Guest: Dr. Louis Weiner, MD, Director, the Lombardi Comprehensive Cancer Center, and Francis L. and Charlotte G. Gragnani Chair and Department of Oncology Chair, Georgetown University Medical Center

Dr. Weiner, please tell us a little bit about you and your role and responsibilities.

Dr. Weiner: Sure. As noted by my titles, I am Director of one of the nation’s 45 National Cancer Institute’s designated comprehensive cancer centers where we are charged with the responsibility of providing excellence in patient care, clinical research, basic and translational research, population research and community outreach.

My role is to oversee those functions and in that context I also still see patients, primarily with gastrointestinal malignancies. I also conduct
research on my own as an antibody-focused trialist. So, my background was in clinical trials of antibody and in antibody engineering for many years. This work has now morphed a little bit into thinking about how to use antibody targeted therapeutics for immunotherapy of cancer.

**What’s your take on the status of unconjugated antibodies in cancer treatment?**

**Dr. Weiner:** Now, this has been quite a journey for me personally and for the field, in general. I started in the field of unconjugated antibody therapy 30 years ago when most of the same people thought I was a madman to have been involved in something as radical and unpromising as the use of antibodies to treat cancer.

There was good reason to believe—in my judgment—that it could work and I was delighted, of course, that my stubborn refusal to listen to smarter people than me turned out to be successful. We have gone from having great skepticism about the role of antibodies to treat cancer to antibodies being the backbone therapies of many important, different cancers and some antibody therapeutics being among the most active clinical agents that there are.

So, I would say that the status of unconjugated antibody therapies are that these are very prominent players and important treatments for many people with different types of cancers and, in fact, there has been a bit of an evolution where we’ve gone away from antibodies that now specifically target cancer-specific antigens to try and focus either signal manipulation...
or immune attack against the cancer cells to really focusing on immunological checkpoints. Looking to actually breakdown the defenses that cancers possess in order to block the immune system from attacking them. This has turned out to be an incredibly powerful new direction for the field.

**What do you believe the future holds, then, for antibody drug conjugates for cancer treatments?**

Dr. Weiner: Well, I think in order to understand the future, we have to have a little bit clearer understanding of where we are right now. So, there are now FDA approved drugs out for nearly 20 years for the treatment of breast cancer and lymphoma, for example, and many derivatives of those molecules have been developed, as well. I think the future is bright for the use of antibodies that can manipulate cancer-related signaling and also induce antibody mediated immune reactions.

On top of that, though, I think the whole field of antibody checkpoints really requires us to be very thoughtful about how we begin engineering antibodies in order to maximize their ability to manipulate immune response. Antibodies that target the PD-1 or PD-L1 targets have exhibited remarkable anti-cancer activity. In fact, I think it can be fairly stated that anti-PD-1 antibodies currently are the most broadly active anti-cancer agents available. They work in more diseases than any chemotherapy drug I know of. So, that’s really quite promising.

Antibodies against CTLA-4 are also showing significant clinical activity and there are many other checkpoint antibodies out there that are being
evaluated. I’m sure some of them are also going to show promising and clinically beneficial effects.

I think what’s really exciting about the future is combinations. For example, anti-PD-1 therapy for melanoma patients—a deadly form of advanced skin cancer—has major anti-cancer activity in roughly 30% of people who are treated, which is nice. Some of those patients do very well, which is even nicer. Treatment with ipilimumab—an anti-CTLA-4 antibody—works in roughly 15%-20% of those patients. Again, nice, but not especially transformative except for those people who have great benefits. But if you combine those drugs together you get major clinical benefits in the majority of patients who are treated. These appear to be very durable responses, thus transforming the field of melanoma therapy.

Now, if you take that as not an exception to the rule but rather a harbinger of things to come, as we begin developing, testing and understanding how to best use antibodies against the many other checkpoints—either alone or in combination with agents that we already have or in combination with each other—you can see that we are really on the verge of breaking down the defenses of cancer that have been erected to avoid immune destruction. In doing so, (it will) really lead to the beneficial treatments of countless thousands or even millions of people with cancer. So, this is a very exciting opportunity.

**Dr. Weiner, could you elaborate on how we actually manipulate an anti-cancer immune response?**
Dr. Weiner: Sure. This is actually one of the neatest stories of all, I think. When any cancer develops in a human being, it has only one active enemy and that’s the body’s immune system. So, every successful cancer, if you will, has to solve the riddle posed by the host immune system. There are many different ways that this could happen. It turns out that one of the most common ways is this notion of inactivating killer T-cells that would otherwise destroy the cancer when those T-cells get too close to the cancer cells themselves. So, a kind of barbarian-at-the-gates approach that the cancer cells use. What they do is incredibly clever. As the activated killer T-cell gets close to the tumor cell, the tumor cell is then stimulated to produce a blocking molecule called PDL-1, which is expressed on its surface. When the T-cell, which expresses the counter ligand for PDL-1—known as PD-1—engages PDL-1, that action actually causes the T-cell to go to sleep. So, basically the cancers are specifically inactivating the cells that are most likely to kill them. It’s an incredibly elegant strategy that has been devised by nature and has obviously been hijacked from normal cellular processes that keep cells from killing each other when they are necessary and important for human survival and function.

“We essentially block that interaction between PD-1 and PDL-1... (so) those T-cells don’t go to sleep.”

So, what we do with the antibodies is essentially block that interaction between PD-1 and PDL-1. What happens is that those T-cells don’t go to sleep. That’s how you can manipulate the anti-cancer immune response. If you take a look at that one specific example and expand it to consider the other ligand receptor interactions that might occur out there and understand how to manipulate them in frame, you can see why this would be an important and exciting area for future research.

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Dr. Weiner: You got it. So, immunotherapy can be thought of as treating the immune system so that the immune system can treat the cancer. I’d like to take credit for that, but I can’t. It was actually a phrase coined by a colleague at Memorial Sloan Kettering Cancer Center named Jedd Wolchok. But it’s no less true because he coined the phrase. It’s a wonderful way of thinking about things.

Thank you so much for joining us today and sharing with us, Dr. Weiner. This has been a real pleasure.

Dr. Weiner: My pleasure.

That concludes this episode of Inside Antibody Engineering.

Dr. Louis Weiner will speak on “Targeting Cancer’s Fragile Strength with Immunotherapy” at the Antibody Engineering and Therapeutics Conference taking place December 7-10 in San Diego.

For more information or to register, please visit www.ibclifesciences.com/antibodyeng

Until next time, I’m Marc Dresner. Thanks for tuning in.

ABOUT THE INTERVIEWER
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