

Making the Most Out of Immunotherapy

Perhaps the decade's greatest achievement in melanoma treatment has been the FDA's approval of checkpoint inhibitors.

June 19, 2018 By [Melanoma Research Alliance](#)

Perhaps the decade's greatest achievement in melanoma treatment has been the FDA approval of cancer immunotherapy treatments called checkpoint inhibitors. This class of drugs include ipilimumab, nivolumab and pembrolizumab. These therapies harness the power of the immune system to fend off disease — including melanoma. Many patients treated with these drugs experience durable responses, and in a fraction of patients experts suspect the drugs are curative.

Predicting Response and Recurrence

While immunotherapy has been an incredible advance, there is still room for improvement. For example, only about half of patients with advanced melanoma respond to these treatments, and in some cases, patients may not see their tumors start to shrink until several months after starting therapy. This is problematic because some patients with advanced disease have widespread and bulky tumors. In addition, immunotherapy can sometimes trigger serious, and at times irreversible, autoimmune conditions such as thyroid dysfunction or diabetes. Researchers do not yet understand why some people develop these side effects and others do not. This is especially important as physicians increasingly turn to adjuvant immunotherapy for early-stage melanoma patients, where a substantial fraction of patients may never experience a recurrence after their primary melanoma is removed.

"We've made tremendous progress in the treatment of cancer with immunotherapy, but responses aren't universal and not always durable, so we need [better predictive] markers of response," stressed Jennifer Wargo, MD, of MD Anderson Cancer Center.

To help understand which patients with advanced melanoma will benefit from immunotherapy, researchers are trying to identify molecular features — called biomarkers — in tumors or in the patient's immune cells that can predict an effective response to treatment. For patients with early-stage melanoma, researchers are searching for biomarkers that indicate high recurrence risk. Several MRA-funded researchers reported on their groundbreaking efforts to find these biomarkers at the latest MRA scientific retreat.

To try to identify biomarkers that can predict risk of recurrence in Stage 2 or 3 surgically

removable melanoma, Yvonne Saenger, MD, of Columbia University in New York City examined patients' tumor samples. She discovered that a particular pattern of gene expression, as well as the presence of one type of immune cell, called a 'killer' T cell, and the absence of another, called a macrophage, were correlated with a greater likelihood of long-term survival. "We hope this will help patients decide whether they should get [adjuvant] immunotherapy after surgery," Saenger said.

Melanoma at Single Cell Resolution

Ido Amit, PhD, of the Weizmann Institute of Science in Israel presented his work using powerful new single cell sequencing and imaging technologies he developed to determine in detail the different immune cell subtypes within and surrounding tumors. "When we wanted to identify biomarkers of responders versus non-responders to treatment, we saw a complex zoo of many different types of immune cells and functions in tumor samples that current markers couldn't describe," he said when explaining why he developed these techniques. "The tumor microenvironment is extremely complex, yet understanding these cells and how they change in patients is critical to identify new markers for rapid and effective tumor characterization, and identification of novel immune modulatory pathways."

One of Amit's technologies, called 'single cell RNA sequencing,' essentially provides a snapshot of all the genes expressed by an individual cell plucked from a tumor. The advantage of this technology is that it gives researchers a much more complete picture of the complex network of cells that make up a tumor and its surrounding tissue. So far, Amit has used his technique on tumor samples from 26 patients with melanoma and has uncovered "very dramatic differences between patients in the types of T cells seen in their tumors," he said. His research identified special populations of immune cells, some of which kill tumors and others that block the anti-tumor immune response. "Our single-cell technologies provide unprecedented opportunities to draw a more accurate picture of the various cell types and underlying tumor-immune interactions and response to therapies."

Can the Microbiome Predict the Effectiveness of Immunotherapy?

Other promising treatment response biomarkers are not found on patients' tumor or immune cells, but rather in the more than 100 trillion microbes that inhabit their bodies, especially those that reside in the gut. This ecosystem of microbes, collectively known as the human microbiome, has become a major focus of cancer research, as mounting evidence reveals it may alter our risk of developing various cancers and how a patient may respond to immunotherapies like pembrolizumab, nivolumab, and ipilimumab.

Thomas Gajewski, MD, PhD, of the University of Chicago found that certain bacteria living in the gut of melanoma patients were linked to patients' ability to respond to immunotherapy targeting the PD-1 molecule. Could gut bacteria be a biomarker for response to immunotherapy in melanoma patients? "It's certainly on par with other biomarkers enriching for responders," Gajewski said, but added that, "The microbiome isn't everything. Tumor mutation factors matter, and germline polymorphisms are also likely important. But it could be a better biomarker than

mutational load and should be explored further and integrated with others.”

In mouse models, Gajewski found transferring the immune response- promoting bacteria to mice with melanoma via stool transplants improved their response to immunotherapy. This suggests that the microbiome may not only serve as a response biomarker, but that one day probiotics designed to contain ‘good’ bacteria may improve the treatment of patients who lack in inflamed tumors.

In an independent set of related studies, Wargo found that the microbiome of patients with melanoma who responded to PD-1-targeting immunotherapy differed from those who did not. Like Gajewski, she also found that an abundance of certain bacteria in the gut correlated with a “hot” immune response to tumors, while a high abundance of other species linked to a “cold” response. Abundant *Bifidobacterium* species did not surface as a major indicator of response in Wargo’s studies, as it did in Gajewski’s research. But the microbial signature Wargo found that indicated an effective response to immunotherapy has also been reported by researchers studying patients with lung and kidney cancer treated with checkpoint inhibitors, Wargo noted. She and others are currently testing a number of strategies to see if they can improve responses to immunotherapies in melanoma and other cancer patients.

“Can we modulate the gut microbiome to enhance responses to immunotherapy? Yes! But that needs to be tested within a clinical trial,” Wargo stressed.

[This post](#) was originally published on June 11, 2018, by the Melanoma Research Alliance. It is republished with permission.