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Inside information on cancer research and drug development

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Conversation with The Cancer Letter

Parker Mantra: Collaborate Like Hell

The Cancer Letter invited Jedd Wolchok, associate attending physician and chief of the Melanoma and Immunotherapeutics Service at Memorial Sloan Kettering Cancer Center, to describe the workings of the just-announced Parker Institute for Cancer Immunotherapy.

Wolchok, director of one of the Parker-funded centers, spoke with Matthew Ong, a reporter with The Cancer Letter.

Matthew Ong: *What was the genesis of this initiative? Whose idea was it and how did it happen?*

Jedd Wolchok: This was really the idea of Sean Parker. Sean, as you know, is a very successful technology entrepreneur, but he also has a very significant interest in immunology, because of some personal allergy issues that he had, and also because of his friendship with Laura Ziskin, the founder of Stand Up To Cancer.

He became very close to her during the time that she had recurrent breast cancer, and educated himself as to different treatment modalities. He became fascinated with immunotherapy, and as a result of that, he started to look at the entire cancer research process as sort of an outsider looking in—as someone who lives in a different world observing this process.

As someone who is—in his own words—fascinated with "disruptive technology," he decided to identify ways in which the process of doing cancer research can be made more efficient, and if there was any way for him to financially support the research process, most specifically in immunotherapy.

I think the emphasis on immunotherapy is probably because of his own personal interest in immunotherapy, but also because it is the sort of disruptive technology in cancer medicine. It looks at the cancer problem from the other side—it looks at it from the patient side rather than from the "What can we do to stop the tumor from proliferating?" side. It fits with his focus.

When he first became interested in immunotherapy, it was more outside the mainstream than now—it's widely considered to be an additional pillar of standard cancer therapeutic approaches. But when Sean first became focused, there were no approved checkpoint-blocking antibodies. There was very little research on CAR T-cells—Chimeric Antigen Receptor T-cells—that this could have the activity that we now know they do. I think that it was certainly more outside the mainstream.

I think that this was probably about six years ago, when he began to try and help Laura Ziskin. I first met Sean almost three years ago, and at that point, he had already made his decision that he wanted to support immunotherapy. At that moment, it wasn't clear to me what the institute would look like. He had made a sizable contribution to SU2C to support the Immunotherapy Dream Team. He also had made a donation to the Cancer Research Institute, which is an organization that's solely focused on immunotherapy. The idea to actually have his own institute really began to gel two, two-and-a-half years ago, in my experience.

MO: *How is the $250 million divvied up? Who are the recipients, and what are the amounts awarded? How is MSKCC going to be a part of it?*

JW: There are six home institutions. In addition to the six Parker Institute sites—MSKCC, MD Anderson Cancer Center, University of Pennsylvania, Stanford University, University of California, San Francisco, and University of California, Los Angeles—there are also extramural member researchers. Individual researchers whose work is thought to be synergistic, co-complementary with the other sites will be supported singularly.

Some of those folks are at Mount Sinai Hospital and Washington University, specifically Bob Schreiber [director of the Center for Human Immunology and Immunotherapy Programs at the Washington University School of Medicine], Nina Bhardwaj [director of immunotherapy and the medical director of the Vaccine and Cell Therapy Core facility at Icahn School of Medicine at Mount Sinai], and Jeff Hammerbacher [chief scientist and cofounder at Cloudera, and assistant professor of genetics and genomic sciences at Mount Sinai].

An initial funding of $10 to 15 million in the first year was given to set up the Parker Institute centers' sites. This investment will continue to grow on an annual basis via additional project grants, shared resources and central funding. That's to really put

infrastructure in place and to fund projects that are germane to the goals of the Parker Institute internally. This is not contract research. The individual experiments are the experiments that the funded researchers at the individual sites want to do, but there are some overall streams of research focus. And obviously, the institute itself will have some money that they'll use and distribute to support institute-wide efforts.

There will be other funds coming from Parker Central, the headquarters in San Francisco, to support global initiatives amongst the six sites. For example, at MSKCC, we launched the first Parker coordinated clinical trial last week, which is a checkpoint blockade trial in melanoma to determine what the best therapy is at the point of resistance to PD-1 blockade. Parker Central, not the individual sites, is paying for the central coordination of the trial.

That trial is actually a very good example of how this institute can accelerate research. That trial was written by Claire Friedman, an MSKCC oncology fellow, and I, and she refined it at the American Society of Clinical Oncology and American Association for Cancer Research clinical trial workshop last summer. It was approved for provision of free drugs by Bristol-Myers Squibb in the fall—it went through all regulatory review and was released as being exempt by the FDA and opened last week.

Ordinarily, to open a trial like that, I would have to apply for grants to pay for the research, to pay for the data management, to pay for the correlative science—especially research biopsies, which are an important part of a biomarker-heavy clinical trial like this. Because I apportioned part of our yearly budget to pay for this, to have those things immediately available, we wouldn't have to go and seek out additional funding. We just hit the ground running immediately.

Now, we can do this at potentially six sites rather than one. We will get done much faster. The number of patients is the same—we've powered it specifically, but it's how quickly you can get those

patients treated and get a conclusion. This is really about answering the right question as quickly as with as much depth as possible.

The other attractive aspect of the Parker Institute is that there's a lot of technology that's coming of age in terms of ability to interrogate single-cell specimens, subtle immunologic changes, multiplex analytics, and each site is now getting access to state-of-the-art equipment with which to ask those questions. We can now ask such questions in a non-overlapping way, but each site can dive into the communal specimens in a more in-depth way. I think this trial epitomizes really what the strengths of the network are.

MO: *You mentioned CAR-T and checkpoint inhibitors—could you explain the research goals in greater detail?*

JW: The three basic research streams were arrived at by the center directors and researchers, and the Parker staff. This is not someone telling us what to do, this is us coming up with essentially a research agenda that we wanted to lay out. The three areas are:

• Identifying the optimal way to adoptively transfer T-cells—CAR-T, transgenic TCR-bearing cells, etc.

• Understanding resistance—the PD-1 blockade and hopefully that will feed forward into what to add the PD-1 blockade to overcome or bypass that resistance, and

• Studying deeply the neoepitope-based vaccine concept—we're very aware now that the immune system can see the products of mutated genes that occur in cancer, either drivers or passenger mutations, and how to identify, most importantly, the qualities or features of mutations that are most interesting to the immune system.

It is really a very current area that needs significant attention, and plays to the strengths of the institute, because of the background of many of the founders of the institute in terms of bioinformatics and big data. Jeff Hammerbacher and Sean Parker, in fact, have

very significant experience and knowledge in Big Data, and can help get through this large amount of valuable data from patient specimens as effectively as possible.

MO: *So basically this initiative is an evidence-driven endeavor by cancer researchers for cancer researchers.*

JW: The idea is to push people to take risks and to collaborate. The really important message that we got from the beginning was, "Collaboration is key." Of course, that's not new, the idea that team science is very important. Stand Up To Cancer, many organizations have been focusing on team science—but here, it's a mantra: "Collaborate like hell." It's time to come out of the siloes and to make progress together.

The really novel part of this is the idea that some quality sites were identified, were given a very generous donation by someone who does study the field, but the researchers are set loose to form their own agenda. The other part is the intellectual property-sharing model. This is a bit of an experiment in what is hoped to be an evergreen foundation or institute where the IP generated by the sites and supported researchers is shared between the six home institutions and the Parker Institute.

The institute will redistribute whatever royalty through licensing agreement, etc., is generated back to the individual laboratories. It's a feed-forward evergreen model, which is an experiment. We hope it works, because this is a really generous gift. As you probably know, doing cancer research, especially when it involves clinical trials, can have a lot of zeros involved in the numbers. This is a really large amount of money, but it could get used up without an evergreen approach. That really is quite a visionary and innovative spin.

MO: *Are the funds only going to be used for basic research, or are there industry partnerships in the works?*

JW: It's both. Yes, there are plans to collaborate with pharma to both get access to agents of interest, to combine with standard available agents, and also to have dialogue about new targets that we may discover.

But I think if you look at the team, they are both basic immunologists—some of the best ones in the world—as well as translational scientists and clinicians. The idea here is to, in a quite literal way, bridge the laboratory with the clinic and have a bidirectional transfer of information. It's both at once, not in phases.

MO: *A good number of initiatives launched this year—by the White House, for instance—also focus on immunotherapy and precision medicine, and the "Moonshot" brand seems to really be in vogue in oncology. Was there a conscious decision to not call this a moonshot?*

JW: I don't think we really spent much time thinking about whether to call it a moonshot or not. I think the goal of this seems, in some ways, very aligned with the other very important initiatives, and we're really glad to see all of the interest in the field. It's very firm evidence for how immunotherapy has taken on a major role in cancer research today, and I think there are some similarities, some differences.

The good news is that we're not constrained to only work with these sites. This is one part of what we do and we have ongoing collaborations with, say, Johns Hopkins. Through other funding mechanisms, we at Memorial co-lead the Stand Up To Cancer KRAS mutated non-small cell lung cancer Dream Team, focused on innovative research and care for lung cancer, and work with some other Parker Institute sites as well as others, which currently are not. This is really a situation where more is better, and the more attention we all can pay to this, the more quickly we will make progress. I know that may sound trite, but I think that's really true.

MO: *Is the foundation planning on working with others beyond the academic cancer center realm, including federal entities like NCI and NIH?*

JW: Right now, we're focused on working with these individual sites, but nothing has been written out. The institute is focused on identifying the most important folks in the field and working with them. I think it's a very dynamic structure.

This is really focused on immunotherapy pretty singularly. I think that we recognize that immunotherapy may need to be combined with other therapeutic interventions to achieve optimal results, but I think the questions are being framed around, "What can we do with immunotherapy alone or in conjunction with other approaches?"

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