AN AUDIENCE WITH…

What's next for an immuno-oncology powerhouse?


Credit: Merck & Co.

Dean Li, the recently appointed President of Merck Research Laboratories, discusses his immuno-oncology ambitions, emerging antiviral opportunities and the changing pace of technological cycle times.

Merck & Co.'s PD1 blocker pembrolizumab is a force to be reckoned with. Already a US$15 billion per year antibody, it is on track to becoming industry's top-selling product by 2023. Approved for treating more than 30 cancer types, it has transformed the oncology landscape. And for Dean Li, the latest president of Merck Research Laboratories, this creates a nice problem to have: how to build out the future of this franchise, without losing sight of other therapeutic opportunities?

Li — a translational scientist and cardiologist who first joined Merck in 2017 as head of Translational Medicine and Discovery — plans to follow both the science and the technology. Insights from immuno-oncology clinical trials could yet open up avenues in other therapeutic areas, he explains, and the pace of technological cycle times is faster than ever before.

It's been 7 months since you took over from Roger Perlmutter. What's your R&D plan?

To contextualize this, I came to Merck in 2017, and that was the first time I'd ever been in a large biopharmaceutical company. Previously I was administratively high up at the University of Utah, I'd run a lab and I'd spun out some companies, including Recursion Pharmaceuticals. But my first "tour of duty" at Merck was shepherding compounds from discovery into first-in-human trials. And this is important background because this transition — from Roger Perlmutter to myself — is not just about us as individuals. It is also about the company being at a different position than it was 10 years ago.

The company has invested incredibly aggressively in oncology, and there is a book of work that has to get done here. It's really important for the field to demonstrate the breadth and depth of checkpoint inhibitors in cancer. That game plan has been set, and we need to focus on execution.

But one of the reasons I think I was brought in for this transition is that we need to keep our focus on what happens in 2028 [when Merck expects to lose patent exclusivity for pembrolizumab] and beyond. Clearly we have to use all of the leverage that checkpoint inhibitors have given us. This is probably the seminal disruption in cancer biology. One could argue that the impact of checkpoint inhibitors is at the level of the advancement of chemotherapy. But for 2028, it is incredibly important that that's not the only thing that we do. We must find other foundational products, programmes, areas of science, areas of biology and platforms that we can use. And so my focus is also on 2028. How do we transition to that future, while recognizing that there's an execution part that we still need to do?

Do you worry about being over-reliant on pembrolizumab?

I think we have to separate the corporate standpoint from a science and medicine standpoint. From a corporate standpoint, you have to think about short-term finances as well as future trajectories. That's always there. When people talk about 2028, and ask about an over-reliance on PD1, they often raise the challenges that other companies have faced, for instance with anti-TNFα antibodies and concentration risk.

But I'd say that the revolution of checkpoint inhibitors, and PD1, is a little bit different. This is something that foundationally, fundamentally changes all of oncology. To put a fine point on it, you cannot be a biotech company in cancer and not ask yourself: how does my approach work in the setting of a PD1 inhibitor? And this gives us an enormous opportunity to learn and understand. That is something that we have to think about even in 2028 and beyond.

But we want to make impacts in many different therapeutic areas, and to follow the science as it evolves. And there are many other opportunities where Merck can and should have an impact.

I'd add that you have to pay attention to movements in science. We've seen that investments in HIV didn't just make an impact in HIV, but fundamentally changed how people understood T cell biology, for example. The same sort of thing is happening now. Yes, we have to build immuno-oncology for oncology. But we also have to build and understand immuno-oncology so that we can understand and apply our learnings to other therapeutic areas.

Such as in autoimmune indications? Was this the basis for your recent $1.9 billion acquisition of Pandion and its IL-2 agents?

That's absolutely right. IL-2 has many different effects. It's a well-known immuno-oncology agent. But low-dose IL-2 also has potential in autoimmune situations. So all of a sudden, expertise in a cytokine — and what it does in cancer — gives you the scientists and technology you need to drive programmes in autoimmunity.

If you look at cardiovascular science and neuroscience, these are also areas where new insights into inflammation and immunology provide new and different ways to think about treating diseases, built on insights from immuno-oncology.

Sticking with cancer a moment longer, other checkpoint inhibitors and dual immuno-oncology combination strategies have yet to make a mark. Why?

When you want to combine an immuno-oncology agent with another immuno-oncology agent, you have to ask whether that second agent does something more than PD1, and whether it has that combinatorial flexibility that PD1 has. But if you take LAG3, CTLA4 and OX40 [T cell checkpoint modulators] and you put them in mouse models, they look indistinguishable from PD1 as far as I'm concerned. And it

is important that if we are going to add an immuno-oncology agent to a PD1 inhibitor, we must demonstrate that the new agent adds something. The fact that PD1 can do so much is what makes this so hard.

So, you have to be a little bit more thoughtful. Now, Merck has a CTLA4 inhibitor, a LAG3 inhibitor, a TIGIT inhibitor and an ILT4 inhibitor, and we believe that all of these can be added onto PD1 to improve that baseline activity. But it is unlikely that that baseline position is going to be altered in all tumours. The activity may be more bespoke, in tumour-specific or stage-specific settings.

Shifting to infectious disease R&D, what lessons have you taken from your antiviral COVID-19 programmes?

To start, the available vaccines have been excellent. Everyone should get one. But what we are seeing is that, increasingly, the vaccines are having a harder time as the virus evolves. They are still able to prevent serious hospitalization, but they haven't held on as well in terms of reducing infectivity. And this has led us to ask: what if we could use an antiviral not only to reduce clinical events, but also to drive down viral loads? That's what is now at stake in the antiviral field.

Molnupiravir, the molecule that we've partnered with Ridgeback on, has this potential. It's one thing to block a polymerase and induce RNA chain termination, which is how most nucleoside analogues work. It's another to mess up the polymerase so much that you cause major genomic alterations within the virus. It's like disrupting the blueprint. And that's how we think molnupiravir works. It has a different mechanism than many of the antivirals.

If this works for COVID-19, it might work more broadly for other RNA viruses, including respiratory syncytial virus. Of course we have to prove this still. But I think this is a really important concept.

Clearly, protease inhibitors and fusion inhibitors that are specific for SARS-CoV-2 are important, and people should continue to work on these. But if you ask what makes me excited about the possibility of a positive clinical trial with an antiviral in COVID-19, I think about it in terms of the impact of patients who need to be treated, the prospects for prophylaxis and the application to other viruses.

Trials of molnupiravir in non-hospitalized patients are ongoing, and we expect to know sometime in the fourth quarter of 2021 about the effect of the drug on clinical events. We are quite confident in its ability to have an effect on viral load, but the critical question is what does it do to clinical events?

> The turnaround time — going from neat and cool to ripe and robust — I believe is shortening

We have also just announced the initiation of a prophylactic study of molnupiravir, encouraged by the data that we've seen so far and recognizing this threat of the increased infectivity with the Delta variant.

Antiviral prophylaxis has historically been very hard to achieve. What is different now?

First is the mechanism, and the ability of our drug to induce viral error catastrophe.

But a hard part of these studies in the past has also been recruitment. You don't know in advance if it is going to be a good year or a bad year for influenza, for example. It's horrible that we have this pandemic, but it does create opportunities to do clinical trials in a fulsome way.

On the vaccine front, you shuttered both V590 and V591, your viral vector COVID-19 candidates, after phase I trials. What have you learned from this work, and from the relative success of mRNA vaccines?

mRNA is an important platform that's now clearly validated. And Merck has made a large investment in mRNA vaccines over the past 5 to 6 years, collaborating with Moderna. But the different vaccine platforms — whether it's DNA, mRNA, viral vectors or subunit vaccines — can still be important. The critical thing is to build out the platform and to focus on the right target and the right situation.

When I think about our measles vector vaccine, it did not work in a sufficient way for us to advance it in relationship to COVID-19. But there is evidence to us that this vector system works. The critical thing is not to drop that platform. It is to explore it in the 2–3 settings that provide a litmus test. And that's what we're doing for mRNA as well. With a monovalent, highly immunogenic antigen, mRNA worked great and it worked fast. The question is, how do you expand that? How will it work in a multivalent setting?

What is actually surprising to me is how fast all of those different platforms delivered. Even if you look at subunit vaccines [developed by companies including Novavax] these were actually developed surprisingly fast. And the reason I emphasize this is because the turnover time of technology and platforms may be changing — not just in this arena, but in many other arenas as well.

Whether it's in data analysis, technologies for antibody or drug conjugate production, or protein engineering, the turnaround time — going from neat and cool to ripe and robust — I believe is shortening.

The issue for a large pharmaceutical company is that while we need to focus on products that have unambiguous advantages, we also have to understand the cycle times in relationship to data and technology. For COVID-19, the successful companies went to their wheelhouses. And large pharmaceutical companies who used to think "well, I can buy this later on" might need to change their perspectives if the cycle times are shortening.

People are innovating in all kinds of areas. The race is whether they can tie up the multiple disciplines to get a product to market, or whether the large pharmaceutical companies who have all of those disciplines already can make the right connections and investments and get there first.

Before joining Merck you co-founded Recursion, a company that combines cell imaging and machine learning to advance drug discovery. How do changing cycle times play out with regards to the adoption and application of that technology at Merck?

There are three places where machine learning creates enormous opportunities: genomics data, imaging data and text. And essentially what Recursion has done is focused on cell imaging as a "biomarker" of a phenotypic response to a perturbation, be it genetic or therapeutic. I can't find anybody that has advanced this technology as quickly or robustly as Recursion has.

But a biopharmaceutical company like Merck doesn't have to be at the cutting edge of this kind of technology. What it needs to do is know where that cutting edge is, and when to incorporate it and use it at scale. I don't sit here at Merck trying to out-Recursion Recursion. And as a board member of Recursion, I definitely do not encourage Recursion to out-Merck Merck. That's not a recipe for success.

Are we doing imaging-based phenotypic screening at Merck? Absolutely, every company is doing it. Do we have to build it to the same equivalent as Recursion? No. Pharmaceutical companies need to know where the inflection points are, and when to partner and integrate emerging platforms to augment expertise within their nodes of specialty. And that's what we are doing.

Interviewed by Asher Mullard

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