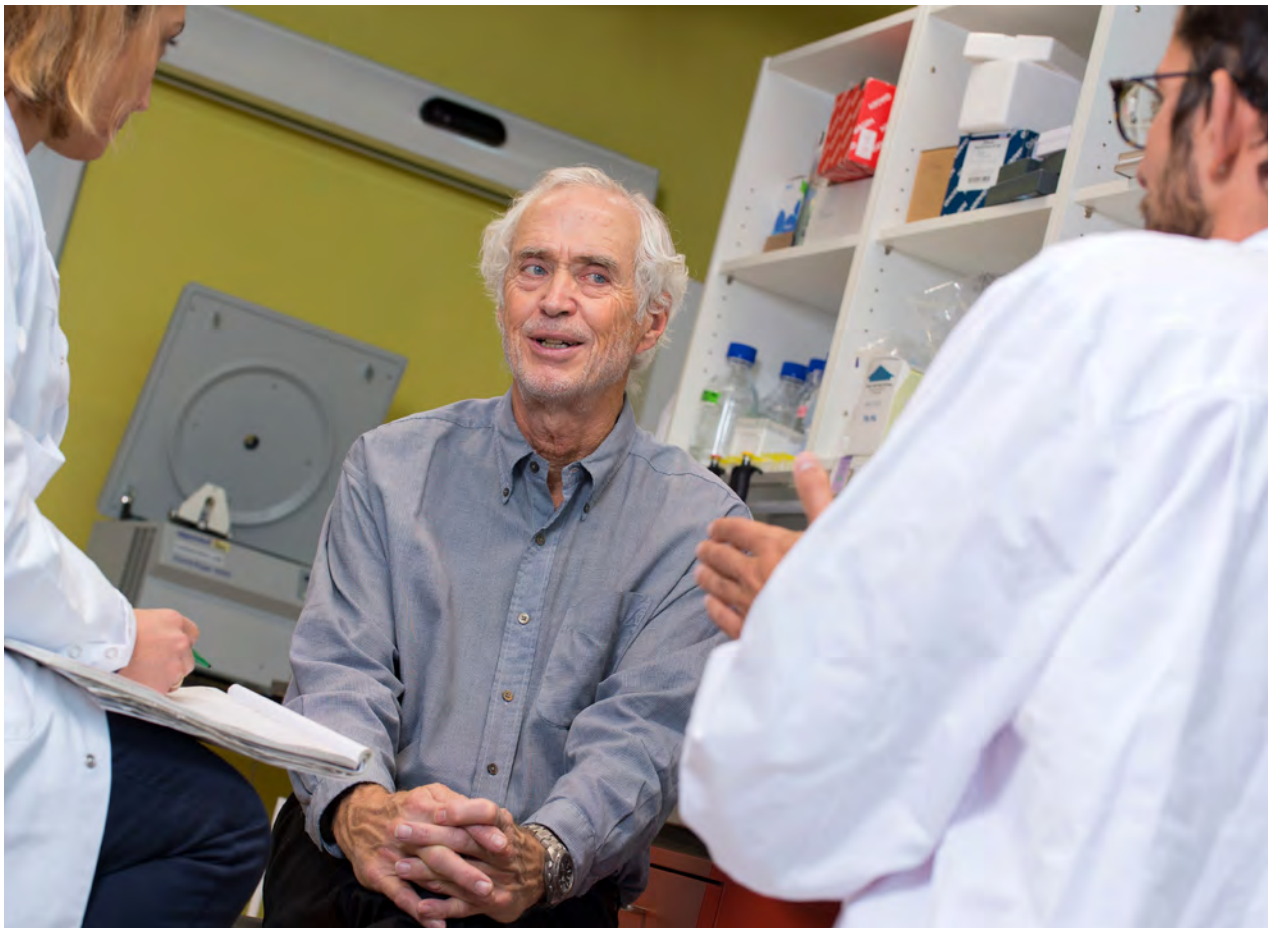

Photo by Felix Imhof

seminal discoveries in cancer biology and immunology to his name.

While still a Harvard graduate student working at the Cold Spring Harbor Laboratory in New York in the 1970s, Hanahan developed new and better methods for gene cloning and bacterial genetic engineering, which were very new biological technologies at the time. "I ended up having a nomadic PhD career, where I went back and forth between Harvard in Cambridge and Cold Spring Harbor in Long Island," Hanahan says.

After Hanahan earned his PhD, he had a life-changing conversation with Cold Spring Harbor Laboratory's Director, Nobel laureate James Watson, who asked him what he wanted to do with his career. "I told him I wanted to study gene regulation by introducing genes into mice. There were a few studies suggesting you could introduce DNA into the mouse germline by injecting fertilized mouse eggs," Hanahan recalled. "Jim said, 'It's really tough. Other people have tried and failed. Why do you think you'd succeed?' I just said I thought I could do it, and he said, 'Well, I want to get this technology working here, so if you want to move down here and make a commitment, I'll support you.' "

Succeed Hanahan did. By the mid-1980s, he had engineered one of the first transgenic mouse models to express oncogenes and develop tumors, which he described in a single-author *Nature* paper. The mice would prove to be an extraordinary asset to the study of not only cancer but immunology, and Hanahan immediately set about using

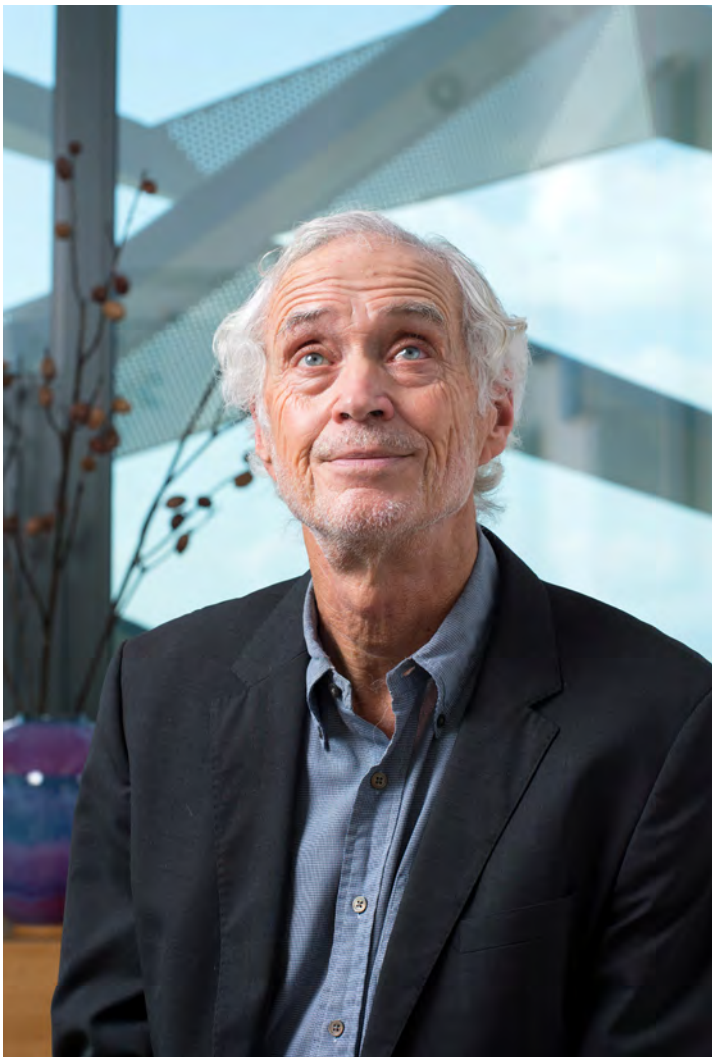

Photo by Felix Imhof

the mice to explore such phenomena as autoimmunity and the induction of immune tolerance. In fact, Hanahan says, his initial interest in cancer was limited to how oncogenes could be exploited to study differentiated cells and to induce cells to undergo proliferative expansion. "You could get access to more cells to study this way," he explains. "Those were the original reasons for my interest in oncogenes."

But when his transgenic mice began developing tumors, he became increasingly curious about the mechanisms of cancer. "One of the cell types I had chosen to focus on was the islet cells that make insulin in the pancreas," Hanahan says. "It became very clear that the oncogene was not instantaneously transforming every cell that expressed it into a tumor."

Rather, he noticed, there was a latent period, and that out of hundreds of islet cells, only a few developed into solid tumors. "As I read more about cancer, it became apparent that what I was observing in the mice fit with the epidemiology and histopathology of the human cancer, in that it was a multi step process that takes time and requires a sequential progression through differing premalignant stages," Hanahan says. "It began to dawn on me that maybe our mouse model is very interesting for studying cancer."

Working with Judah Folkman, who died in 2008, Hanahan used the model to first report in 1989 that the transition from precancerous growth to malignancy is preceded by the assumption of angiogenic potential by a subset of abnormally proliferating cells. When enough tumor cells become angiogenic, the tumor can grow and eventually metastasize. The pair described an "angiogenic switch" that allows blood vessels required for solid tumor growth to form—showing that about a quarter of the rapidly proliferating cells developed this capability. They went on to identify the protein factors that trigger the transformation and later explored the pharmacological inhibition of the switch and its effect at distinct stages of tumorigenesis, contributing critically to the development of anti-angiogenic drugs for cancer therapy.

Hanahan and his colleagues also employed transgenic mice to explore tumor immunology. They showed in the late 1990s, for example, that antigens expressed in solid tumors are poor stimulators of T cell attack, and that the tumor microenvironment suppresses immune responses. In various other studies, they showed how immune cells contribute to angiogenesis and other events essential to tumor growth and survival.

And so, by 2000, Hanahan's sprawling exploration of multi-stage tumorigenesis using mouse models developed in his laboratory was already eliciting routine invitations to speak at cancer conferences—one of which took place in Maui, where he and Weinberg would have their fateful conversation atop Haleakalā.

MOTIVATING TEACHERS

Hanahan credits inspirational college mentors for putting him onto a scientific track. It wasn't biology that excited him at first, however, but physics.

"During my sophomore year at the University of Washington, I had a physics teacher, Lowell Brown, who was terrific. It was a really hard course, but he was inspirational," Hanahan says. When Brown encouraged Hanahan to transfer to another university with a better physics department, Hanahan set his sights on MIT and was accepted.

At MIT, Hanahan took a general biology course, where he encountered another inspirational teacher, Nobel laureate Salvador Luria. "He started the course talking about how the single cell fertilized egg of a human, through the selective expression of the information encoded in the genome, divides and differentiates and evolves into an organism with all the amazing characteristics that we have," Hanahan recalls. "It was something I hadn't thought about before and which I found very intriguing."

Luria also told his students a revolution was afoot in biology involving recombinant DNA and cloning. This was in 1975, the same year as the famous Asilomar Conference in California, where 140 professionals—including biologists, lawyers and physicians—convened to draw up guidelines for ensuring the safety of recombinant DNA technology. "The revolution that was happening, and the controversy and debate around it, stimulated a transition into biology for me," Hanahan says. "I wanted to get involved in this revolution and to do molecular biology and clone genes."

> "Amazingly enough, that same mouse model of cancer that I first created in 1984 continues to teach us interesting lessons about biology."

After graduating from MIT, Hanahan entered the Biophysics PhD program at Harvard. "There is a grand tradition of physicists who've moved into biology and have made epic contributions, so this program has long had the view that bringing in people with a background in physics was a good thing," Hanahan says. "The main lesson from physics that I brought into my PhD research was the notion of problem solving, because throughout your physics training, you're given very difficult problems and you have to figure out how to solve them. Often, you try one kind of a strategy, it doesn't work, so you go back and try another and you keep persisting, now having some sense that the problem had to be solvable. I really brought with me that sense of determination to solve problems and to try different angles."

At Harvard, Hanahan joined the lab of Paul Doty and worked on cloning collagen genes. By that time, the Asilomar conference had prompted a moratorium in Cambridge on the cloning of mammalian genes. Fortunately, Doty was able to arrange for Hanahan to continue his work at Cold Spring Harbor,

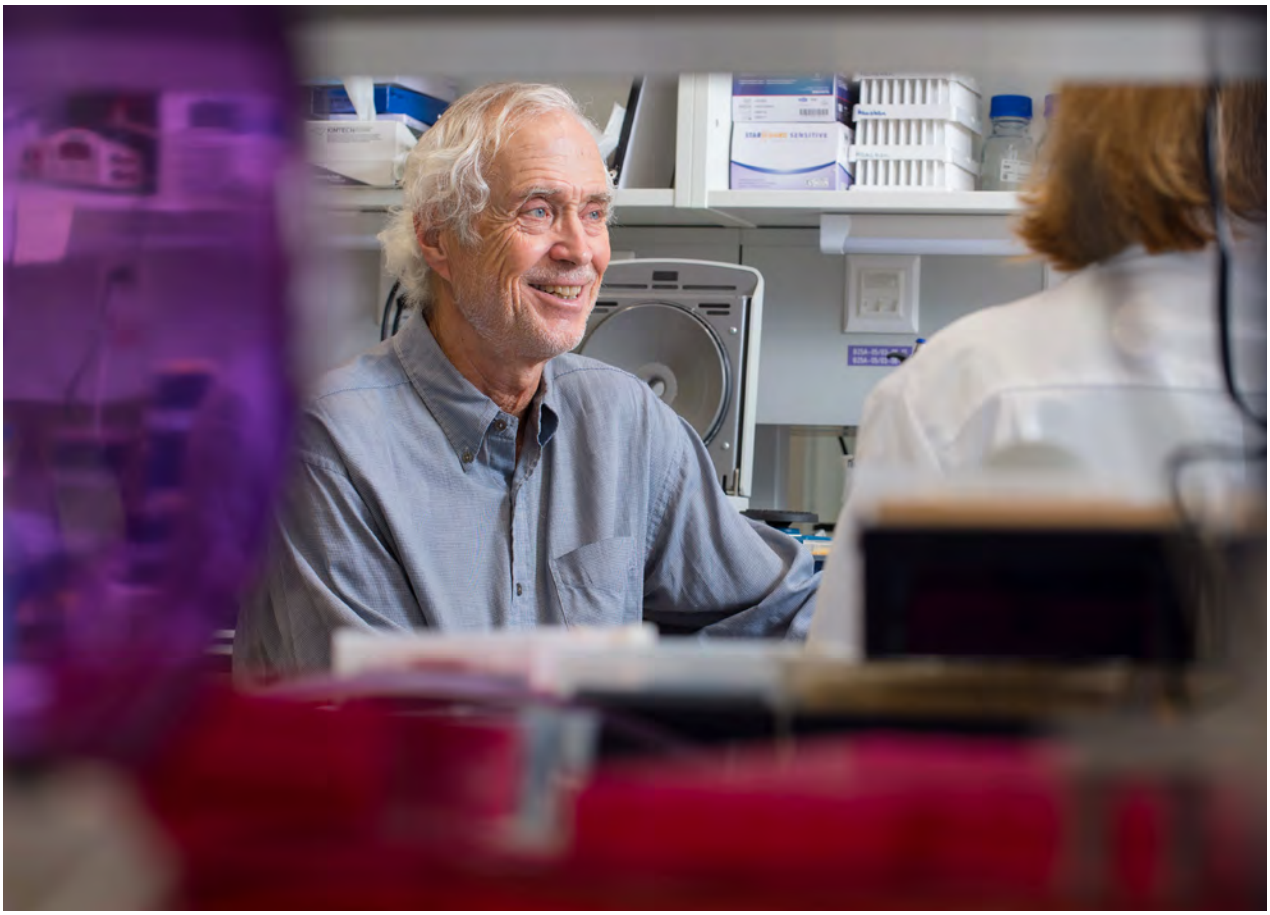

Photo by Felix Imhof

one of the few places on the East Coast possessing so-called biosafety-3 level facilities where such research was allowed at the time.

"When I was down there working, I met a bunch of the scientists and got really excited about the notion of cloning tumor associated genes," Hanahan says.

GET OUT, MOVE AROUND

The genetically engineered cancer mouse models Hanahan first developed at Cold Spring Harbor would remain a staple of his research, even as he became a professor of biochemistry and biophysics at UCSF in 1988, and then director of the Swiss Institute for Experimental Cancer Research at EPFL, in Lausanne, starting in 2009.

The mouse models became platforms for elucidating the mechanisms underlying each stage of tumorigenesis and the acquisition of hallmarks of cancer. In the early 2000s, for example—led in part by Ludwig Lausanne's Johanna Joyce, who completed her postdoc in Hanahan's UCSF laboratory—Hanahan's lab described in a series of studies how specific protein-snipping enzymes known as cathepsins contribute to distinct stages of tumor growth and metastasis. In 2009, Hanahan's team used a mouse model to identify sets of microRNAs—which regulate gene expression—that contribute to each step of tumorigenesis and the acquisition of specific hallmark traits. His lab today continues to explore the biology of some of those microRNAs.

"Amazingly enough, that same mouse

model of cancer that I first created in 1984 continues to teach us interesting lessons about biology," Hanahan says.

Earlier this year, for example, a team led by Hanahan published a study identifying a previously unrecognized mechanism by which pancreatic cancer cells methodically retrace their developmental pathway to an immature state of cellular development to spawn highly aggressive tumors. The discovery provided concrete evidence that such cellular de-differentiation, widely observed across cancer types, is not merely a random occurrence but rather an independently regulated and separable step in tumorigenesis.

In addition to pancreatic cancer, his team is also studying mouse models of melanoma and glioblastoma, cervical cancer and breast cancer. "We've got a broad based set of models of different forms in human cancer that we're interrogating in different ways," Hanahan says. His team is today especially interested in how the tumor microenvironment collaborates with cancer cells to manifest malignant disease and resist therapy.

He and his colleagues are exploring new technologies—in part as participants in Ludwig's multi-center Tumor Atlas Project—to interrogate tumors in greater depth. In another collaboration with Ludwig Lausanne colleagues, Hanahan's team is studying how the tumor microenvironment contributes to drug resistance, with a particular focus on its role in thwarting anti-tumor immunity. In addition, the lab is studying mechanisms of adaptive resistance to therapies targeting hallmark capabilities and exploring ways to circumvent such drug resistance through the use of combination therapies that simultaneously target distinct hallmark capabilities.

"My engagement with the Lausanne Branch of the Ludwig Institute, and increasingly with the Ludwig community at large, is stimulating collegial interactions that are spawning new collaborative opportunities based on complementary expertise and insights, both for me and my research team," says Hanahan. "This will enrich our agenda and foster our progress in cancer science."

THINGS ARE HAPPENING

In their 2000 Hallmarks of Cancer essay, Hanahan and Weinberg predicted that in 25 years, cancer research would develop "into a logical science, where the complexities of the disease described in the laboratory and clinic will become understandable in terms of a small number of underlying principles."

Hanahan doesn't think his field has yet achieved this goal, but he remains optimistic that one day, perhaps sooner than anyone expects, it will. "Things are happening," he says. "There has been an explosion in enabling technologies to interrogate tumors, particularly at the single cell level. I think you can foresee that the field is becoming more logical and we're starting to understand more than ever about cancer."

Reflecting on his career, Hanahan says he thinks a hallmark of his own life has been a willingness to go out and experience new environments. "Whether it was moving from Seattle to MIT, MIT to Harvard, Harvard to Cold Spring Harbor, Cold Spring Harbor to San Francisco, or now most dramatically from the US to Europe, I was happy and successful in each place I lived and worked," Hanahan says. "I was never *obligated* to move but, rather, was *inspired* to move. I tell my students that you shouldn't think that you work in the same institution until you're ready to retire. You should instead make strategic moves, getting out of your comfort zone, taking on new challenges with no guarantee of success, but with exciting opportunities to make an impact."