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Photo by Eric Déroze

Tapping TILs

Among the biggest challenges of truly personalized immunotherapies for cancer lies in developing standardized processes to reliably and swiftly identify the best immune cells to grow or genetically manipulate for subsequent therapy. At Ludwig Lausanne that responsibility is shared by the Human Integrated Tumor Immunotherapy Discovery & Development Engine (Hi-TIDE) and the Immune Monitoring Core of the Center for Experimental Therapeutics (CTE).

If there was ever any doubt that Ludwig Lausanne is up to the challenge, a study published in 2018 in *Nature Communications* has probably put it to rest. In the paper, a team led by Ludwig Lausanne's Alexandre Harari and Director George Coukos reported their development of a process to isolate cancer cell-killing T cells from tumors and optimize them for use in personalized, cell-

based immunotherapies. In the months since, their method has been scaled up and standardized for application in clinical studies of personalized immunotherapy that will be carried out at the CTE with support from the Hi-TIDE.

"Our development of this method illustrates the advantages of coordinating basic and clinical research from the outset to solve difficult problems in medicine," says Coukos. "We are excited to put this new T cell therapy to the test in patients—and very hopeful that it will be to their benefit."

As cancer cells accumulate mutations across their genomes, they express aberrant proteins—or antigens—that reveal the malignancy to the immune system's cells. Some of these antigens are common to various cancers, but the majority are

randomly generated, so such antigens vary wildly from patient to patient, even within the same type of cancer. Killer T cells recognize mutated bits of these antigens that are known as neoepitopes, destroying the cells that bear them.

Many researchers have developed sophisticated methods to isolate, grow and infuse T cells into patients for therapy. But the cells used for such treatments are typically isolated from the bloodstream, and the proportion of T cells that recognize neoepitopes tends to decline significantly when circulating T cells are expanded in culture.

The method developed by Harari, Coukos and colleagues selectively expands the most reactive tumor-infiltrating lymphocytes (TILs) for individualized immunotherapy. Their analysis also demonstrated that even ovarian tumors—which tend not to be heavily mutated and have long resisted immunotherapies—harbor TILs that react vigorously to neoepitopes and can be harnessed for therapy. This suggests that other tumors with low mutational burdens may also be similarly infiltrated.

Comparing TILs with T cells from each patient's blood stream, the researchers showed in their study that TILs grown using their method are much better at recognizing neoepitopes than are circulating T cells. "We could even compare T cells from the two compartments that target the exact same mutation and show that the TILs were more functional than the T cells we collected from the peripheral bloodstream," says Harari, who is a team leader at Hi-TIDE and director of the CTE's Immune Monitoring Core.

Such selectively grown and optimized TILs have become a key asset in Ludwig Lausanne's plans to develop and standardize the production of tailor-made cell therapies for cancer, efforts in which the Hi-TIDE and the CTE are playing a central role.

Tumor samples from patients at the Swiss Cancer Center-Léman, which houses the CTE, will be handled primarily by two groups at the Hi-TIDE. The first is led by Michal Bassani-Sternberg, who has combined cutting edge genomics-related technologies to predict the neoepitopes generated by cancer genomes that are likely to be recognized by killer T cells. The selected neoantigens are then moved on to Harari's team, which has developed assays to validate the predictions and prioritize the neoantigens that provoke the most potent T cell responses.

Harari and his colleagues at the Hi-TIDE and the Immune Monitoring Core then isolate those T cells from patients and grow them in a manner that gets the most out of them using methods described in the *Nature Communications* paper. These optimized T cells can then either be used for experimental therapies at the CTE or be sent to Melita Irving, whose Hi-TIDE team can engineer them to further boost their anti-tumor activity. "What George has established in the Hi-TIDE is a network of subgroups with distinct but extremely complementary expertise," says Harari.

While much of the scientific tinkering goes on at the Hi-TIDE, the clinical manufacturing, regulatory coordination and the trials themselves are done by the CTE. But the work flows freely between the two units. "It's dynamic," says Harari. "We have people going from one side to the other every day."

The CTE now has two facilities qualified by Swiss authorities to make cellular products for immunotherapy. One is already operational, and the other—which will expand the number of patients who can be treated with individualized cell therapies tenfold—is currently validating its instruments and will open its doors in 2019. Their capabilities will soon be put to the test in a planned trial of T cell therapy for multiple tumor types that is based on Harari and Coukos' new method for isolating and growing therapeutic TILs.