Medical Xpress

Researcher creates 'Instagram' of immune system, blending science, technology

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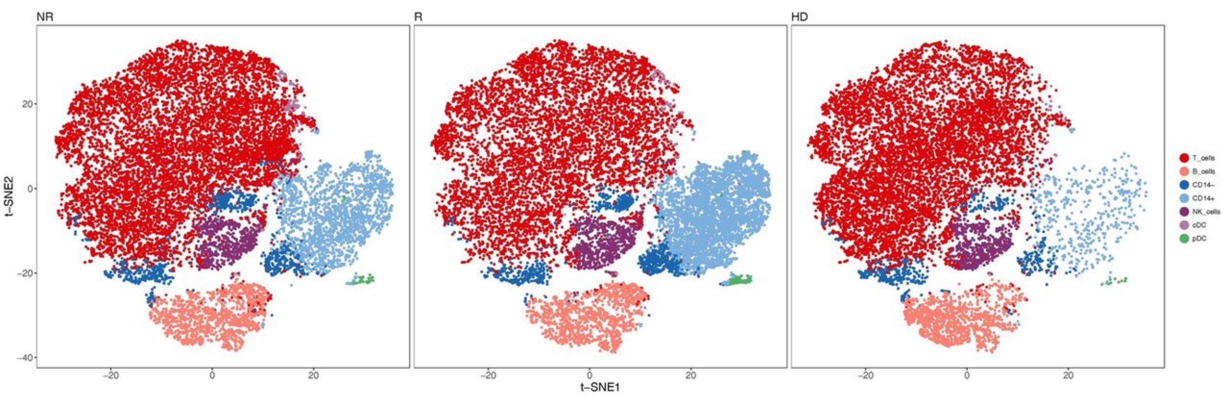

Using artificial intelligence and bioinformatics, researchers can create a two-dimensional mapping that can read test results, creating an 'Instagram' of millions of blood cells. Credit: Dr. Carsten Krieg, Medical University of South Carolina

Being on the cutting edge of science and technology excites Hollings Cancer Center (HCC) researcher Carsten Krieg, Ph.D. Each day, he walks into his lab that houses a mass cytometry machine aptly labeled Helios. Krieg explains how it can heat plasma up to 6,000 degrees Celsius, levels comparable to temperatures found on the sun.

This allows the German native, who recently joined the faculty of the Medical University of South Carolina's departments of immunology and dermatology, to accomplish an interesting feat. He creates a sort of

'Instagram' of a person's immune system. For cancer patients on experimental immunotherapy treatments, the practical application is obvious and exciting, he said.

"What I use here is a very new and nerdy technology, which is called mass cytometry, that allows you with a very high sensitivity to make pictures of your immune system. And this is possible because there's artificial intelligence, machine learning combined with algorithms that can make a very complex system easy to visualize." ??Basically, how it works is that researchers stain cells using rare metal-conjugated antibodies that target surface and intracellular proteins. "Normally in biological tissues, there are no rare metals, so this technique offers greater sensitivity in detecting targets."

Inside the Helios, the cells are ionized using an inductively-coupled plasma. The ions derived from each stained cell are maintained in discrete clouds that can be detected in a mass spectrometer. The technique can potentially detect up to 100 markers per cell, although, due to practical restrictions, about 40 are more realistic, he said. Then researchers use artificial intelligence and bioinformatics to create a two-dimensional mapping that can read the results, creating an Instagram of millions of blood cells.

"It's an easy way to look at a complex response such as one you would find during immunotherapy."

This is critical as Krieg and other cancer researchers hope to advance the field of immunotherapy. Though immunotherapy has shown great promise, the vast majority of patients either don't respond, have adverse side effects or relapse. Krieg, who comes to HCC from the University Research Priority Program (URPP) in Zurich, Switzerland, wanted to know if the technology could be used to predict which patients might respond to certain treatments.

While in Zurich, he and his colleagues decided to use the technique to study melanoma. Research featured on the cover and in the February issue of *Nature Medicine*, titled "High-dimensional single-cell analysis predicts response to anti-PD-1 immunotherapy" identified biomarkers in the blood that can predict whether metastatic melanoma cancer patients will respond positively to immunotherapy. The goal was to see if a blood test for these biomarkers could identity those who are likelier to benefit, while allowing "non-responders" to begin other treatments without losing time, he said. "It's a decision instrument for physicians and for the health care system."

It's also a powerful research tool as it gets to the mechanisms behind what makes immunotherapy work. The recent study found an immune cell type known as classical monocytes in the peripheral blood may be a potential biomarker for patients who will respond to anti-PD-1 immune checkpoint therapy in metastatic melanoma. "Surprisingly, what we clearly found is that it's the frequency of monocytes that is enhanced in responders over non-responders before immunotherapy."

Krieg said he was eager to join HCC to work with immunotherapy researchers here and to take advantage of the synergy he feels across departments. He wants to continue his work in melanoma as well as look at using this technique for other cancers, including head and neck, gastrointestinal and lung cancer.

Dr. Krieg uses a mass cytometry machine aptly labeled Helios to heat plasma up to 6,000 degrees Celsius, levels comparable to temperatures found on the sun. Credit: Emma Vought, Medical University of South Carolina

Zihai Li, M.D., Ph.D., chair of the Department of Microbiology and Immunology and co-leader of the Cancer Immunology Program at HCC, said MUSC is fortunate to have recruited Krieg.

"He brings not only his wealth of knowledge in immunology but also his expertise in mass cytometry technology and its applications. This technique offers a powerful platform for high dimensional analysis of patients' blood on the single cell level."

Krieg's recent study in *Nature Medicine* demonstrates that the technique can be used in the clinics to profile patients' immune systems to better guide decisions about immunotherapy treatment. "Importantly, MUSC has already invested in this technology by obtaining a second-generation instrument," Li said. "Dr. Krieg's arrival will catalyze the rapid development and application of this technology to benefit the patients in the state of South Carolina."

Beyond looking for predictive biomarkers, Krieg said scientists can use this technique to closely examine how cells interact in the microenvironment of the tissue and the tumor. "We now have Instagram pictures, a picture before therapy and a picture during therapy. But you can make many more of these pictures, so you're looking after three months, after half a year, a year," he said. "This allows more of a Facebook approach, so every time you get a picture of the immune system, you're getting context."

Krieg sees the technology as ushering in a new era in cancer research. Looking back only a couple of decades, chemotherapy was the main course of treatment, he said. Then science advanced to sequence genomes and find mutations in the DNA for which specific inhibitors were developed.

"After DNA and the transcriptome, the exciting thing about this technology is the next step in evolution: we're now looking at the proteome."

The proteome is the complete set of proteins being expressed by a genome or cell at a certain time under certain conditions. "I am so excited about the work because it's the next step in science. This actually is what makes the interactions happen, where the immune cell interacts with an immune cell or a tumor cell. We're studying this whole networking of cells in your body and how they react toward your environment and in immunotherapy.

Doing real-time monitoring in patients based on their specific genetic make-up and the immunotherapy treatment they are receiving opens all kinds of research possibilities. This allows physicians to apply precision medicine to help patients and researchers to use systems biology to discover the mechanisms of disease, he said.

"I hope to make a difference in the clinic so that patients are on the right therapy from the start. Then on the research side, we want to understand how this works. Which elements do you need, when? Which element of the immune system needs to be kicked in?"

More information: Carsten Krieg et al, High-dimensional single-cell analysis predicts response to anti-PD-1 immunotherapy, *Nature Medicine* (2018). DOI: 10.1038/nm.4466