AN AUDIENCE WITH…

COVID-19 vaccine success enables a bolder vision for mRNA cancer vaccines, says BioNTech CEO

Uğur Şahin, an oncologist and mRNA pioneer, discusses his firm's development plans for cancer vaccines, mRNA-encoded proteins and more.


Credit: BioNTech

When Uğur Şahin read in January 2020 about the emergent threat of SARS-CoV-2, he immediately started thinking about how BioNTech's mRNA platform could be used to rapidly deliver a vaccine. His company and its partner, Pfizer, have since helped to rewrite the vaccine development textbooks. Their vaccine offers 95% efficacy, and secured emergency use authorization from the FDA in record time. The collaborators have delivered more than 700 million doses of their vaccine worldwide. Moderna, the other mRNA vaccine frontrunner, has also shipped hundreds of millions of doses of its vaccine.

This unprecedented feat has transformed interest in mRNA-based therapeutics — and the prospects for the companies who pioneered these. Before the pandemic, BioNTech's lead candidate was a phase II cancer vaccine that was years away from the market. Now, it expects 2021 revenue of €12.4 billion for its COVID-19 vaccine. Researchers and investors, as a result, are lining up to work on mRNA platforms.

For Şahin, this windfall provides a chance to rethink BioNTech's development approach to its first priority — mRNA-based cancer vaccines. Despite high hopes for vaccines that teach the immune system to recognize cancer cells, these have so far failed to yield compelling activity in the clinic. New mRNA chemistries and delivery approaches, combined with recent insights into when to best apply these candidates, were already on track to overcome some of the pitfalls of the past, says Şahin. Bolstered by its COVID-19 achievements, BioNTech can now place bolder bets that could increase its odds of success, he adds.

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Q ***What big lessons have you learned from your success with a COVID-19 vaccine?***

We've gained a number of important insights. It was the first complete chain of demonstration that an mRNA vaccine, delivered in a well-tolerated dose, is able to induce neutralizing antibody responses and strong $CD8^+$ and $CD4^+$ T cell responses. And this translates into all kinds of effectiveness, including protection against disease, severe disease, hospitalization and infection, which is the highest hurdle.

We've learned about the relative robustness of the vaccine-induced immune responses against variants. We've seen real-world evidence not only for the original parental strain, but also against the [Alpha] variant, which has a substantial number of spike protein mutations. We did not even see a significant reduction in efficacy. And we have now also seen this type of efficacy against the [Delta] variant, which is now the emerging variant. This is encouraging.

The other good finding is that an mRNA vaccine is suitable as a booster. If subjects had pre-exposure to COVID-19, these subjects had strong antibody responses to our shot. There are emerging data showing the suitability of these mRNA vaccines after the viral vector vaccines as well, which is also encouraging. And we are also generating data for a third injection booster. One important insight is that repeated vaccination is possible and appears to be well tolerated.

Q ***Prior to the pandemic, your first priority was cancer therapies. How much will you now focus on infectious disease vaccines?***

We were always interested in infectious diseases, but they were not a priority. Now we have an approved product, and we have of course ideas about how to develop other infectious disease vaccines.

For example, the first-generation approved product is a nucleoside-modified lipid nanoparticle-based vaccine. But we are working in parallel on self-amplifying vaccines [in which the mRNA construct carries instructions to make copies of its antigen-coding sequence] and trans-amplifying RNA vaccines [in which one mRNA construct carries the antigen-coding sequence and another carries the instructions to make copies of the first]. Each of these will have its own evolution. I believe that the trans-amplifying technology could have quite a few additional advantages, including reduced dosing that could enable multivalent efficacy.

Q ***Do you expect this work on infectious disease vaccines to impact how much you can focus on cancer vaccines?***

Well, we now have the funding to accelerate our cancer pipeline and make it even bolder. It's not that we are shifting resources, but rather that we can now be much bolder than we were before.

As an externally funded biotech company, we had to make our plans according to our funding. And that means of course compromises for the speed and the depth of our studies. With our new levels of resources, we can ask whether we would do our trials in the same way as initially planned, or whether we can do them in a manner that will provide us with better chances of success.

Q ***How are those discussions playing out?***

This is still an ongoing discussion here. And this is one of the surprises of our success, that we can reconsider our whole plan. But at the end of the day we will have more randomized trials, in more patients, run out of more clinical trial centres. And instead of a sequential de-risking approach, we can

accelerate our development plans and ask five questions at once.

Whereas the traditional approach to cancer drug development is to test new drugs in late-stage disease, cancer vaccines may need to be used in early-stage disease, when patients have functional immune systems. Does your new approach to de-risking include more evaluations of cancer vaccines in patients with early-stage disease?
Yes, absolutely. We believe the superpower of cancer vaccines is really in patients with early-stage disease. We recently started a clinical trial of the cancer vaccine BNT122 in patients with colorectal cancer who have undergone surgery, comparing chemotherapy alone to standard of care plus vaccine. This trial is using circulating tumour DNA as a biomarker. This is sort of a blueprint trial, in which we are enriching for early-stage patients with minimal residual disease. We will likely start a few of these.

Some of your cancer vaccines teach the immune system to recognize 'tumour-associated antigens' that are shared between patients, while others focus on 'neoantigens' that are unique to each patient. Which of these is more likely to succeed?
I believe that both have their place. Shared, non-neoantigen vaccines have been considered to be weakly immunogenic. But we have shown that we can overcome this weak immunogenicity with a nanoparticulate mRNA vaccine that is targeted to dendritic cells. In a recent melanoma trial we showed that in patients who had progressed on checkpoint blockade, the addition of the tumour-associated antigen vaccine BNT111 resulted in a significant percentage of objective responses.

Now, checkpoint blockade primarily activates T cell responses against neoantigens. Tumour-associated antigen vaccines seem to bring in an immune response against non-neoantigens as well, which are otherwise neglected and not empowered by checkpoint blockade. This creates new $PD1^+$ T cells, which we can then re-sensitize with checkpoint blockade. That's one hypothesis.

This would be a completely new approach. These results motivated us to run a phase II trial evaluating checkpoint blockade plus vaccine versus checkpoint blockade alone versus vaccine alone in melanoma patients who have failed prior checkpoint blockade.

We are also now running clinical trials where we combine CAR-T cell transfer with tumour-associated antigen vaccines to stimulate CAR-T cell activity.

Then we have the neoantigen candidates, which we believe could be well suited for patients with early-stage disease, in the neoadjuvant or adjuvant settings. Colorectal cancer is an ideal example because there are no shared tumour antigens in this setting, if you ignore CEA. And because the mutational load in these tumours is relatively moderate to low, this type of tumour does not respond to checkpoint blockade at all. That means mRNA vaccines could be really well positioned here.

We also have a phase II trial evaluating pembrolizumab plus the neoantigen vaccine BNT122 versus pembrolizumab alone in first-line melanoma that will read out in 2022.

Beyond vaccines, there are hopes that mRNA approaches can be used to deliver therapeutic proteins too. How do you think about that opportunity?
We are doing this already. We have one clinical trial already running with BNT151, an mRNA that encodes IL-2. Already, there is a renaissance of interest in IL-2, and there are various companies using pegylated IL-2 to improve the pharmacokinetics of this cytokine. We have created a mutant IL-2 that does not activate regulatory T cells, and by delivering that with an mRNA approach we can further improve the pharmacokinetics. Rather than dosing IL-2 three times a day, we have the opportunity for 3-weekly dosing. We believe that this molecule could be complementary to checkpoint blockade, and we have seen in preclinical testing that vaccine responses are much stronger when combined with IL-2.

We are also working on mRNA-encoded antibodies, and particularly bispecific antibodies. We think these too can overcome problems of suboptimal pharmacokinetics. We have shown that we can go for weekly dosing of bispecifics. And whereas bispecifics tend to form multimers and aggregates when they are stored in vials, we can circumvent that problem. We have invested a lot of effort in coming up with the right backbone for these candidates, and if the backbone works we can just exchange the sequences and could bring multiple candidates into the clinic.

This could be a real door opener for bispecific antibodies. We have some evidence that they are even better tolerated than their original protein-based counterparts.

The beauty of mRNA vaccines is that you turn a 'bug' into a feature: the immunogenicity of mRNA helps prime the immune system. How big a challenge is immunogenicity for mRNA-encoded proteins, cytokines and antibodies?
Immunogenicity is the greatest challenge. We have to see if we have invested enough in reducing immunogenicity. That is ongoing research.

Another way to ask this question is: what are the lower-hanging fruits and what are the highest-hanging fruits of these applications?

The highest-hanging fruits need high doses of a molecule that are injected repeatedly, for months or years, to ensure that you have a protein-replacement effect. We are not yet there, in my opinion. If we can accomplish that, then much more is doable. But you have to solve immunogenicity — both against the lipid nanoparticle itself as well as against the encoded protein. We are working on strategies to achieve this, but it's too early to talk about these.

But the technology will evolve via the development of mRNA-encoded products that are delivered just a few times. And that space will be significantly bigger than the infectious disease and the cancer vaccine space.

Also, although we are talking about mRNA, it's really about delivery. We have to acknowledge that we are reliant on the maturation of innovation from different technologies as well, including lipid nanoparticles and polymer-based delivery approaches.

There has been an influx of investment into mRNA technology as a result of the success of the COVID-19 vaccines. How has this impacted the field?
It's fantastic that the field is now recognized. It feels like the early days of DNA cloning, which resulted in the founding of hundreds of companies. We don't call these recombinant protein companies anymore, and I believe we should not call every company an mRNA company either.

But of course there are technologies that will evolve, including circular mRNA and self-amplifying mRNA. We can't forget that between mRNA and siRNA, there are microRNA approaches. The whole field will benefit.

Interviewed by Asher Mullard

Questions and answers have been edited for length and clarity

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