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Turning Cold Tumors Hot With mRNA COVID-19 Vaccines

**Dr. Blevins:**
Welcome to *COVID-19: On the Frontlines* on ReachMD. I'm Dr. Hallie Blevins, and my PhD is in pharmaceutical science with a focus on medicinal chemistry.

**Dr. Maeusli:**
Hi, I'm Dr. Mimi Maeusli. My PhD is in medical research with a focus on infectious diseases.

**Dr. Blevins:**
Today, we're just getting together to chat about this paper that was published in November 2025 in *Nature.* It was looking at the COVID-19 vaccine and how it sensitizes tumors to immune checkpoint inhibitors—importantly, tumors that have been immunologically cold, which would mean that they don't traditionally respond or aren't expected to respond to immune checkpoint inhibitors. And this study focused on non-small cell lung cancer and melanoma.

**Dr. Maeusli:**
I'll add that what oncologists are really trying to do is take these cold tumors and turn them into hot tumors—so, to have the T-cells infiltrate the tumor cells. And cold tumors are often the case in prostate, ovarian, breast, pancreatic, and brain cancers.

**Dr. Blevins:**
Yeah. To be honest, I don't think I realized how common it was for people to have cold tumors or not respond to immune checkpoint inhibitors. I don't have any clinical experience, but this paper says that this is a really big problem in the clinic and that a lot of people don't respond to these therapies. So, I think that this is a really interesting topic involving how something that's already approved can help improve the response to another therapy that's already approved.

**Dr. Maeusli:**
Yeah. And I think another important and interesting point the investigators pointed out is that there are personalized mRNA cancer vaccines in development, but they're expensive, and then they take a while to produce. And so this would, like you said, really help in getting something that's already on the market and on the shelf available to patients immediately.

**Dr. Blevins:**
Yeah. I agree with that.

Well, let's get into how this all started. The investigators who ran the study first started with some retrospective human clinical trial data, and they found that among patients who specifically had non-small cell lung cancer and were stage three or four, those patients who had received the COVID vaccine within 100 days of receiving or initiating ICI therapy had a longer median overall survival than patients that had not received the COVID-19 vaccine. And it was a difference between around 21 months for patients who hadn't received the vaccine versus about 37 months for patients who had received the COVID-19 vaccine. And this was a pretty similar trend with the three-year overall survival as well.

**Dr. Maeusli:**
I think what's really important and impressive to point out is that's a 17-month difference—so over a year. And if we look at the hazard ratios, basically, what that translates to is that this mRNA COVID-19 vaccination was associated with an approximately 49 percent lower risk of death compared with those who didn't receive vaccination.

**Dr. Blevins:**

Yeah. The other thing I wanted to mention was that this was pretty consistent for stage three and four as well as for patients who had received just the priming, just the booster, or the priming and the booster within 100 days. And it's also regardless of manufacturers. It's pretty consistent.

**Dr. Maeusli:**
They also tested this hypothesis against pneumonia and influenza vaccines within 100 days of initiating those immune checkpoint inhibitors, and they didn't experience the same overall survival benefit. And so what this really says is that this is specific to these mRNA vaccines.

**Dr. Blevins:**
Yeah. That's a good point.

**Dr. Maeusli:**
And I think the last thing that I wanted to add here is that they also looked at whether narrowing the vaccination window to 50 days from 100 days had any difference in overall survival. And what we saw was that there was a similar overall survival. So really, it's an effect that can be seen within the 100-day window.

**Dr. Blevins:**
I thought that was interesting. You would think, maybe if you're looking at this effect from an outside lens, that getting the vaccination closer to ICI initiation would enhance it, but it's pretty similar, which I thought was really cool.

They also found that this was similar with metastatic melanoma. The median overall survival for patients who had not received the COVID vaccine was 27 months versus it not being met for patients who had received the COVID-19 vaccine. Very interesting. Also, this was pretty similar with the median progression-free survival of four months with patients who didn't receive the vaccine versus 10.3 months with patients who had. So, it's pretty similar in both disease types.

But these are the things that they observed in the clinic. Of course, it's not causation; it's just observational. So, they wanted to get into the nitty gritty and figure out, why is this happening? Is it correlated? Is one thing affecting the other? And that gets into the mouse studies.

So, from what I understand, these investigators used the spike protein to make their own mRNA COVID vaccine in their own lab. Based on the human studies, they used the cell line B16, which is a melanoma immortalized cell line, and Lewis lung carcinoma cells to implant mice with these tumors to replicate those two human studies that we just talked about. And then they treated the mice with immune checkpoint inhibitors with or without vaccination as well as the COVID-19 vaccinated mice. So they had one of every group.

**Dr. Maeusli:**
I actually had something that I wanted to ask you about, Hallie, based on your background. Basically, I see here that they designed their own mRNA constructs in this lipid nanoparticle system. Is that something, to your knowledge, that is done for the COVID-19 vaccine? Or is that a way in which they do that for just the lab?

**Dr. Blevins:**
Yeah. For the mRNA vaccine, the COVID vaccine is also in nanoparticle form.

**Dr. Maeusli:**
Okay. I wasn't sure about that. Thank you.

The first, most important question that they had asked is whether treatment with the RNA lipid nanoparticles and the immune checkpoint inhibitors would inhibit tumor growth. And so they did see that, measured by lung weights in the mice, correct?

**Dr. Blevins:**
Yeah. For both the B16 melanoma tumors and the subcutaneous LLC tumors, they noticed that the combined treatment of the COVID vaccination as well as the ICI treatment had the best outcome for decreasing tumor size.

**Dr. Maeusli:**
So, after they basically verified that the tumor growth was inhibited, they were curious about looking into the type one interferon signaling and seeing how this mechanism actually plays out. The first step that they did was block type one interferon signaling, which completely abrogated the inhibition of the tumor growth. And then, they also did the opposite of this, which is adding large doses of the type one interferon to stimulate the anti-tumor effect. So, I think what was clever in this sense is that, by doing so, they realized that the interferon signaling is required for the vaccine-mediated anti-tumor effect.

**Dr. Blevins:**

I saw this throughout the paper too, and I was initially confused about it, but when I think about it, it was kind of interesting. You're right that when they blocked the IFN receptor, it abolished that anti-tumor activity. They also tested IL-1, which they pulled from a different study. They had suspected that it might have some impact, but it didn't have any impact. So, IFN was the primary driver of this anti-tumor effect. The blocking worked. But when they administered the IFN at high doses to the mice, they actually did not see a response.

And that continues throughout the paper, which I thought was interesting because if they're buying in on this story that interferon is the reason for this activity, then you would think that administering interferon would replicate that antitumor activity. But from what I understand, the interferon dose is like a one-time dose, whereas what we're getting ready to talk about is that the lipid nanoparticle in the COVID vaccine elicits more of a cellular response as well where it triggers antigen presentation cells. It's got more of a well-rounded immune response. It's not fully reliant on interferon, even though interferon plays a massive role. That was something that I thought was interesting.

**Dr. Maeusli:**
That's an excellent point. The other thing I want to bring up—probably leaning more towards something that you may have experience with—that I thought was very interesting and, again, clever, was when they swapped out the *N*1-methyl-pseudouridine with uridine.

So, if I understood this correctly, mRNA vaccine strategies swap uridine for *N*1-methyl-pseudouridine to suppress innate immunity, thereby maximizing antigen expression and driving this adaptive immunity. But in cold tumors, if I understood correctly, it's the lack of innate immune activation that is the problem. So, what was clever here is—and I believe this is something they've also done in more standard vaccine development—the investigators swapped this *N*1-methyl-pseudouridine back to uridine to try to boost innate immunity and anti-tumor immunity with the immune checkpoint inhibitors.

**Dr. Blevins:**
Yeah, you're right. That's what I understood as well. I thought that was really interesting too because you would think that it would boost it quite a bit, but they say that it only provided numerical improvement in anti-tumor response.

Before we move on, I first want to talk about how during the mouse studies, after they figured out it was interferon, they then did some ELISA assays with the plasma from some of these mice and found that IFN Alpha specifically was the primary driver.

I wanted to touch on something else really quickly. So, when they replaced the mRNA from the spike protein with a different antigen, it showed that it was just mRNA itself. But what they don't really understand is how that results in an IFN activity. IFN activity primarily stems from what they say is activation of the receptor MDA5, and MDA5 detects double-stranded RNA, which is primarily produced by viruses and things like that. So, if we've got a single-stranded mRNA activating a receptor that only recognizes double-stranded RNA, that's kind of strange.

And they know that the COVID vaccine that's already on the market can occasionally have traces of double-stranded RNA—very small amounts. And they found that their formulation also had very small amounts of double-stranded RNA, but they removed that and found that there was no difference in their outcomes and what they were seeing in the results.

But when they looked a little deeper, they found that their RNA lipid nanoparticles in their vaccine were forming some type of secondary structures, which resembled the weight of double-stranded RNAs. And so that's what they think is causing the activation of this MDA5 sensor. It thinks that it's a double-stranded RNA, but really, it's just a secondary type of structure of the single-stranded mRNAs, which I thought was really interesting.

**Dr. Maeusli:**
I appreciate that you explained that part because it did confuse me. Breaking that down was extremely helpful.

**Dr. Blevins:**
Oh, good. I'm glad. They also looked at another receptor that senses double-stranded RNA, and it was not activated. So, it's clear that it's not the double-stranded RNA that could or could not be in the vaccine formulation that's activating MDA5. It's probably the secondary structure. But again, this is a theory; I just thought it was neat.

**Dr. Maeusli:**
I think what's important to talk about in this next step is how the investigators were able to tie the mechanistic drivers that are consistent with this theory of the immune priming and how that involves, essentially, adaptive immunity afterwards. At a high level, from my understanding, they were essentially able to support that the interferon alpha activates the antigen-presenting cells in the lymph nodes and spleen, which primed the CD8 T-cells, so that's bringing in the adaptive immunity.

So, these activated CD8 T-cells release an inflammatory response with the interferon alpha, and that essentially stimulates the tumors to

respond by increasing PD-L1 expression. So, essentially, the PD-L1 is activating the brakes on the T-cells by binding into the PD-1, and then that's what allows for the immune checkpoint inhibitors to come in and block the brake system of the PD-L1.

**Dr. Blevins:**
That is pretty much the overarching mechanism of what they found. Beautifully said, Mimi.

So, they see a lot more CD8-positive T-cells that are tumor reactive. They are responsive to the tumors that are growing, and that caused more CD8-positive T-cells to go the tumor to help fight the tumor cells.

But like you said, the PD-L1 and the PD-1 are upregulated, and they are there. So, the tumor is basically telling the immune cells, "Don't worry, I'm supposed to be here." That's where the immune checkpoint inhibitors come into play, and they are able to block that interaction and release the wrath of the CD8-positive T-cells.

One thing that I thought was really interesting is that for the COVID vaccine, the formulation that the lab had plus ICI combination treatment increased the PD-1 expression in those tumor-infiltrating CD8-positive T cells more than 20-fold to the control mice, which is pretty significant.

**Dr. Maeusli:**
For those just joining us, you're listening to *COVID-19: On the Frontlines* on ReachMD. I'm Dr. Mimi Maeusli.

**Dr. Blevins:**
I'm Dr. Hallie Blevins.

**Dr. Maeusli:**
Today, we're exploring how mRNA COVID-19 vaccines sensitize tumors to immune checkpoint inhibitors.

As we wrap up the murine studies, we are moving on to looking at data within humans. What the investigators did here was to confirm that this signaling pathway with interferon alpha is mirrored or reflected in humans as was seen in those mouse tumor models.

**Dr. Blevins:**
Yeah. The first thing they did—I assume it was the fastest thing they probably could do—is they just found five healthy volunteers excited to donate some blood after they get their COVID vaccine, and they just looked at the cytokine profile of what the healthy volunteers were producing after their COVID vaccine.

What they found pretty much matched what the mice were saying, which is that IFN alpha was the most upregulated cytokine, and it increased by an average of 280-fold compared to their baseline. And it was 280-fold at 24 hours after vaccination. It had some other cytokines that were involved, of course, but interferon alpha was exactly what they wanted to see.

And then, they also found that when they did flow cytometry that the cells were also increasing, there was increased expression of PD-L1 on the myeloid cells, which are in the innate immune system. So, it's in line with what they're seeing from the mouse studies.

And it's worth noting that they also repeated the study with a different mRNA COVID vaccine, which contains less mRNA than the COVID vaccine already on the market. And the cytokine profile was similar, but it was reduced, which was interesting because that would suggest a dose response to the mRNA.

**Dr. Maeusli:**
You bring up a really good point there. So, once they had confirmed some of these signals in the healthy human volunteer samples, they went back and started looking into RNA vaccines within the patients with non-small cell lung cancer. It was retrospective data. So, the purpose of this was really to confirm whether the PD-L1 hypothesis in the mice was relevant to human tumors. So, we moved from the healthy volunteers to looking through pathology reports in the patients with non-small cell lung cancer.

They wanted to evaluate whether the patients who received the COVID-19 mRNA vaccines expressed higher tumor PD-L1 in their pathology reports. One thing that was maybe intuitive to you—I'm not an oncologist, but one thing I wanted to point out is they evaluated biopsies that reported their tumor proportion scores, or the TPS. That's the percent of viable tumor cells that are PD-L1-positive. And so when they were reporting data, effectively, we can look at the TPS as a proxy or a measure of PD-L1.

**Dr. Blevins:**
Yeah, that's what I got too.

**Dr. Maeusli:**
So essentially, what they were able to discover by taking three groups—they looked at patients who had received the mRNA vaccine less than 100 days before biopsy, over 100 days before biopsy, and then those who didn't receive the COVID-19 vaccine. And what they

found was, effectively, that the vaccine timing matters and that that signal of the PD-L1 expression is transient, so to speak. What they found was that the tumor PD-L1 expression was increased only when the COVID-19 mRNA vaccine was given more recently, so less than 100 days, and that effect was absent in pathology reports for patients who had received the COVID-19 vaccine at least 100 days before their biopsy.

**Dr. Blevins:**
Yeah. In one of their figures, they point out that PD-L1 expression decreases over time, which is to be expected; it's a vaccine, so you get a spike in immune response, and then you level out over time. But my thought here is, how does this go if there's no long-term data? If the patients are showing really good results now, in a few months, they might not have that same PD-1 and PD-L1 expression, and therefore, they might not be responsive to ICI therapy as well.

And this is a particular problem because when they talk about how TPS of 50 percent is a clinical threshold to determine whether patients are eligible for a single-agent immunotherapy instead of chemotherapy, patients who received the COVID vaccine were 29 percent more likely to exceed or meet that 50 percent threshold over patients who are not vaccinated. So, this puts those patients in that category to receive that ICI treatment, which is good in a way. But if the vaccination is not accounted for in their charts, does that set them up for not responding to their therapy later on when they lose that PD-1 and PD-L1 expression?

So, I think it can be taken either way; again, I'm not clinical. I think that this is really good to know in terms of treating patients now, and a good heads up to look for when you're treating patients. But I'm not sure, without repeated vaccination, how that treatment holds up in the long term, if that makes sense.

**Dr. Maeusli:**
You bring up an excellent point, and if you think about the importance of timing of the vaccine in the study, I think what would be interesting is how many times can you get the COVID-19 mRNA vaccine. Even if they're not giving the COVID-19 mRNA vaccine, it could be a different one. Maybe you need to formulate something where you can stimulate this effect repeatedly in a safe manner in these patients.

**Dr. Blevins:**
Exactly. I think that was something they hinted would be interesting for future development. We talked about how personalized vaccines are taking a lot longer to get approved and manufactured, and they're probably going to be pretty expensive, I would think. But if we can make a generalized mRNA vaccine that has just a general tumor antigen, at least the mRNA is there, and at least maybe it could be given in conjunction with ICI therapy whenever ICI therapy is given. I thought it was interesting.

It's something that I wanted to flag because I think this paper is really good for future developments and where we go with mRNA vaccines from here, and it opens this area to other possibilities, but it's also relevant to what we're seeing in the clinic now. So, if you have a patient who has recently had their COVID vaccine, and you're trying to figure out whether they're eligible for single-agent immunotherapy, and it says they are, maybe check them again later on in a few months to see if they still are responsive to their immunotherapy, or maybe be on the lookout to make sure that they stay responsive to their immunotherapy.

**Dr. Maeusli:**
That's a really important point, and I'm sure that the investigators are considering that. I read somewhere that they are going into clinical trials with this hypothesis in mind.

**Dr. Blevins:**
That’s good. The last thing I wanted to mention was that they did generalize this to all tumors. They took kind of a bunch of data from a variety of primary site tumors and histologies, and they still saw that COVID vaccination within 100 days was associated with an increase in TPS. So, I think that this could be generalized to a few different tumor types and maybe some more than others. I feel like that's a good avenue for future research as well—to figure out if it's different for different tumors or if it's generally the same.

**Dr. Maeusli:**
I have so much respect for oncologists and cancer scientists. It's something that is such a complex set of diseases, and, I study more of the bacterial side, which is the simple system for a reason.

The last thing before we wrap up—the last section is where they took all of these ideas together and checked whether these RNA vaccines can restore immune checkpoint inhibitor sensitivity in patients with cold tumors. So, this part was also retrospective, and they were looking at the stage four patients who had pathology reports with low baseline PD-L1 expression. In theory, these would be people who would typically respond poorly to these immune checkpoint inhibitors. These patients were vaccinated within 100 days of starting immune checkpoint inhibitor therapy.

When they looked back at the data, they saw that the overall survival was comparable to patients who had baseline PD-L1-positive tumors and TPS scores greater than one percent. So, this really brought the whole study together and is consistent with the restored immune checkpoint inhibitor sensitivity theory.

**Dr. Blevins:**
That's super cool.

**Dr. Maeusli:**
Yeah. And one last thing that I thought was interesting—I'm wondering if their reviewers asked this or they had received this because of the timing of when these pathology reports were taken—basically, they wanted to rule out confounding changes in cancer care during the pandemic era. Essentially, what they found out is that there was no difference in the unvaccinated patients with low PD-L1 before and during the pandemic; they showed poor outcomes. What they found at the very end is that this survival benefit is associated with the vaccination instead of the pandemic-era-related treatment changes.

**Dr. Blevins:**
I think that's an important distinction to make as well.

**Dr. Maeusli:**
Also, I think it's important that we highlight the clinical implications, maybe as one last thing before we wrap up. I wanted to restate what you said earlier when we started that conversation—that the COVID-19 mRNA vaccines are readily available on the market and on the shelf. It would reduce the cost relative to developing personalized mRNA vaccines for these cancer patients.

So, what these investigators found could be something that is very important for these patients and does potentially have a meaningful effect on their survival. It'll be really interesting to see what they do next.

**Dr. Blevins:**
I agree with you. Anything that studies drugs that are already available on the market, I feel, is research that can be immediately applied in the clinical setting. Again, I don't have a clinical background, but I would imagine that's probably the way this is being approached.

On top of that, it's going to make clinicians aware of vaccination records for when they're initiating patients on ICI therapy. And I think that it opens doors on where to go with mRNA vaccines—for future development, especially to optimize manufacturing processes, cost effectiveness, and things like that. There were a lot of good points in this paper; I really enjoyed it.

**Dr. Maeusli:**
I'll add one last thing I think will be interesting in terms of future studies. They looked at the 100-day window, right? But this involved starting immune checkpoint inhibitor therapies and then getting vaccination within 100 days. But it would be interesting to go back and see, if you get it five or 10 days before immune checkpoint inhibitor therapy, whether that kind of timing has an effect on sensitivity to immune checkpoint inhibitors as well.

**Dr. Blevins:**
Well, this has been so fun. Thank you, Mimi.

**Dr. Maeusli:**
Of course. I learned so much from you, Hallie. I'm really grateful for the opportunity to talk this through with you.

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