Going global to meet local needs in China [1]

Discovery [2]
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Six years ago, Novartis researchers in Shanghai, China started investigating a form of head and neck cancer called nasopharyngeal carcinoma (NPC). The disease is uncommon in North America and Europe, but in Southeast Asia it is alarmingly frequent.

While studying tumor samples from patients and using their expertise in genomics to understand the drivers of tumor growth, the Shanghai team learned that the tumors were infiltrated with immune cells. They wanted to learn more, but immunology fell outside their skill set. So they enlisted the help of Marc Pelletier, an investigator in the ImmunoOncology department based at the Novartis Institutes for BioMedical Research (NIBR) in Cambridge, MA, who joined the Shanghai team for a 3-month mini-sabbatical, one of the many programs dedicated to associate development [3].

During that short visit, Pelletier set up experiments designed to explore how NPC responds to Novartis' collection of immune-regulating drugs. His early results were so promising that the team now has a 3-year plan to continue the research. They are also applying the system Pelletier developed as a research model for other cancers with an immune component, such as liver cancers, which are also common in China.

"We could not have imagined doing these immunology studies because we had no expertise in this specialized field," says Yao Yao, a senior oncology investigator at NIBR in Shanghai. "Marc opened the door for us. He is guiding us through and we see the path ahead."

A Puzzling Disease

In some areas of China, particularly in southeastern regions near Hong Kong, rates of NPC are about 20 times higher than the rest of the world, according to a study [4] from the National Cancer Center in Beijing, China. Yao's collaborators at the Cancer Center at Sun Yat-sen University [5], in Guangzhou, see nearly 4000 new cases per year. "That exceeds lung cancer in that hospital. Can you imagine? It's a real unmet medical need," she says.

Nearly all people with the disease in China also have had Epstein-Barr virus (EBV). A combination of exposure to that virus alongside other factors, such as diet, smoking, and genetics, might increase the risk of the disease. If caught early, a combination of radiation and chemotherapy provides lasting responses for most patients.

But NPC grows silently, so many people aren't diagnosed until the disease has advanced and spread. Symptoms, if any occur at all, may include a persistent stuffy nose, a lump in the neck, ear pain, or hearing loss. For patients with an advanced case, says Yao, the disease is

incurable.

About six years ago, when Yao's team began studying the disease, they formed an NPC Working Group with Novartis Bioinformatics to understand how NPC might respond to targeted therapies. Targeted therapies attack vulnerabilities in tumor cells, so most of their work focused on understanding genetic alterations that drive tumor cell growth.

But they also noticed high numbers of immune cells inside the tumor samples they studied. The finding was puzzling, since immune cells have the power to destroy both virus infected cells and tumor cells. "They had these virus-positive tumors surrounded by immune cells, yet the immune cells aren't killing the tumor," says Pelletier. "They're all suppressed."

Meeting a Need

Such immune suppression is a known tumor defense mechanism. The tumor wraps itself in a sort of a biological invisibility cloak. New forms of immunotherapy, however, strip away the cloak.

In these studies, the Novartis team tested the impact of four drug candidate molecules, each poking holes in the tumor's invisibility cloak in different ways. In response to the group's findings, Novartis initiated a clinical trial to test one Novartis immunotherapy in advanced cases of NPC.

In addition, in 2016 she invited Pelletier to come to Shanghai for a mini-sabbatical. His job was to set up experiments that would reveal more about how immunotherapy drugs affect immune response in tumor samples from patients.

Pelletier's sabbatical was slated to begin in September 2016, but he started preparing for it months earlier so that he'd be ready to go on arrival. The tumor samples, as small as the head of a pin, must be handled immediately to be sure the cells don't die or change too much before testing. He didn't want any of them to go to waste.

His experiments involved isolating the immune cells on a plate and adding fragments of Epstein-Barr virus protein. Normal immune cells would react to the virus products, but these suppressed immune cells don't. Pelletier then added immunotherapy drugs to some cells and a placebo to others and observed the effects on immune cell behavior. He was able to perform a handful of experiments, refine the process, and train Yao's team to continue the research.

He was also able to see positive early results. Immune cells treated with the Novartis immunotherapy drugs started to produce cytokines, a key step in mounting an immune response to an invader. "The drugs are lifting the cloak," says Pelletier.

Yao and her team are continuing the experiments to determine if these early results hold up. She also is about to set up a similar system to experiment with liver cancer. Liver cancer is also more common in China than in other countries and is often driven by hepatitis-B virus infections and represents a major unmet medical need.

“Our research is focused on the regional needs in China, but to meet those needs, we need to draw on expertise across Novartis,” says Yao. “We got great results from this global collaboration.”

Tags:
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