Another Transformational Breakthrough?

Lieping Chen, MD, PhD

He may have done it again. Lieping Chen, MD, PhD, United Technologies Corporation Professor in Cancer Research, Professor of Immunobiology, Dermatology, and of Medical Oncology, and Co-Director of the Cancer Immunology Program, believes he has found another transformational key to treating cancer.

The first originated twenty years ago when Dr. Chen discovered that cancer cells emit signals that trick the immune system into shutting down. He identified one culprit: a protein named PD-L1 that bound to PD-1 in a tumor's microenvironment, disabling the immune system. When he blocked this pathway with an antibody, the T-cells in the tumor reignited and started killing cancer cells.

Using drugs to incite the body's own immune system against cancer is called immunotherapy, and Dr. Chen is one of its foremost pioneers. Since his original discovery, the FDA has approved six drugs that target the PD-1/PD-L1 pathway to fight more than a dozen different cancers, with more approvals expected soon.

But not every tumor expresses PD-L1, so the drugs that block it are effective in only about 30 percent of cancer patients. That other 70 percent is now Dr. Chen's focus. He knew that in tumors without PD-L1, other molecules must be disrupting the immune system; and so the search began. He and his colleagues used a sophisticated screening assay called a T-cell activity array, which Dr. Chen developed about 10 years ago.

"We ran almost 7,000 molecules through this big assay looking for potential suspects," Dr. Chen said. "Then we started to map which bad molecules shut down T-cell activities, and then we looked for which molecule was responsible for which type of tumor."

One promising candidate was a protein called Siglec-15 (S15). Like PD-1/PD-L1, S15 does its mischief in the tumor microenvironment, but with different tactics. When cancer cells express PD-L1, provoking T-cells to attack, PD-1/PD-L1 counterattacks. "When we found this mechanism," said Dr. Chen, "we were amazed that the tumor can do such things." S15 operates with less belligerence in a tumor's macrophage. When the cancer cells express high levels of S15, drawing an army of T-cells, the S15 molecules don't attack, but somehow soothe them into stillness.

"We're still trying to figure out biochemically what kind of signal this is. Different tumors develop different weapons, so we have to deal with them differently."

The next step was to develop an antibody that blocked S15 to see if that reanimated the immune system. With the PD-1/PD-L1 antibody, Dr. Chen had to wait more than 10 years for the first large clinical trial. His frustration with that long gap led him to explore ways to shorten the trip from lab to clinic. In 2016, he became the scientific founder of a biotech startup called NextCure, which raised $67 million to develop his future breakthroughs on an accelerated schedule.

In October 2018, NextCure's S15 antibody, currently called NC318, received the green light from the FDA and went into trials at several sites, including Smilow Cancer Hospital, less than five years after Dr. Chen's initial insight.

"It's a new model," he said. "We want a smooth transition from discovery to developing the drug to the clinic. I think this drug can save lives, so you want to bring it to the clinic as quickly as you can. This antibody is the first example to prove that we can make this new model work. That's very exciting, almost as exciting as the drug itself."

Dr. Chen is confident the new antibody will work. Like PD-1/PD-L1, S15 is expressed in many types of solid cancers. A preliminary study found it in lung, breast, ovarian, pancreatic, thyroid, and head and neck cancers. Theoretically, an S15 antibody should work against all of them.

"I will predict that it will target another 20 to 30 percent of cancer patients," said Dr. Chen. "So it could be very exciting, and that's why we're excited the phase one trial has started."

At Yale the trial is led by Patricia LoRusso, DO, Professor of Medicine and Associate Director of Experimental Therapeutics. Because the drug has never been used in humans, the trial will start small. "Once we hit the right dose," said Dr. LoRusso, "we'll expand into certain tumors to see whether or not there is a signal of activity. Within 18 or 24 months, we'll have a lot of information."

Roy S. Herbst, MD, PhD, Ensign Professor of Medicine, Professor of Pharmacology, Chief of Medical Oncology, and Associate Director for Translational Research, is so excited by Dr. Chen's research that he spent six months of his recent sabbatical in Dr. Chen's lab. Together, they built a clinical team to work on S15 at Yale.

"I am so proud of this project," Dr. Herbst said. "It will be helping patients here in New Haven where it began as part of our Lung SPORE research project and will surely expand to patients worldwide. Lieping is a proven winner who's already brought us a drug that's treating millions of people. We're very optimistic that this is another drug that will target the engine of tumors and successfully stop cancer."