



THE PERSONAL VACCINOLOGIST

Lana Kandalaft's scientific journey, which began in Jordan, led to an ongoing collaboration in translational medicine with a leading immuno-oncologist and their creation of a personalized cancer vaccine.

The plan was that Lana Kandalaft would get her PhD and then return to Jordan. That, at least, was what she'd told her dad, a surgeon and her role model, when she first informed him she wanted to study abroad. But as she wrapped up her doctoral studies in pharmaceutical cell biology and drug delivery in the UK in 2003, Kandalaft realized this wasn't going to happen. She wasn't entirely sure what she'd do next, but she was sure about a couple of things. One was that a young scientist in a hurry wasn't likely to hurry anywhere professionally back home. The other was that whatever she wound up doing, she wanted to see her science in action. "I was so attracted to applying what I had learned," she says, "not just doing drug delivery for the sake of delivery, but actually curing a disease."

In 2018, Ludwig Lausanne's Kandalaft passed a milestone on the road to realizing that dream. A study she led with George

Coukos, director of the Lausanne Branch of the Ludwig Institute for Cancer Research, and her colleague there Alexandre Harari, showed that an entirely new type of personalized cancer vaccine she and Coukos developed over the course of a decade induces clinically effective immune responses in patients receiving a combination of standard therapies for recurrent and advanced ovarian cancer. Reported in *Science Translational Medicine*, the study revealed that the vaccine—made from a processed sample of a patients' tumors and delivered via their own immune cells—is well tolerated and elicits therapeutically effective immune responses when delivered in combination with a pair of drugs currently used to treat ovarian cancer.

A pathway to science

Kandalaft was born in Germany, where her mother, a dentist, and father both got their postgraduate training. Soon after her

A close-up portrait of a woman with long, dark brown hair, smiling gently at the camera. She is wearing a blue and white striped scarf and a dark top. The background is a plain, light blue-grey color.

**LANA
KANDALFT**
LUDWIG LAUSANNE

Photo by Jeanne Martel



Alexandre Harari, left, Lana Kandalaft and George Coukos.

parents returned to Lebanon, however, civil war broke out and the family emigrated to Jordan. An all-round athlete and excellent student, Kandalaft got a scholarship in 1995, at the age of 16, to join the University of Jordan's School of Pharmacy. After graduating in 2000, Kandalaft enrolled in a PhD program at the Welsh School of Pharmacy at Cardiff University, where she focused on drug delivery.

In 2004, Kandalaft started a three-year postdoctoral stint at The National Cancer Institute, in Bethesda, Maryland, studying cancer therapeutics, and then continued

for an additional year as a senior research fellow. She also met her future husband, a fellow globetrotting Lebanese émigré who worked in private equity and who was, like her, an avid runner.

As her postdoctoral studies drew to a close in 2008, Kandalaft came across an advertisement from the University of Pennsylvania (UPenn) for a coordinator for translational science and clinical development at a new Ovarian Cancer Research Center. The job was posted between Coukos, the founding director of the Center, and Carl June, who had



Photo by Felix Imhof

pioneered a promising immunotherapy for cancer known as chimeric antigen-receptor T cell (CAR-T) therapy. After more than a dozen interviews, Kandalaft was hired.

Toward translation

Carl June had already built a translational research capacity in developing his CAR-T therapies, and Coukos wanted to do the same for his new Center. That would be Kandalaft's primary responsibility. Her first task, however, was to develop a clinical trial protocol for a CAR-T therapy for ovarian cancer and obtain approval for its clinical evaluation from the U.S. Food and Drug

Administration. "It was totally different from my background in drug delivery, but it was a new challenge and I was very excited to work on it," says Kandalaft.

Next, Kandalaft worked with Coukos on a clinical trial applying a novel cancer vaccine developed by a biotechnology company in combination with a targeted therapy, bevacizumab, designed to inhibit new blood vessels in tumors. Coukos was interested in the vaccine's potential to treat recurrent ovarian cancer. "It was George's vision to bring immunotherapy to ovarian cancer patients," says Kandalaft.

Cancer vaccines, like other inoculations, teach the immune system's T and B cells to recognize small fragments of proteins, known as antigens, whose molecular aberrations betray disease. A few cancer antigens are shared within and across cancer types, but the majority are generated by random mutations and are frequently unique to individual patients. These are known as "neoantigens." Ovarian cancer has relatively few such mutations and had long resisted immunotherapy. Coukos, however, suspected the tumors could be coaxed to respond under the right conditions.

The experimental vaccine they initially tested was based on dendritic cells. These are immune cells that patrol the body for suspicious biological detritus, which they gobble up and process, "presenting" antigens to T cells to inform them about a looming threat. The dendritic cells of the vaccine were exposed to the cellular contents of each patient's tumors, or "whole tumor lysate," before being given to the patients. While managing this trial, which produced modestly positive results, Kandalaft enrolled in a master's degree program in translational medicine at UPenn. She also started working with Coukos to

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develop their own dendritic cell vaccine for ovarian cancer.

Kandalaft was by then collaborating with a postdoctoral fellow, Cheryl Chiang, who would play an integral role in the coming vaccine development. Chiang’s previous studies had demonstrated that treating tumor lysates with hypochlorous acid made them better provocateurs of immune responses. Working with Coukos, June and their UPenn colleagues Daniel Powell Jr. and Bruce Levine, Kandalaft and Chiang began preclinical studies to develop a more potent version of the vaccine.

The next few years were extraordinarily busy. Kandalaft had her first son in 2011, when the trial of her dendritic cell vaccine was well underway. She also learned from Coukos that he was in discussions to move to Lausanne, where he hoped to establish a new translational research center dedicated to developing personalized immunotherapies for cancer. He wanted her to come along to oversee this center. Fortunately, her husband, whose clients

live all over the world, didn’t mind where they went so long as he had easy access to an airport. As opportunities go, Kandalaft realized, this one was tailor-made for her.

A tailored vaccine

The pilot study of the dendritic cell vaccine continued apace as Kandalaft and her family moved to Lausanne in 2013. Her first job there was to set up a Center of Experimental Therapeutics (CTE), a collaboration between the University of Lausanne, the Lausanne University Hospital and Ludwig Lausanne. “The CTE is the infrastructure for taking these innovative lab projects from Ludwig laboratories to patients,” says Kandalaft, who is its director, overseeing some 130 staff and participating researchers.

Kandalaft, Coukos and their colleagues had already reported in *Clinical Cancer Research* in 2013 that the acid-treated tumor lysate vaccine induced potent antitumor immune responses in mice and even in patients. The study published in *Science Translational Medicine* in 2018 evaluated the same type of vaccine for recurrent ovarian cancer. But the clinical protocol of its delivery was designed to maximize the vaccine’s immunologic kick.

Many tumors evade immune attack by barring entry to killer T cells. They also selectively recruit and retain regulatory T cells (Tregs), which suppress any killer T cells that slip through those barriers. Coukos and his colleagues had previously shown that VEGF-A, a factor secreted by tumor cells to stimulate the growth of blood vessels, also keeps killer T cells from infiltrating the tumor; others had found that the same factor suppresses dendritic cell maturation.

Bevacizumab blocks VEGF-A activity. Another standard of ovarian cancer care—the chemotherapy cyclophosphamide—



Photo by Felix Imhof

had been previously shown to suppress Tregs when given in low, repetitive doses. Kandalaft and Coukos wanted to use both these therapies to boost their vaccine's effects.

To make the vaccine, the researchers gently separated out the cancer cells in tumor samples obtained from patients with recurrent ovarian cancer and treated them with hypochlorous acid before breaking them open to collect their contents. Next,

they isolated precursors of dendritic cells from patients and coaxed them to mature in a dish. They then pulsed each patient's dendritic cells with her tumor lysate to generate a personalized vaccine.

The vaccine was delivered directly into selected lymph nodes in patients. "The lymph nodes," Kandalaft explains, "are the headquarters where dendritic cells meet T cells." One cohort of patients received just the personalized vaccine. A second received

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vaccine along with bevacizumab. The third got, in addition to bevacizumab, low doses of cyclophosphamide.

Though not a randomized, placebo-controlled trial, the study's results were compelling. One year after receiving the vaccine, all patients who received all three treatments were still alive, as compared to 60% historical survival rates for patients receiving just bevacizumab and cyclophosphamide. "The regimen used for the third cohort really made a difference—first in eliciting an immune response in patients who received it, and then in the progression-free survival and the overall survival of those patients a year and even two years after receiving the therapy," says Kandalaft. One woman with stage IV ovarian cancer remained cancer-free five years after completing the regimen.

The immune analysis of the vaccine's effects, led by Kandalaft and Alexandre Harari, was just as encouraging, and it validated the clinical protocol.

"This was our first mission, our first

challenge," says Harari, who directs the immune monitoring core of the CTE and co-directs the antigen discovery unit of the Hi-TIDE (for Human Integrated Tumor Immunotherapy Discovery & Development Engine) at Ludwig Lausanne (see page 19). "We were still establishing the assays we'd need to analyze patient T cell responses, so it was a bit tricky. But in the end, it all came together, and the main observations were in line with the most ambitious hypotheses George and Lana had formulated for this trial."

Studies of killer T cells isolated from patients showed that the immune responses elicited by the regimen were vigorous and targeted known cancer antigens as well as a broad variety of neoantigens. Intriguingly, following immunization, the T cells not only recognized a broad spectrum of pre-existing neoantigens but new ones as well. The T cells were also far more sensitive to lower levels of those antigens, and more fiercely activated when exposed to them.

Looking ahead

Work on the dendritic cell vaccine

continues. Coukos, Kandalaft and their colleagues at UPenn completed in 2018 the clinical phase of another small trial built out of the cohorts of the first. Its three cohorts are evaluating the effects of the individualized vaccine in combination with aspirin, with the therapeutic immune factor interleukin-2 and when bevacizumab is given prior to vaccination with the intent of boosting T cell infiltration into tumors. Analysis of the samples from that trial should be completed at Ludwig Lausanne in 2019.

Aside from directing the CTE, Kandalaft is also building on her vaccine research in her own lab at Lausanne, addressing follow-up questions from the *Science Translational Medicine* study. She is working with Ludwig Lausanne's Michal Bassani-Sternberg, a protein chemist who directs the antigen discovery unit with Harari, to determine how whole tumor lysate vaccines compare with synthetic vaccines based on computationally predicted neoantigens. Is one better than the other? Or would they work best in sequential combination? Kandalaft is also trying to engineer dendritic cells as agents of vaccination. "We have the translational facilities here to take these cells to their maximum potential," she says.

Those translational facilities are already being deployed in a clinical trial examining the selective reinfusion of tumor-targeting T cells as a treatment for melanoma. Other immunotherapies translating Ludwig Lausanne science are being planned as well.

This is, in other words, Kandalaft's dream job. "Being in the middle of it is very rewarding because you really get to see all the innovations scientists come up with to get to the clinic, and then see it in the patients, and get to change some lives," she says. "Maybe not as many as we want yet, but we're getting there." ■



Photo by Eric Déroze

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