

New recruit has big dreams for cancer immunotherapy ^[1]

Discovery ^[2]

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An oncologist by training, Glenn Dranoff fell into the field of immunology in the mid-1990s after his residency and clinical fellowship. He was working as a postdoc at the Whitehead Institute, where he was using new cloning technologies to study how blood forms, when a surprising observation changed the course of his career. The research team accidentally triggered an immune attack on tumor cells, killing the miscreants.



Glenn Dranoff, Global Head of Immuno-Oncology, Novartis Institutes for BioMedical Research

“We ended up stumbling across a strategy of cancer vaccination that seemed to work in mice,” Dranoff explains. “I thought that we might be able to apply this approach to cancer patients, and that’s what I set out to do as a faculty member after finishing my postdoc.”

Fast forward 20 years. Dranoff is still obsessed with using the immune system to fight cancer, but now he’s in good company. With clinical successes mounting, immunotherapy is poised to become a cornerstone of cancer treatment. To capitalize on this opportunity and bring new

medicines to the clinic, the Novartis Institutes for BioMedical Research recently launched a research group focused on Immuno-oncology, recruiting Dranoff from the Dana-Farber Cancer Institute and Harvard Medical School to lead it. The group will build on recent acquisitions and collaborations—including a new deal with the biotech company Aduro ^[3]—to transform promising research into treatments.

Dranoff and his partners will explore therapeutic approaches that fall into three main categories. First, they'll search for ways to “prime” or “educate” the immune system, so that it can recognize a threat. Second, they'll attempt to unleash immune cells that have already been primed. This is called immunomodulation. And finally, they'll find ways to make the tumor microenvironment more hospitable to immune cells, which must infiltrate the diseased tissue to be effective.

“These categories cover the major mechanisms that tumors use to thwart an immune attack, and we plan to address all of them,” says Dranoff.

The team is off to a running start. Dranoff brings with him cancer vaccine research, which falls into the first category. And—spurred by the 2014 acquisition of a startup called CoStim—Novartis is already investigating “checkpoint inhibitors,” which fall into the second category. The new collaboration with Aduro focuses on the tumor microenvironment.

Novartis is also pursuing treatments that bypass conventional immune activation through a collaboration with the University of Pennsylvania. Investigators extract T cells from patients and reengineer them to recognize and destroy cancer.

The new Immuno-oncology group will continue and expand on these existing efforts. Dranoff is particularly excited about combining more than one approach in the same patient, a strategy that stems from his work at Dana-Farber. In early clinical trials, cancer vaccines generated only modest clinical benefit, disappointing many researchers. But Dranoff and others now believe that vaccines could be paired with immunomodulators to produce a significant, durable response in certain types of cancer.

“The field has matured to a point that we can come up with reasonable hypotheses about how to apply and combine immunotherapies, based on clinical data,” says Dranoff. “It’s a remarkable privilege to be working at this time, when the expectations are quite high for making significant advances across a large array of dreadful diseases.”

It seems that immunotherapy’s time has arrived. It has been a long road to today, however, and up until recently, scientists were skeptical of the field’s clinical relevance. Following is an excerpt from a conversation with Dranoff about his professional journey and vision for Immuno-oncology research at Novartis.

When did most researchers working in oncology realize that immunotherapy was going to be big?

When they saw the striking clinical activity of the PD-1 checkpoint inhibitor in 2010. Many different types of tumors responded to immune modulation with a single molecule, which was a big surprise, even to me. Based on all the information that was available prior to the studies of PD-1 blockade, you could not have predicted that result. And it was the first clinical evidence that strong endogenous immune responses really do occur, just as the scientific

legend [Paul Ehrlich](#) [4] hypothesized in the early 1900s. He suggested that if you didn't have an intact immune system, then cancer would develop more frequently and be more aggressive. This is the concept of immunosurveillance.

Why did the immunosurveillance hypothesis fall out of favor?

A number of reasons. One was the discovery of the nude mouse, which lacks a fully-functioning immune system. People said, "If Paul Ehrlich's hypothesis is correct, then surely this immunodeficient mouse should develop a higher incidence of cancer." But lots and lots of nude mice were tested in every way for tumor susceptibility and it wasn't increased. We've recently learned that these animals retain key elements of the immune system that are involved in tumor protection, which explains the earlier results.

As groups studying the nude mice raised questions about cancer immunology, genetics was marching ahead. Oncogenes were discovered, and everyone became convinced that cancer would be solved by putting tumor tissue in a dish and figuring out the cell biology. Even when investigators confirmed in the early 1990s that our T cells can recognize cancer cells, the feeling was, "So what." It didn't prove that the immune system impacts the disease as a whole.

Why didn't you follow the herd and focus on the cell biology movement in oncology?

I stumbled into cancer immunology by accident, but there was enough there to keep me interested. I have a strong sense of optimism, fostered by Trudy Elion, my mentor in medical school. She was a chemist who, together with George Hitchings, made a series of advances that were later recognized with a Nobel Prize. Over the course of 40 or 50 years, their ideas were transformed into new medicines for organ transplantation, autoimmune disease, cancer and more. And each drug to emerge from their work was a 10-year story. So I learned to be patient and optimistic that my research might eventually lead to a very beneficial outcome for patients.

You were trained as an oncologist. Were you hesitant to shift toward immunology?

I'm most interested in areas where disciplines overlap. That's what appeals to me about medicine in general. Medicine ultimately impacts a human being with feelings, needs and desires. To be a healer, you need to understand each patient's story and how a treatment will affect his or her life. Then you need to integrate all of that knowledge with more objective ways of looking at medical issues, bringing rigorous scientific analysis into play. In my own research, I enjoy building connections between areas that don't immediately appear to overlap. And initially it was helpful that I was immunologically naïve because I didn't have as many biases.

Scientifically, what is your proudest accomplishment?

I'm proud to have been part of the work that led to the demonstration that immunity really matters in cancer. Many researchers have contributed, showing that careful, mechanistic-based studies of novel immunotherapies in humans can be done. And now the early-stage clinical trials are proving relevant at a larger scale. The fact that pharmaceutical companies are now interested in what I've spent all of my time doing is exciting.

Why are you moving from academia to industry and why Novartis?

At a certain point, after a principle is established in an academic setting, that principle needs to be applied in an industry setting, where real drugs are made. The cancer immunology field has matured to that point. And I think that the opportunities are great at Novartis because of its impressive portfolio of targeted cancer drugs. The cell biology movement was very productive, yielding many drugs that target the alterations in tumor cells. But drug resistance has emerged as a problem. We might be able to couple targeted therapies with immunotherapies to convert dramatic regressions into long-lasting responses.

And it turns out that some of the existing targeted therapies hit molecular pathways that are relevant to immune function. In other words, we didn't fully understand how they work from the outset. We might be able to repurpose some of these compounds to overcome immune suppression by tumors. This will require a lot of collaboration, and we'll need to leverage expertise from across the company and beyond to be successful.

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