Expert Interview: Cancer resistance to immunotherapy

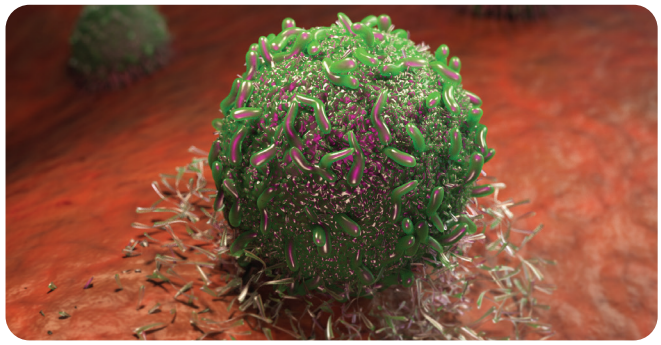
Introduction

Every patient has the ability to respond to immune therapy but too often tumors fail to regress due to either primary or acquired resistance. Here, we discuss the mechanisms behind immune evasion and how understanding the barriers to effective treatment in each individual patient can create a roadmap to a more effective and personalized treatment strategy with the goal of prolonged survival.

We were fortunate to speak with Dr. Siwen Hu-Lieskovan, PhD, MD, in a discussion on cancer resistance to immunotherapy. She is the Director of Solid Tumor Immunotherapy at the Huntsman Cancer Institute, University of Utah with research focused on immunotherapy resistance and its underlying mechanisms. In participation with the National Cancer Institute and SWOG, Dr. Hu-Lieskovan oversees the sub-study portfolio for iMATCH, a precision medicine trial for biomarker stratification.

Revvity: **I'd like to begin by asking how immunotherapies have transformed the cancer treatment landscape?**

Dr. Hu-Lieskovan There are many different kinds of cancer therapies originating with chemotherapy, radiation, surgery, later targeted therapy, and most recently, immunotherapy. Traditional cancer treatments focus on the tumor. If traditional cancer therapies kill 99.9% of cancer cells, but even one remains, the disease will resurface at a later time. The difference of immunotherapy is that the treatment doesn't focus on the cancer, the treatment focuses on each individual patient's immune system as a way to use mechanisms prevalent in tumor as a means of rallying the immune system against the tumor with the hope of eradication. Checkpoint inhibitors were a breakthrough in immunotherapy by activating immunogenicity mechanisms to elicit their cytotoxic effects. Immunotherapies are FDA approved in more than 10 indications as a result of prolonged overall survival of patients when compared to other treatment options. Immunotherapy can work, however, overcoming mechanisms of immunosuppression characteristic of tumor cells requires a highly specified approach based on the individual functioning of each patient's immune system.



Meet the physician and scientist

Dr. Siwen Hu-Lieskovan, PhD., MD
Director of Solid Tumor Immunotherapy at the Huntsman Cancer Institute, University of Utah

Dr. Hu-Lieskovan is a board-certified oncologist, chair at the SWOG Immunotherapeutics Committee, translational lead of cross NCTN-protocols, as well as a consultant within the pharmaceutical industries. She received a hematology/oncology fellowship and faculty training at the junior level from UCLA with Dr. Antoni Ribas.

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Revvity: What factors would you say contribute to immunotherapy resistance?

Dr. Hu-Lieskovan, PhD. MD: Each tumor type exhibits unique features, and unfortunately, immune resistance mechanisms are universal across all types of cancer. Immunotherapy resistance may be observed primarily or following treatment as tumor cells mutate and evolve in their ability to evade the immune system. There are many steps involved, with tumor immunogenicity as step one. The immune system can recognize the tumor, and after that, primes the immune system to attack. Success depends on how strong the immune system is, and how immune cells overcome the tumor microenvironment.

Revvity: And how often does resistance therapy result in hyperprogression in tumor growth?

Dr. Hu-Lieskovan, PhD. MD: That is an interesting question. There have been reports of hyperprogression, but even defining the term is difficult. If the patient does not respond to therapy, they have progressed. How fast is hyperprogression compared to progression? There isn't a definitive number or percentage, so whether a patient progresses more rapidly or not, without a defining set of criteria, the concept itself is kind of a myth.

Revvity: Regarding your research, how has it contributed to the understanding of resistance mechanisms?

Dr. Hu-Lieskovan, PhD. MD: I was at UCLA for a long time focused on translational research. We focused on what was going on with each individual patient. Again, we're treating the immune system, not the tumor. That's why we collect a patient's tumor and blood samples, to study those samples before and after treatment, for toxicity, to investigate if there are any changes. Primary resistance is difficult to study, from a genomics standpoint because of the heterogeneity. Acquired resistance is easier to study on a single patient basis, if the patient initially responds to immunotherapy but later exhibit resistance, you can study the progressing tumor compared to the baseline and to assess the difference.

Revvity: What did you learn from studying acquired resistance?

Dr. Hu-Lieskovan, PhD. MD: While I was working with our group under Dr. Antoni Ribas MD, we studied primary and acquired resistance. Our research involved loss of function mutations in beta 2-microglobulin (B2M) and Janus kinase (JAK) of which have been predictive of potential resistance to anti-PD-1 therapy in melanoma patients. Homozygous loss of function mutations in JAK 1 and JAK 2 were observed to be associated with the interferon (IFN)-receptor pathway. IFN exhibits pro-apoptotic and anti-proliferative functions and is therefore an important immunogenicity activator. Understanding the impact loss-of-function mutations have on suppressing anti-tumor immunity allows for the improvement of better immunotherapy treatment approaches.

Revvity: Are there diagnostic tests that can predict immunotherapy resistance?

Dr. Hu-Lieskovan, PhD. MD: There are currently no diagnostics that are approved by the FDA. There are biomarkers approved to predict potential response. For instance, microsatellite instability can be predictive of potential immunotherapy resistance. PD-L1 is a somewhat controversial predictive biomarker, and is approved in a few histologies, while not in others. Tumor mutational burden is a marker measured by counting the number of mutations present in a tumor cell, and a recent breakthrough was that in patients with a tumor mutational burden of more than 10 the patient is treated with anti-PD-1. The approval is therefore biomarker driven, which is new.

As clinicians, we utilize genetic testing and a lot of these tests tell us what the tumor mutational burden is, what the PD-L1 expression is, is there inflammation present, and information on what mutations may be present. These data are applied to try and predict whether a patient may or may not respond to immunotherapy. It allows us to try and figure out what could be the potential resistance mechanisms ahead of time, but so far everything is speculation.

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Revvity: On the topic of inflammation — how does it act as an independent biomarker?

Dr. Hu-Lieskovan, PhD. MD: PD-1 is an inflammatory marker because it is predictive of adaptive immune response. CD 8 T cells are also informative as a predictor of adaptive immune response, in some cancers like melanoma it is more informative than PD-1. Their presence alone makes it difficult to discern if they are acting simply as bystanders, or if they are actually doing something. There are more and more efforts to examine gene expression profiles of the tumor to determine what mutations are present that could cause immunotherapy resistance.

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Revvity: How can researchers and clinicians combat resistance to create better outcomes for patients?

Dr. Hu-Lieskovan, PhD. MD: That is the goal. Antitumor immune response is a process with many steps involved. In what way can the immune system be primed to promote anti-tumor activity? How strong can the immune system be? How well can therapies overcome the tumor microenvironment and intrinsic tumor mechanisms? These questions contribute to the complexity in overcoming immunotherapy resistance. Using biomarker investigation, researchers and clinicians can determine what specific mechanisms may be contributing to immunotherapy resistance within the tumor microenvironment. Better outcomes are observed when relevant biomarker data is used to apply a combined therapeutic approach targeting the various mechanism that contribute to unregulated tumor progression.

Revvity: And finally, how can combination therapy approaches be tested in a clinical setting?

Dr. Hu-Lieskovan, PhD. MD: I am performing research with the National Cancer Institute focused on using different combination approaches to address different resistance mechanisms in a clinical study scheme. A difficult part of testing combination therapy is the diversity of the micro-tumor environment across individual patients in the clinical trial setting, we do not know how to select patients for combination therapy because the standard approach does not work for treating the immune system. In a standard approach, certain combinations may show promise in the Phase I space, but in larger Phase III studies of which are randomized and blinded into treatment and placebo groups, most biomarkers fail to meet the benchmark. Without biomarker selection, the success of combination therapeutic strategy is low. It is not to say the therapies are not working, but we are not finding the patients for the combination trials.

The goal of iMATCH is to use biomarkers, right now we are using TMB, and the inflammation score, and to use this combination to categorize the patients. We organize patients into high/high, high/ low, high/low, low/low groups to determine one, which subgroup is most suitable for combination therapy development, and two, whether the combination has efficacy signal in each subgroup. The field is realizing that it is important to test combination therapy in this more individualized manner.

> "The response signal to combination immunotherapies might be different in these biological subgroups and it can help to find the patient population that is most suitable for a certain combination therapy development."

ImmunoMATCH or iMATCH is a precision trial being managed at SWOG with the National Cancer institute. Categories based on resistance mechanisms are organized into different groups through biomarker analysis of each participant's tumor biology and intrinsic immune functioning. Using immune profile testing, researchers will group via resistance mechanisms for precision.

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