AN AUDIENCE WITH...

Leena Gandhi


Credit: NYU Langone Health

Leena Gandhi, a thoracic oncologist, started working with cancer immunotherapies in 2008 in one of the first trials of the PD1 inhibitor nivolumab and has been hooked on the field ever since. In the subsequent decade, she coordinated dozens of immuno-oncology trials — first at Dana Farber Cancer Institute, then at New York University's Perlmutter Cancer Center — including a seminal study defining the use of PDL1 as a biomarker for PD1 inhibition in lung cancer. After a 2-year stint overseeing immuno-oncology at Eli Lilly, Gandhi is now returning to the Dana Farber Cancer Institute as Director of its new Center for Therapeutic Innovation. She spoke with **Asher Mullard** about the appeal of immunotherapies, how they have impacted academic drug development, and the hunt for better biomarkers that can unravel their complicated biological effects.

What was the appeal of immunotherapies for you back in 2008?

I came to medicine a little bit backwards. I had done a PhD on DNA replication and telomerases at the University of California, Berkeley, before I went to medical school at New York University, and I'd always wanted to work in translational medicine. Early drug development specifically appealed to me because it seemed like that's where understanding drug mechanisms in humans was possible. Immuno-oncology turned out to be a particularly unique setting because the human immune system is just so different than model systems. And what I really liked about PD1 inhibitor development is that, because there was some activity with these, we could start to look at the biomarkers of activity early on, and how they are different in different contexts.

You spent the subsequent 10 years running immuno-oncology trials in academia, before joining Lilly in 2018. Why the transition?

To be honest, I was not necessarily looking to move from academia to industry. And I didn't look at other industry jobs at all. I went to Lilly because of the opportunity to lead a broader effort in immuno-oncology and because of the appeal of the organization Levi Garraway, a former colleague, was building.

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You were only there for 2 years. Why now come back to academia?

I would not necessarily have moved so soon. But a lot has changed since Loxo Oncology took over oncology development at Lilly. [Lilly acquired Loxo Oncology in January 2019, and placed the Loxo management team in charge of oncology that December.] The focus shifted away from immuno-oncology, and that is really my interest. So I thought it was time to look around at different opportunities. I also felt like there were things I missed about academia, and I missed being a doctor.

Industry has taken over so much of the clinical trial activity from academics in the past decades, and one of the downsides of this is that there's been this creation of a little bit of a silo because industry researchers are not seeing patients. And that's why they need to partner with academic research physicians. The physician–patient experience informs our work and how we develop immuno-oncology drugs in particular. I really do feel that immuno-oncology is a clinically defined field: we're figuring out what questions to ask based on what's happening to our patients, how our patients are responding and the kinds of side effects they're getting. The opportunity to join Dana Farber again came up, and I feel like now that I've seen a little bit of both sides I can work towards more effective partnerships and smarter clinical development.

How will the new Center for Therapeutic Innovation do trials differently from the previous setup?

This is a new center, but to be fair our goal is to combine various efforts that are being run a little bit piecemeal across Dana Farber. Dana Farber, like many other institutions, has evolved these kinds of separate cancer drug path development paths over the past decade, because there was this feeling early on that immuno-oncology agents were so different from other types of cancer drugs that they needed to be studied differently. Now, immuno-oncology has become part of the standard of care across a wide spectrum of malignancies, and a foundational part of cancer care. It's not some separate thing anymore, and the drug development path is not some separate thing either.

Under the current landscape, people are looking at all kinds of drugs as immuno-modulatory agents. And all drugs are immunomodulatory agents in some way or another. So it's semantics to say that these fields are different.

What's unique for me, and what I like about this opportunity, is that if we want to study the immunomodulatory effects of these drugs, we have to do that as close to human models as possible, with samples from human patients and in early clinical trials.

The field is still working out how to do this. Where do you think the field is in terms of biomarker usage, versus where you hoped it would be by now?

It's a very good question because I think a lot of people in industry, and probably elsewhere as well, feel that maybe PD1 inhibitors were a little bit of a flash in the pan. We haven't seen things evolve a lot from there yet and wonder whether that's a question of patient selection. I think actually the difference is that anti-PD1s and PDL1s were a bit easier to work with because they had activity in a fairly broad setting.

Maybe these responses weren't dramatic, with 80% of patients not responding, but because there were clear responders and non-responders the community could really tease out what was happening. This activity profile lends itself very well to rapid — if imperfect — biomarker development.

Biomarker development is harder when agents don't have a lot of very obvious activity from the beginning. But that's really where I think the challenge and the excitement of early drug development is. And we're developing much better tools. If we can better understand the mechanisms and the potential biomarkers from the beginning, we can tailor clinical development to enhance the chance of being able to catch an agent's activity.

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I'll add that there has been a paradigm shift in terms of early drug development. The fields had suffered a little bit in that the traditional anticancer drugs were just all chemotherapies that all kind of work in similar ways, affecting some aspect of DNA replication and cell cycling. That whole model of drug development was really based on maximum tolerated dose and safety parameters, and not on specific biomarkers. You just set out to combine these all together and see which were least toxic. Targeted therapies changed that a lot. But these too are relatively straightforward to work with once you figure out a genomic tool that can be used to identify and select patients.

Immunotherapy is more complicated because of the higher order of interactions that are happening. You have to interrogate very complicated interactions not just within the immune system components, but also with the tumour–immune microenvironment. If we develop really good tools to actually interrogate these factors — just like we're now very good at understanding tumour genomics to identify oncogenic drivers — we can tailor therapies better right from the very beginning. But it's a lot harder with immuno-oncology than it is with targeted therapies. These are dynamic interactions, with protein expression patterns changing all the time.

As we get better at handling big data, functional genomics, single cell genomics, spatial proteomics, and more, we will be able to do smarter drug development.

Q ***How does biomarker development change as the field increasingly moves from monotherapy to combination immuno-oncology applications?***

What we are learning is that as immuno-therapies get combined, biomarkers that seemed important with monotherapy may not have the same influence. Because chemotherapies influence the immune system, for example, the pre-existing tumour mutational burden status may not have the same exact influence as it would with monotherapy. And Jim Allison's group has shown that when you combine CTLA4 inhibitors with PD1 inhibitors, you are not getting only an additive effect but that the combination can affect immune subsets differently.

So the biomarkers may be actually different. And instead of working retro-spectively to see if the same biomarkers apply, I think we need to work more prospectively to think about these things at the earliest stages of clinical development. I think that's been part of the problem of combinations so far. We don't fully understand PD1 resistance,

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and yet we're often testing combinations in the setting of very pleomorphic resistance mechanisms and then trying to understand what's driving the effect in a few responses. But the population is so heterogeneous, it feels like looking for a needle in a haystack.

I think a lot of things have been thrown out because they've been just tested in unselected populations, without any biomarkers.

Q ***There are also concerns that, despite thousands of ongoing immuno-oncology trials, we still don't really know very much about what is happening at the cellular and biochemical levels in humans, at least in part because of insufficient biospecimen sampling and analysis. Is this something you hope to address?***

That's a very good point. And even if many trials are now collecting serial specimens, we haven't seen all of the correlative biomarker work associated with those trials published as yet. The interpretation of how relative changes in the expression of different biomarkers on different cell types, and how that influences whether you're getting activity of your drug, is something that requires some real thought. I think we're still in the nascent stages of what are the best assays, and how we can streamline them for clinical use.