



George  
Coukos

Photo by Eric Deroze

## 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.

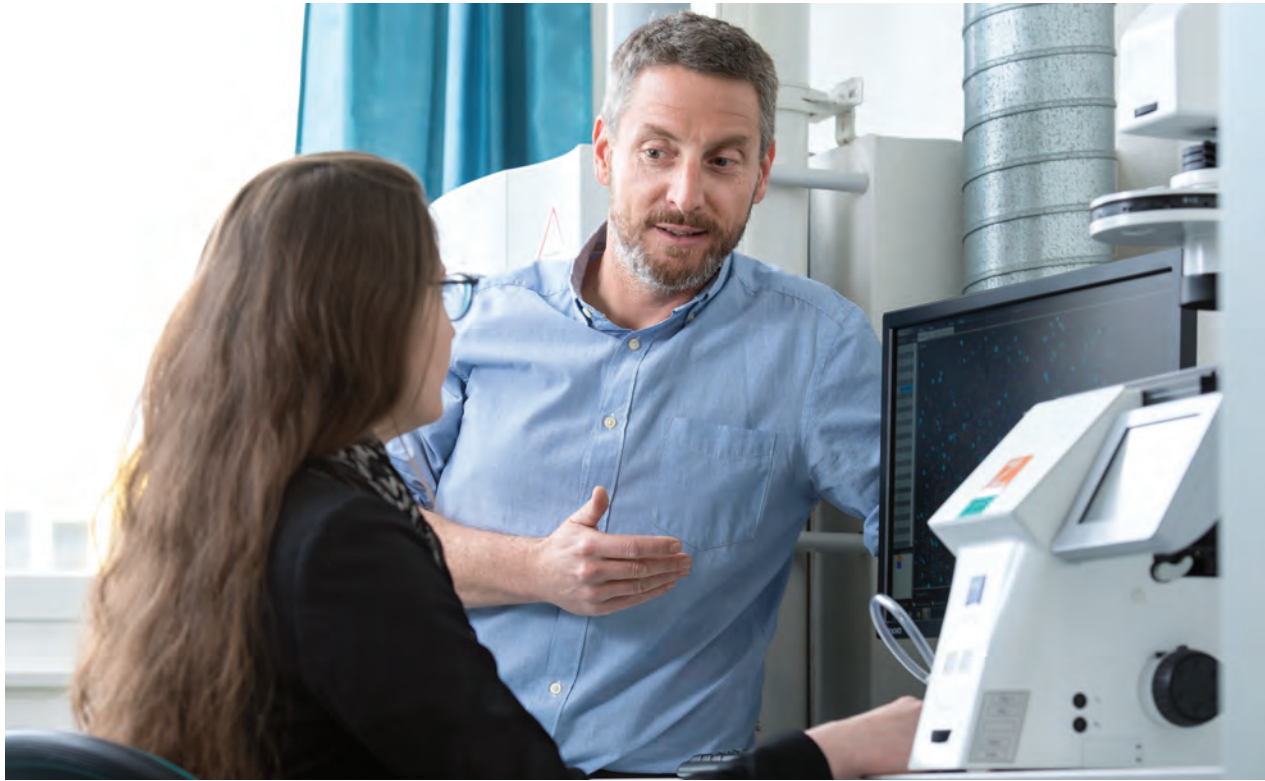
On the other hand, as he learned more about the opportunity, it became increasingly clear that if he wanted to build a truly pioneering program for developing advanced immunotherapies, Lausanne was just the place for it. Coukos would find in CHUV a sophisticated hospital and at UNIL and beyond a vast 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





Alexandre Harari

Photo by Eric Deroze

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.

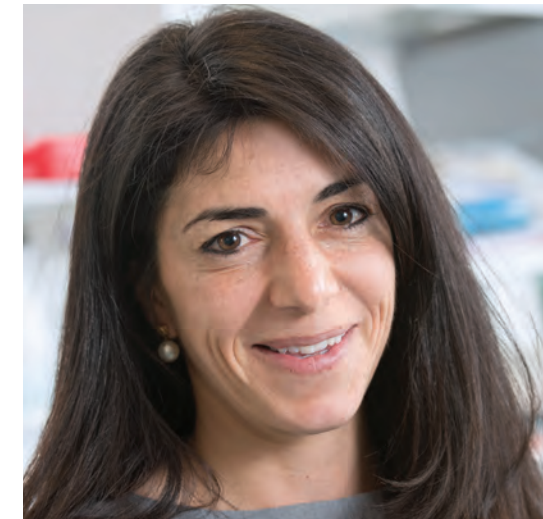
Adoptive T cell therapies offer an alternate route to stimulating immune attack. In these so far experimental therapies, a variety of TILs are extracted from a patient, selected for their cancer-detecting chops and then grown in the lab before they’re reinfused into the patient. Alternatively, T cells 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

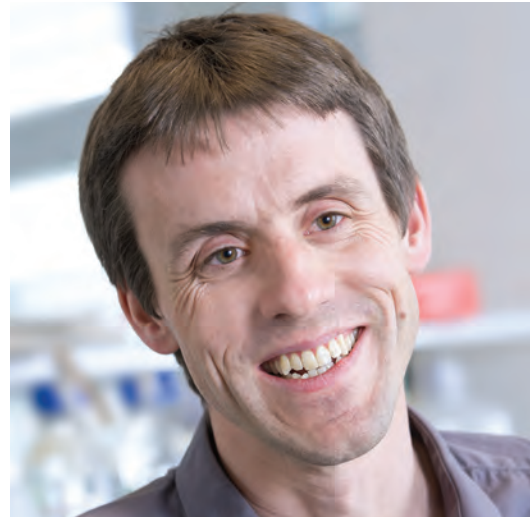


Michal Bassani-Sternberg

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



David Gfeller

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

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



Steven Dunn

Photos by Eric Deroze

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

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



Sylvie Rusakiewicz

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

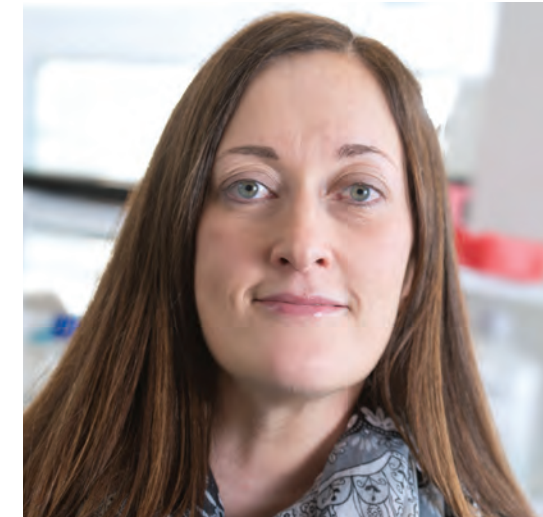


Ping-Chih Ho

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



Johanna Joyce

Photos by Eric Deroze

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.” ■