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Going global to meet local needs in China

Marc Pelletier traveled from Cambridge, MA to Shanghai, China, to launch new lines of research for the treatment of cancers that are common in China.

By Elizabeth Dougherty | May 25, 2017

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.

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 <u>study</u> from the National Cancer Center in Beijing, China. Yao's collaborators at the <u>Cancer Center at Sun Yat-sen University</u>, 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. 1/3

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."

A NIBR researcher's sabbatical in Shanghai opens new doors in oncology research.

I traveled to Shanghai, China, to study a disease that is common there and rare almost everywhere else.

A river divides Shanghai, China, in two. To the west is the old city. It is a thousand years old. But the east is modern and similar to cities in the US. That's where my family and I lived, and it's also where the new Novartis Institutes for BioMedical Research (NIBR) campus is.

People told us that just 30 years ago, the east side was nothing but swamps and farms. Now it is home to the second tallest building in the world and a maglev train going right through the city. We lived on the 8th floor of a 14-story building, a pretty typical living situation, and from there we could walk or take the subway everywhere, including to the NIBR campus where I worked doing research on a form of head and neck cancer

called nasopharyngeal carcinoma (NPC).

We had come to China so that I could join my Shanghai colleagues for a 3-month mini-sabbatical to better understand this mysterious disease.

Yao Yao, a NIBR oncology investigator, and her team in Shanghai had been studying NPC for years. They'd focused on finding the molecular drivers of tumor cell growth. But they'd also noticed large numbers of immune cells in the tumor samples they'd examined. Yao had reached out to my group in Cambridge, MA, hoping to find someone willing to help them set up a research program to understand more about the immunological aspects of the disease.

I had taken on the challenge and prepared for the visit by planning a series of experiments to determine if any of the four Novartis immunotherapies might unleash these immune cells and trigger them to attack the cancer. When I arrived with my family in Shanghai in September 2016, Yao and I were able to hit the ground running.

While I worked, my family explored. We sent my sons, who were 10 and 11 years old at the time, to the local school two mornings a week. The classes were in Mandarin, but the school was incredibly welcoming. They even assigned each of my boys a desk-mate to help with translations. But it was the students who were most excited about their new Western friends. When my kids got to school, the place would erupt as if Justin Bieber had just walked in.

In fact, my sons were treated as VIPs everywhere. Western kids are a rarity there, and special. No matter where we went, people wanted to take selfies with the boys. My wife, Sharon Berke, and my boys were taking Mandarin lessons while they were there, but early on they learned one word from Yao, who was our family's friend, translator, and travel guide. That word was piàoliang () – beautiful – and my boys heard it over and over again everywhere they went.

Meanwhile, in the lab our experiments showed promising early results. Based on those findings, Yao's team decided to develop a 3-year plan to continue the research. In fact, they are also applying the methods we developed to do similar tests for liver cancer, a deadly disease that occurs much more frequently in China than in other countries.

During our travels, we ate great food and were able to take several mini-vacations in China and Japan. Sharon and I could have stayed longer, and we did consider an assignment that would have lasted a few years. If my sons were not at such a formative age — after a few months, they were ready to get back home to friends and soccer games — we might have stayed much longer.

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