Dr. Ofrat Beyar Katz is an immuno-automotive engineer of sorts. She works with CARS. Not sedans, SUV’s or station wagons, but CART-19 cells, CART-38 cells and more – CARs, as they are referred to in the world of immune-based blood cancer treatment.

“We’ve made a lot of CARs here in my lab,” says the 39-year-old hematologist, an APF 2019-2020 Postdoctoral Fellow in Immunotherapy at the University of Pennsylvania’s Center for Cellular Immunotherapies. “It’s very exciting.

“What I love about this field is that it really holds hope for patients who have not responded to any treatment until now – not chemo, stem cell transplant or anything else.”

The therapy itself is called CAR-T cell therapy, a process that harnesses the body’s immune system to fight its cancer. It includes all the different CAR treatments such as CART-19, CART-22 and CART-38. The different numbers refer to the harmful cells being targeted, Beyar Katz says. “The most common and only FDA-approved CAR treatment uses CART-19 cells. The rest are in clinical trials.”

The concept was invented in 1987 by Israeli scientist Zelig Eshhar and has been developed as a treatment in the years since by centers such as the one at Penn.

“Now for one disease, acute lymphoblastic leukemia (ALL), there is an 80-90 percent response rate with CAR-T cell therapy in patients who’ve responded to nothing else, Beyar Katz says. “And with aggressive lymphomas, patients respond in 50 to 60 percent of the cases.”

CAR (chimeric antigen receptor)-T cell therapy uses specially engineered white blood cells, called T cells, to hunt down and destroy abnormal cells, including cancer cells. The body’s T cells, for unknown reasons, don’t always recognize cancer cells or don’t mount an all-out attack on them, allowing tumors to take root and expand. Turning them into CAR-T cells seeks to overcome these deficiencies by directing them against the tumor.

To make CAR-T cells, a machine that resembles a dialysis unit first draws blood and centrifuges it. The process takes a few hours. Later the cells grow and are expanded in the lab. Technicians genetically engineer the cells to sprout special structures, the chimeric antigen receptors, on their surfaces. When these CAR-T cells are reinjected into patients, the receptors may help the T cells identify and attack cancer cells throughout the body.

Antitumor effects can show as soon as two to three days after treatment. A post-injection scan is done after four weeks.

Side effects include: fever, lower blood pressure, low oxygen level and neurological problems such as being unable to think clearly and, in rare cases, seizures.

Obviously, some patients do not respond to treatment and some relapse. Others with particularly aggressive cancers can’t utilize this protocol because of the time it takes overall. “But that doesn’t mean our work is hopeless,” says Beyar Katz. “It’s not ‘one CAR fits all;’ we are constantly modifying a lot in this field.”

Beyar Katz, herself, was leading game-changing work in CAR-T cell modification in her Penn lab for two years. “I’ve been working on a process whereby a patient is injected with a virus immediately and it finds the T cells and modifies them to attack the cancer. The engineering of the T cells happens in the patient’s body."
“There is no harvesting and engineering, so it really saves time. It would be an off-the-shelf virus, available whenever you want.”

With Beyar Katz gone, a team of three will continue this work. The virus project may be ready for clinical trials in three to four years.

Also marked for the future and already in trials (not at Penn) is a process that doesn’t use the patient’s own cells. It uses cells from a healthy donor, one who’s never had chemotherapy, she says.

“The cells are harvested and modified to target specific T cells, and extra modified to prevent rejection. They are already expanded and suitable for any person. It’s ready to go, ‘off the shelf CAR-T cells,’ called *allogeneic* CAR-T cells.”

Beyar Katz spent about four days a week in the lab and one day a week doing clinical work with her mentor, Dr. Saar Gill, Penn Assistant Professor of Medicine and Director of the school’s Gill Laboratory in the cellular immunotherapies center. She’d arrive at 6:15 a.m. and get home around 6:30 or 7 p.m. On weekends she was at the lab and back before anyone at home was even awake.

During her fellowship years she also attended weekly clinical meetings for discussions of unusual lymphoma and leukemia cases; gave regular presentations on her work, attended conferences, trained new laboratory post-docs and more.

How did she manage work/life balance?

“I managed day by day. It’s kind of crazy moving the entire family to the United States. And my husband Ariel, an engineer, has a company in Israel and had to go back almost every month to manage things. Our sons, Noam, 11; Noy, 9 and Lyshai 6, (daughter Maor was born in June) didn’t know English and that was a big adjustment.

“I tried to do my best in both areas and never felt I was doing enough. But I think I did OK.”

The Hertzelia resident says she knew from a young age that she wanted to become a doctor.

“Whenever I remember myself as a very young girl, I remember myself wanting to become a doctor.

“My father is a cardiologist and I remember seeing lots of his patients coming up to him in restaurants and other places, thanking him for saving their lives. I saw that and knew that was what I wanted to do.”

Beyar Katz was so intent on attending medical school that, when she didn’t get in the first time, she completed an entire undergraduate degree in medical laboratory science at Ben Gurion University of the Negev before applying again. This time she got into Technion. “I knew if I didn’t get in somewhere that time, I’d go abroad to study. I just wasn’t willing to give up.”

In her sixth year of medical school she was “rotating” in hematology, loved it and made her career choice. “Patients came in very very sick and the doctors seemed like angels! I knew that was what I wanted to do. I just didn’t know if it would be adult medicine or pediatrics.”

At first it was pediatrics. Her medical school thesis topic was, “T cell Lymphoblastic Lymphoma in Children and Adults – A Retrospective Study in Israel Between the Years 1999-2006.”

Eventually, however, she chose adult hematology. “Many adult hematologists told me that their work, compared to pediatrics, was more interesting and complex because of co-morbidities and side effects.

“Now I think the fields are kind of similar actually. But now as a mother, I don’t think I could handle pediatrics on a daily basis. Overall, I think I made the best decision.

“I also love the long-term relationships you make in hematology, following patients for years. They become like family.”

After medical school Beyar Katz did an internship at Rambam Healthcare Campus, followed by a combined fellowship in internal medicine and hematology at Rambam and Bnai Zion Medical Center (Haifa).
During her fellowship Beyar Katz completed and published several studies and presented work abroad, one year winning an entire 50 percent of her time protected for research. (Fellows wrote grants and “won” protected research time based on success of grant applications.) “One year I got no time and had to squeeze my work in after 24-hour shifts instead of going home, and at night and whenever. Overall, I’d say, over the years, it worked out to 70 percent time on clinical and 30 percent time on research.”

But that was not enough.

“During my fellowship in hematology I was overwhelmed by many young patients with leukemia/lymphoma who were treated with aggressive chemotherapy with no response. It was very frustrating to stand by with no treatment options.”

So Beyar Katz also completed a PhD focusing on how one type of immune cell increases after chemotherapy administration. She studied a certain variety of targeted chemotherapy treatment for a rare blood cancer found in bone marrow.

The Haifa native was getting recognized. Minds were at work planning her future.

“It was not my idea to study CAR-T cell therapy. Dr. Irit Avivi, head of hematology at Tel Aviv Sourasky Medical Center, who knew me from my hematology fellowship and as a student, contacted me and said she wanted to open a CAR-T unit at Sourasky. She asked me if I would like to be the one to study abroad and bring it back to Israel.

“I knew a little about CAR-T, that it was not yet FDA-approved, that many people didn’t believe it would benefit patients and that very few patients were being treated. At the time I didn’t know if it was wise to go.

“Now I know it was one of my best decisions.”

She did some reading on the subject and toured U.S. medical centers for fellowship possibilities, settling on Penn. “I was overwhelmed by the CAR-T cell work being done there. I’m certain it’s the best in the world. And I met Dr. Gill, who was just great.

“I didn’t know how the treatment worked; it all seemed very complex. And I realized I would have to get a lot of background on genetic engineering. It sounded like science fiction.”

That was then and this is now.

Now she is back in Israel, soon to become the first head of immunotherapy at Sourasky. And together with head of hematology Avivi, she will establish the hospital’s first devoted immunotherapy unit.

ANY MENTORS YOU’D LIKE TO NOTE?

“Dr. Gill was wonderful, an amazing physician/scientist. I couldn’t have hoped for a better teacher and role model.

“Dr. Avivi directed me to the CAR-T field and supported me professionally as well as personally.

“Dr. Jacob Rowe is now head of hematology at Shaare Zedek Medical Center in Jerusalem. He supported me through my residency/fellowship and helped me get into the program at Penn.

“Professor Yuval Shaked, at Technion, is a bright scientist and an amazing person who triggered my passion for science. He taught me how to conduct research and ask scientific questions.”

HOW DID YOU MAKE USE OF THE APF MONEY?

“My husband and I flew with our sons to Israel to celebrate some very special occasions with family. It’s very hard to find money for tickets for five.

“We also used the money to help pay the rent. The expenses are a lot more overwhelming than you’d expect; it’s so hard to prepare. Just the medical insurance for a family of five is crazy, and you can’t not have it. It’s very different than in Israel.

“I want to thank the APF very much for the generosity in supporting me during this fellowship and the Schmidt family who chose me to sponsor.”
HOW WILL YOUR FELLOWSHIP EXPERIENCE BENEFIT HEALTHCARE IN ISRAEL?

“The fellowship made me a better doctor. The knowledge gained working at this extraordinary place made me understand the CAR-T treatment better. I’ve returned to Israel knowing how to improve it going forward.

“A lot more work is required in this field. We must improve response duration so that patients won’t relapse. We must also continue to create more CARs that would be effective for other hematological diseases (such as acute myeloid leukemia) and reduce side effects.

“The new immunotherapy unit will help cancer patients receive a variety of novel CAR-T cell therapies that would be developed initially in our lab, but soon will be administered to patients in clinical trials. We will be collaborating with Penn (part of a long-term relationship) in the development of these CAR treatments. Our hope is that they will advance the field and improve clinical results for cancer patients. We are aiming to treat hematological cancers as well as solid cancers, such as breast cancer.

“While the field is already developing in Israel, it’s not in all the hospitals. And now it’s mainly outside companies who handle the cells. We are going to have an entire manufacturing facility at Sourasky that soon will be producing CAR-T cells. Ours will be only the second such facility in Israel.

“All this comes from my fellowship.”