Understanding mRNA Covid-19 Vaccines

Messenger RNA vaccines, also called mRNA vaccines, are some of the first COVID-19 vaccines authorized for use in the United States. mRNA vaccines are a new type of vaccine to protect against infectious diseases. They teach the cells of our body to make a protein that triggers an immune response. This immune response leads to the production of antibodies which protects us from getting infected if the real virus enters our body.

We are sitting down with Dr. Drew Weissman, who with his former colleague Katalin Kariko, developed the mRNA technology enabling the creation of the Covid-19 mRNA vaccines, to learn more about the science behind mRNA, the technology and his journey.

Dr. Weissman is a professor of Infectious Diseases in Penn's Perelman School of Medicine and has been working on using RNA in vaccines for more than 15 years.

Full Transcript:

Priya Menon: Hello and welcome to Cure Talks. I'm Priya Menon and today we are discussing Messenger RNA Covid vaccines. Joining me on the Cure Talks panel is David Stanley, Matt Goldman and Dr. Herbert Geller. Our featured guest for today is Dr. Drew Weissman, Professor at the University of Pennsylvania. Dr. Weissman co-developed, the messenger RNA technology being used in the covid-19 vaccines produced by Pfizer, Biotech and Moderna. Dr. Weissman, welcome to Cure Talks, thanks for joining and taking the time to speak with us today. So, I think we can begin with a brief history of this type of vaccines, that is the mRNA vaccine now being used in Pfizer and the Moderna and you have been working on this for quite a few years. So, it'd be great, if you can give us a little bit of history of how this vaccine works.

Dr. Drew Weissman: Sure, so I came to Penn 23 years ago and met Katalin Kariko at a copy machine and I've studied dendritic cells and vaccines and she studied mRNA but wasn't getting very far and nobody in the RNA field was advancing. So, we started to investigate RNA in the immune system, and we figured out that RNA was highly inflammatory and that was problematic. Because if you give RNA to a patient, you don't want to get sick from the RNA. So, we figured out what made it so inflammatory and then we figured out how to avoid that inflammation and that was our breakthrough in 2005, it's called nucleoside modified mRNA. And what we essentially did is we changed the RNA, so that the immune system in our bodies didn't recognize it as foreign. And that's the RNA that's used in the Moderna and Pfizer biotech vaccines.

Priya Menon: So, you are mentioning the initial problem with these vaccine was that when you were doing your research the mRNA was highly inflammatory, but with the small tweak, you able to incite the right amount of immune response and protein production.

Dr. Drew Weissman: Exactly and we actually got rid of all the immune recognition and that greatly increased the amount of protein made.

Priya Menon: So, do you think like do these mRNA vaccines have an advantage over the other type of vaccines and if so, what are some of these that we're seeing in for covid-19?

Dr. Drew Weissman: So, the two RNA vaccines the Moderna and Pfizer are the first ones licensed. So, this

is the first comparison that we've got. And the comparison is 6 months old. So, it's hard to say are they better, did they have advantages. What we do know is one of their advantages is that they're incredibly quick to make. So, if you have to make an inactivated virus vaccine, that's a lot of work. You have to figure out how to grow the virus, how to inactivate, it how to purify it, how to make sure it's safe. With RNA you only need the sequence of the protein of interest. So, for Coronavirus, that's the spike protein and we've known for over 20 years that the spike protein is the principal vaccine component. So, the day that this sequence was released on January 12, we made an RNA vaccine for it. So, it's very quick. It's also very effective. We've seen that in the clinical trials and in the patient's used 90-95 percent efficacy against any symptoms and hundred percent efficacy against serious symptoms and death. There are a lot of unknown still and will learn those over time.

Priya Menon: Doctor, the new Covid variant, we are seeing across the world, how effective do you think mRNA vaccines would be?

Dr. Drew Weissman: What we know so far is that the RNA vaccines still appear to be effective against all other variance so far. What we don't know is what's going to show up in the future, more variants are going to occur until we can vaccinate the entire world, variants are going to keep appearing. So, the concern is that in the future a variant might appear that the vaccine is completely useless against. For mRNA vaccine, it's very simple to make an update of, a booster and improvement. I was talking with Uger Sahin who runs Biotech who said it would take them six weeks to have a new vaccine in patient's arms. So, RNA allows you to very quickly update vaccines which I suspect will be important as new variants appear.

Priya Menon: Dr. Weissman, panel has great questions lined up for you. So, I'm going to let them start with their questions. David, please ask your questions.

David Stanley: Okay, my turn. All right. So, Dr. Weissman, I'm familiar with Dr. Nubik's work at MSU on mRNA interruption. And I know, it's very different the way these treatments, the way these inventions work. But do you think mRNA manipulation is a holy grail for other diseases as well?

Dr. Drew Weissman: I think it's too early to say that and I think you're asking a father whether they like their children. So, I think the therapeutic platform has enormous potential. It's worked unbelievably well for Covid in two different companies' hands. We're doing clinical trials for five more pathogens right now Biotech and Moderna are doing additional clinical trials. RNA vaccines are in Phase 2 clinical trials for cancer as personalized vaccines and have really shown great success or better success so far. RNA Therapeutics, monoclonal antibodies are being delivered with RNA. So, it has enormous potential and my guess is that it's going to be a turning point in medicine, but you will have to see.

David Stanley: Okay, I mentioned to a friend who does virology that I was going to be speaking with you. They shared the study; I think it was Canadian that came out in January about blood types and it was correlated with susceptibility and morbidity and mortality. What's your take on that? Is that study something that's worthwhile and should be pursued or is this just something that it's like another case of correlation is not causation?

Dr. Drew Weissman: We don't know yet. I mean, it's pretty clear that certain blood types A in particular has increased risk from infection. We see this with a lot of diseases where there are genetic associations with disease that position and severity. So, I take it very seriously, and I think it deserves more research to understand exactly how that happens.

David Stanley: Okay. Now we were talking a little bit about variants of the covid-19 popping up pretty regularly because of course evolution likes that sort of thing. Do you feel that the vaccine is going to be pretty adaptable because sooner or later one of those variants obviously, it's going to pop up that the vaccine that we're currently using isn't going to be effective against right?

Dr. Drew Weissman: Yeah, so there's a lot variance they keep appearing, they're going to keep appearing

until we can vaccinate the world. The only way to stop the variance is to stop the virus. So far, the main variants that vaccines work less well against are the South Africa, the 135. Although the Brazilians are likely to fall in that category as well and new ones keep appearing. What I've seen at the data the vaccines, the RNA back scenes are still effective against the South African in Brazilian variance. But you're correct at some point variance is going to appear. It's going to be like influenza where variance keep appearing that are resistant to vaccines. We're going to have to either figure out better vaccines for the long term. So, what moderna and biotech are doing right now is they're making a booster with the South African variant. And that's great. It'll take care of the South African variant, but it probably won't take care of the next ones that appear. What we're working on is making a booster, a new vaccine that takes care of all of the variants that have appeared. And any variants that might appear in the future and I think that's a better approach. The Moderna approach to making a South African variant is quick. The FDA already said they won't require efficacy trials; our vaccine is going to require efficacy trials. But it's going to be years before the world is vaccinated, so I think we have to think in the future on how to prevent all variants to stop this.

David Stanley: I have two more questions. They're both I think pretty quick. Before you came on, we were talking about our second dose side effects. I felt a little lousy, a couple friends of mine felt terrible, my wife felt nothing. Dr. Geller's wife was very sick. Is there any data that relates these second dose side effects with manufacturers, or this is just in case of immune systems are funny and they are individual?

Dr. Drew Weissman: So, if you look at the side effects 80 to 90% of people get sore arms, swelling at the site and a smaller percentage gets systemic effects. This is telling us that the vaccines are working. This is the immune system responding to the vaccine. It has nothing to do with manufacturing. It has nothing to do with contaminants or any other problems with the vaccine. They appear to be purely our immune system responding. So, in my mind, it's a good thing if you have an adverse event because it means the vaccine is doing its job. Not to say that we are working on newer vaccines that have fewer of these adverse events, so that the vaccine is better tolerated.

David Stanley: Got it. Thank you for clearing that up too because there's a lot of talk out there obviously about it. The conspiracy theories are wild. This is my last question, Dr. Weissman. I have some familiar arthritis in my CMC joints right, at the base of my thumb. And I seem to have gotten like within 12 hours of my second shot, I really got some severe arthritic flare-ups. Is this the sort of thing that you might expect when my immune system gets amped up from that second shot?

Dr. Drew Weissman: Yeah, we just don't know. I mean look at the vaccines in the phase 3 clinical trial, people with arthritis and autoimmune diseases weren't included in those trials. So, we don't know that there's no scientific evidence from any animal studies or earlier human trials that the vaccines will cause a flare in an autoimmune disease. But that's not to say it may not happen when your immune system is amped up, is boosted by your back seen there's a potential that it will recognize other antigens, autoantigens that it regularly recognizes. So, this is something that needs to be studied.

David Stanley: Because I feel fine, I felt fine really. Yesterday was the first day my second booster was on Tuesday night and my thumbs were fine again yesterday. So, three four days, of some arthritis pain is worth it, but I wondered if there were any other kind of implications exactly what you went to with the autoimmune discussion. Priya, those are my questions. Thank you. Dr. Weissman.

Dr. Drew Weissman: And also, to know that some of the adverse events from the vaccine are arthritic type of complaints. So, this could be completely unrelated to your ongoing arthritis, and they simply be another adverse event of the vaccine.

David Stanley: Got it. Thank you, sir.

Priya Menon: Thank you, David. Next on the panel we have Matt. Matt, please go ahead and ask your questions.

Matt Goldman: Okay, first of all, Doctor, thanks for your time. As far as we know at this point are mRNA vaccines less effective on cancer patients or even more specifically blood cancer patients? I'm hearing a lot of both side of coin on this.

Dr. Drew Weissman: So, there's a big clinical trial of a personalized RNA vaccine on going across the world. This came out of earlier work that was melanoma work where they made personalize RNA cancer vaccines for patients who had an expected survival of approaching zero. And the results of those trials were, I think it was around 25 to 30 percent achieved remission, some complete remission, which to me is a fantastic improvement. It's not as good as Car Ts with liquid cancers, but for a vaccine against the disease that has no hope of cure to get 25 to 30% clinical remission is fantastic. We're still early in RNA cancer vaccines. We're still learning how to make them best, how to choose the right immunogens, how to deliver them, what to deliver them with, checkpoint inhibitors etc. So, that to me, that's a pretty good start and I think we're going to be learning more and improving cancer vaccines in the future.

Matt Goldman: But in terms of the effectiveness of the coronavirus vaccine on cancer patients and blood cancer patients, is there less effectiveness for them with the vaccines that you've been working on?

Dr. Drew Weissman: Certainly, for anybody with an impaired immune system of vaccine is not going to work as well. So, if anybody that's had their B-cells depleted with CD19 antibodies or CD19 Car T's, they're not expected to make much of any antibody response. They'll still make some T-cell response which offers some protection. We don't have good data yet, but the more immunosuppressed the person is, the less well they're going to respond to a vaccine and there's nothing we can do about that. Because when your immune system is impaired when it doesn't work well you just don't respond well to vaccines.

Matt Goldman: But one should still get vaccinated, nonetheless, correct?

Dr. Drew Weissman: Yeah, even the worst vaccines in clinical trials still protect people from serious disease and death. So, any response you get from the vaccine I think will help you.

Matt Goldman: And is it the genetics of the… because I'm a multiple myeloma patient. Is it the genetics of the cancer or I'm on an amino therapy now, which a lot of people are, myeloma patients, it's really effective? But is it the workings of the treatment overall or is it the cancer itself that's sort of changing our immune system and making us less viable I guess patients for the coronavirus vaccine to be effective?

Dr. Drew Weissman: So yeah, what we know is that multiple myeloma, CLL, other liquid tumours impair the immune system. They impair the bone marrow, they impair immune responsiveness, and that's the effect. So, if you've got somebody with CLL or AML that's been cured, their immune system will work nearly as well as a normal individual. If you've got somebody with active disease their immune system is impaired.

Matt Goldman: And so, for vaccinated cancer patients, a lot of folks that have normal immune systems are getting vaccinated, they are feeling like they can go back to living a somewhat normal life. But for cancer patients and immune-compromised folks, are they waiting for a certain of percent of the population to be vaccinated or herd immunity? What are they looking at in terms of return to normalcy?

Dr. Drew Weissman: Yeah, so that's a hard thing to address. The first is that we don't know how good a single patient is going to respond to the vaccine. And there's probably a lot of variables and somebody with multiple myeloma on immunotherapy that has a good response, they're probably going to respond better to somebody who has much worse disease. So, for an individual patient, we don't know how well they're going to respond and how well they respond is going to correlate with whether they'll get the disease, what the efficacy of the vaccine is. So, on a population basis we know that people with active cancer have reduced immune responses, but for each individual patient, we just don't know what that means. Ideally, we want to reach herd immunity in the United States and the world to slow this and to stop this pandemic. Once that occurs people can go back to normal. My guess is that in any way I tell this to my immune deficiency patients as well, you need to really wait for herd immunity to be achieved before you can go out without a

mask and return to your normal life. I don't know how well those patients are responding to the vaccine, but I say that out of caution because I don't have the answers.

Matt Goldman: And sort of related to something that was mentioned earlier, is it correct or incorrect for a patient to infer the efficacy of the vaccine if they have zero response to the first hand or second shot?

Dr. Drew Weissman: We've seen no correlation between adverse events and how well you respond. So, it's not that people that have no response didn't respond to the vaccine. They were lucky enough not to have adverse events. So, no data has been released that associates with that.

Matt Goldman: Okay, that's all I have. I definitely appreciate your time. Thank you.

Dr. Drew Weissman: Thank you.

Priya Menon: Thank you, Matt. Next, we have Herbert here, who was a prostate cancer survival. Herbert, please ask your questions.

Dr. Herbert Geller: Right. Thanks for joining us, Dr. Weissman. My first question would be what do we know about the duration of action of the immune response? Meaning, we're only six months into this. So, we really don't have any long-term data.

Dr. Drew Weissman: No, you're exactly right and you actually have to look at it two ways. So right now, Moderna, Pfizer Biotech are measuring antibody levels over time and in the latest data from Pfizer shows that at six months people are well-protected, antibody levels are high. We can predict that means that at a year they'll probably be well protected, but we don't know is the vaccine going to last a year, five years, ten years. The other issue is that a vaccine does two things, it makes memory and it makes effector. So, active antibodies and T cells, they are only measuring active antibodies in the blood. There are memory B cells that respond very quickly. And for all we know you could have zero antibodies in your blood. But if you've got good memory cells, you'll make a response fast enough and you are completely protected. So, it's really going to be following people over time and seeing when do they start getting disease again, and that will tell us when the vaccine needs to be boosted.

Dr. Herbert Geller: All right. So, yeah, I mean the other question is related and that is what these vaccines are all against the spike protein and when we are using mRNA, you're using a discrete region of the spike protein versus the traditional method where you're using potentially a larger segment. So, are there regions of the spike protein for instance, which are less subject to mutation, that would be better targets, or do they happen to be the ones that are not immunogenic?

Dr. Drew Weissman: That's a great question. So, another thing that my lab is doing is we've been working on a pan coronavirus vaccine and what that means is that, there have been three coronavirus epidemics in the past 20 years. It would be foolish to not think that we're going to have more. We're definitely going to have more coronavirus epidemics and potentially pandemics in the future. So, what we started doing last summer is trying to make a vaccine that would prevent or protect against any bad coronavirus has that have the potential to infect humans. The way we're doing that is we're looking at conserved regions of the entire virus as well as conserve regions of the spike protein, and we're trying to make vaccines that induce those responses. We had some success; we've made a vaccine that can prevent SARS which was the first coronavirus we know about and covid-19 as well as all of the bad coronavirus we've tested. So, it looks like we have the potential to make a pan coronavirus vaccine. But you're right, it's identifying the right immunogens, the right regions of spike and the entire virus to use in a vaccine.

Dr. Herbert Geller: Getting back to a continuation of one of the previous questions about cancer vaccines. I mean mRNA can be essentially ordered with any sequence you want and so there are lots of potential antigens on the surface of various cancer cells. However, I mean liquid tumour seem to be much more susceptible to immunotherapy than solid tumours in general. So, do you think mRNA techniques can

overcome that or you think we still have to deal with other issues like exhaustion and things like that?

Dr. Drew Weissman: So, the clinical trials that are ongoing are looking at all of those issues. The first one was melanoma, which is a solid tumour that responded. Well, the clinical trial includes many different types of cancer including breast, colon, lung and renal and others. The part of the trick is that tumour cells are cells that have mutated. So, identifying the right antigens that will kill the tumour cells but not kill our own good cells, there's a problem. So that's being investigated. The vaccines are being combined with what are called checkpoint Inhibitors, which are antibodies against antigens that tell our cell to become senescent, to the stop working and by blocking it you wake up those cells. So, it's a multifactorial approach to making a good cancer vaccine and they're in clinical trials, they're showing effectiveness, they're being improved. I have great hope for the future.

Dr. Herbert Geller: I mean in general; vaccines are one way but there's actually lots of different immunotherapy approaches these days in the therapy of cancer. I mean Car T cells, by specific antibodies, you have any sense of which is the most likely to be successful? You think they're all eventually going to be figured out?

Dr. Drew Weissman: That's a very complicated question and I don't have time to answer it fully. But that there are many immunotherapies, the Car Ts against liquid tumours are fantastic. They have not worked well against solid tumours. We're trying to figure out why that is and ways of making them work better. So, my guess is that we're going to need many different immunotherapies, Car Ts, bites, cytokines and vaccines to interrogate all of the different types of cancers and see which one's work best for each type of tumour.

Dr. Herbert Geller: All right, and then one last question from me for now, I mean getting back to the Covid situation. Is there a difference in the antibody repertoire between mRNA-based vaccines and attenuated virus vaccines?

Dr. Drew Weissman: So, there are a couple of differences and then this hasn't been investigated well yet. We've investigated in animal models what we see is that the RNA vaccines give much higher levels. So, even in the phase 3 trials the level of antibodies and vaccinated people were about five times higher than convalescent patients. Other vaccines, the antidotes typically give level similar to the convalescent patients. So, the RNA vaccines make higher levels of antibodies. As part of that some of those antibodies neutralize the virus, kill the virus before it can infect a cell, those levels are also higher. We're looking at specificities. So, particular parts of the spike that the vaccines can recognize, and we've identified some that RNA induces well, that infection doesn't induce and some of those are conserved antigens that may offer broad protection. So those are new and ongoing studies. In general, the RNA vaccines are better than most other vaccines. They give higher levels of antibodies.

Dr. Herbert Geller: Okay. Well, thank you for now. I'll let my co-panellists continue.

Priya Menon: Thank you, Herbert. Dr. Weissman, I had one more last question. I just want to circle back before the internet cut me out. So, I think you just touched upon how mRNA insights response. But my question is why do we need two shots to make mRNA vaccines create more antibodies or why is there a more pronounced reaction after two shots? And what is shows about delaying the booster dose?

Dr. Drew Weissman: Yeah. So, those are great questions, but we don't have answers to all of them. We've developed probably over 30 different vaccines using mRNA for everything from Zika to Ebola to genital herpes, HIV, influenza, hepatitis C. Some of those vaccines work well with a single injection other require multiple. If you look at the phase 3 trials both the Moderna and the Pfizer vaccines are 80% effective after a single immunity. What we don't know and what the concern was that how durable that response is and that gets into basic immunology. And in basic Immunology the first time you see a pathogen or an antigen, the response is limited and it's usually not very potent and the immune system requires a boost, a second vision of that pathogen to make a better response. And that's why most vaccines are given two, three, four times to boost and to improve the response. We see the same thing with RNA, the titters, the level

of antibodies goes up about 10 to 20-fold when somebody gets a booster. And that's why you go from 80 to 95% protection. The effect on longevity we are now investigating. Nobody or very few people got a single vaccine with the RNA. So, it's going to be hard to know will one vaccine dose give you years of protection. But the people wanted 95% protection and good durability and that's why they get two doses.

Priya Menon: Thank you, Dr. Weissman. And I think we have a couple of more questions from the panel. We have 5 minutes. So, David you can go first and then Matt we will have yours.

David Stanley: Okay. Dr. Weissman, as a high school science teacher, I can tell you that not everybody is as familiar as those of us on the panel are as lay people, Herbert is not a lay person but throwing around these words mRNA and could you give us a quick rundown exactly what is the role of mRNA, DNA have a little basic science refresher for people who are listening to this who might not be as familiar with that conversation that we're having.

Dr. Drew Weissman: Sure. So, the way our cell and our body work, is that our DNA contains all of our genetic information. So, every protein in our body, that makes up our body is coded for in the DNA. The way the body makes a protein from that DNA is it uses an mRNA, a messenger RNA. So, an enzyme, copies of protein off of the DNA, the RNA then travels to a machine, that machine is called a ribosome. But it's essentially a machine that can read the code in the RNA and turn that into a protein. So, it's kind of a middleman. It's in between the DNA and the protein. It is responsible for making proteins in a cell. So, the way the RNA vaccine works is that we encode the spike protein from coronavirus as an RNA. We give it to a cell and the ribosomes; the cell machines read the RNA and produce the spike protein. The body then recognizes that Spike protein as foreign and makes an immune response against it.

David Stanley: That's perfect. I think people appreciate hearing that.

Priya Menon: Thanks David for that question. Matt, your question.

Matt Goldman: Yeah, thank you. Where can we learn about some of the trials that are going on that you mentioned a little while ago, Doctor?

Dr. Drew Weissman: So, the trials that are being planned for have been submitted to the clinicaltrials.gov website. That's a website where you can learn about any clinical trial going on in the world. We have published papers and scientific journals that describe these vaccines, but these aren't understandable to a lay audience. So, I think the first time a lay audience will have broad exposure to them is when they're on clinical trials that go, and the media starts talking about them.

Matt Goldman: We just need to tune in at that point.

Dr. Drew Weissman: Yeah. Sorry about that.

Matt Goldman: Okay. No, thank you.

Priya Menon: Thank you. So, I think that kind of wraps up all our questions. Dr. Weissman, thank you for your time today, and I want to congratulate you for your instrumental role in bringing this technology of mRNA vaccines for Covid and kind of help to save the world. So, it's been a pleasure talking to you. Thank you very much. Matt, David and Herbert, thank you for joining and all the great questions. I hope you got the answer to things that you wanted to. So, it was great to have all of you here on Cure Talks. Thank you. Thank you.