Changing the Nature of the Game

Sitting Down With…
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What motivated your career in pathology?

I knew all along that I wanted to do mechanistic research. I was in medical school thinking, "What's my quickest route back into the lab?" My mentors were doing lab-based work and patient care, so I asked, "How can I do that?" They said, "Don't. Go into pathology."

Although choosing pathology meant I gave up seeing patients, I never gave up interacting – I see the doctors and their patients as "my patients," which is just as rewarding.

I arrived at the University of Rochester fairly pluripotent as a pathologist; I could have developed in a number of different ways. I wanted to join a group I could learn a lot from, so I became an immunologist. Immunologists and pathologists speak different languages, and by having a foot in each world, I was able to translate things. It set me on the path of understanding what I call immune subversion – that is, how tumors block the immune system.

Why the move to pharma?

Personal reasons took me to the Bay Area and, out of the blue, a fantastic job emerged at DNAX, which is legendary in immunology. Schering-Plough, amazingly, funded this research institute and never put much pressure on drug development – so for almost 20 years, it produced great science. When they decided to make DNAX a drug discovery enterprise, they brought in John Curnutte, a strong proponent of translational medicine. He felt they needed pathology to understand tissue architecture and cellular organization. I took the job in a heartbeat and never regretted moving into pharma.

What was the story of PD-1?

The PD-1 program came to DNAX when we acquired Organon, who had planned to move forward in human development without "companion" mouse studies. This was a bold approach. Although it was clear from the literature that anti-PD-1 was a strong candidate molecule for immuno-oncology, Schering-Plough were more conservative and tasked us with building the mouse surrogate program. When Merck and Schering-Plough merged, the PD-1 program was deprioritized until Bristol-Myers Squibb published their candidate's Phase I data. Then it was like Lazarus – raised from the dead! It's amazing that Merck still got first approval in the US. I think they benefited from going after ipilimumab-refractory melanoma patients as their main indication; that triggered the breakthrough therapy designation.

It's exciting that we have such a good idea of who responds to anti-PD-1 and who doesn't. That's critical to why PD-1 development is going so fast – in large part, we understand the mechanism of action. My first ah-ha! moment came when I saw tumors IHC-stained with PD-1 and PD-L1. Patients who respond to anti-PD-1 have cytotoxic T cells in their tumors; you only need immunology 101 to say, "Wow! The T cell coming in is generating a cytokine which upregulates PD-L1 to shut off the T cells." It's a homeostatic mechanism we evolved – every immune reaction contains its own brakes, and tumors hijack them.

It took a long time to convince the scientific community that immunotherapy would work – over 100 years of chasing Dr Coley's vision of harnessing immune responses to treat tumors. If you think about where we are with anti-PD-1 today, where might we be if this transformation had happened earlier?

What new treatment strategies hold most potential?

The future is in combination immunotherapies – I predict they'll become the backbone in many indications. We just need to figure out how to use current targeted agents and chemotherapies judiciously.

Immunotherapies are not innocuous. PD-1's safety profile is pretty good, but when we combine therapies, we'll have to be sensitive to synergistic immunotoxicity. That's a benefit of a multimodal therapeutic paradigm that includes intratumoral therapy – we can harness treatment efficacy without systemic exposure and toxicity.

I think the most important question we need to answer in immuno-oncology now is: how do you make PD-1 non-responders into responders? That's our current strategy at OncoSec, and our primary candidate is intratumoral delivery of IL-12.

Some of the luminaries in the literature today are beginning to talk about intratumoral therapy. I think we'll see these therapies come of age in the next decade; Amgen's T-VEC, a virus that encodes GM-CSF, has met with some success, but there are many different ways you can approach it and I think others will follow suit.

I also think we'll come back to DNA damage and repair. Tumors depend on their ability to mutate but this can be their Achilles heel; they become dependent on DNA checkpoints, unlike normal cells, so we have a therapeutic leverage point. I think we'll see a resurgence of this as a field to explore.

How do you see the role of pathologists evolving?

It's going to be increasingly important for pathologists to perform and interpret companion diagnostic tests in clinical labs. On the research side, we need pathologists to further our understanding of interactions within tumors, discovering potential mechanisms and research angles. That's where I've spent my entire career. The technology is coming, but you still need the brain behind the scope.

I think we really are at this transformative moment in oncology. We're no longer just trying to out-poison the tumor; we're changing the nature of the game. I think everyone should be as excited as I am – it's a brilliant time to be in this field!