Sue Nelson
Hello, I'm Sue Nelson and welcome to the Create the Future podcast, brought to you by the Queen Elizabeth Prize for Engineering. Celebrating engineering visionaries and inspiring creative minds.
[Music]
Dr Margaret Liu is known as “the Mother of DNA Vaccines”, a CEO of PAX Therapeutics and the Board Chair of the International Society of Vaccines. She's also an adjunct professor at the University of California San Francisco, in their department of Microbiology and Immunology, and an honorary doctor at the Karolinska Institute in Sweden, a physician by training at Harvard Medical School and MIT. She's an expert in gene delivery, vaccines and immunotherapy, and has pioneered two new technologies for vaccines and treating cancer. She has also been the Senior Advisor in Vaccinology at the Bill and Melinda Gates Foundation, Executive Vice Chair of the International vaccine Institute in Seoul, Korea, and is a long-time member of the Scientific Advisory Board of the Jenner Institute, which developed the AstraZeneca COVID-19 vaccine. If that's not impressive enough, Margaret is the scientific lead for the World Health Organisation drafting group, writing guidelines for messenger RNA or mRNA vaccines, the Pfizer-BioNTech, and Moderna vaccines being the first authorised vaccines to use mRNA technology. So, I began by asking Dr Liu to explain mRNA.

Margaret Liu
mRNA is one of the fundamental parts of how our body makes new proteins and therefore new cells. So we think of DNA as kind of the blueprint, and the DNA resides inside the nucleus of our cells. But then it has to get translated into something that's real, that is the proteins. And so, what happens is, DNA is a code, it's got a sequence of four different bases. And those codes have complimentary nucleotides that go on to make RNA. And this RNA is actually called messenger RNA because it takes the message from DNA. And then the messenger RNA leaves the nucleus goes out into the cytoplasm of the cells, where it in turn, gets translated, it's like a code again, gets translated into the proteins. So, if you think of it in terms of like a spy code, what would happen is it would be comprised of the letters or the dots and dashes or symbols that then get translated from that, if somebody had the key, into specific amino acids that then get turned into protein.

Sue Nelson
And so how do mRNA vaccines work then?

Margaret Liu
So, what mRNA vaccines do is instead of giving somebody the protein, or let's say a killed virus, that is already the proteins that are already in the shape of the virus, what the mRNA does is it's simply like handing off this code, that then your body can say, “Oh, this is pretty much the same stuff I use to make proteins”. But in this case, it codes for the vaccine itself, which is the spike protein in the case of the COVID vaccines. So it then instructs your body to make this protein that is in fact a protein from the Coronavirus rather than being one of your body's normal proteins.

Sue Nelson
So, it's effectively instructing our bodies to set up a defence or biological defence against COVID-19.

Margaret Liu
Well, it is but it is indirectly because what it's doing is it's, it's helping your body make the Coronavirus protein without your body actually having to get infected, but also because it only codes for this one protein rather than coding for all of the proteins in the virus. So, it can't actually cause you to be infected, but what happens now is your body will see this protein from the virus, it will recognise it as a foreign protein, and therefore will now make an antibody response and it as well a T cell response, the two types of immunity that you really want to protect yourself, then if you do get exposed to the virus,

Sue Nelson
The Pfizer-BioNTech and the Moderna vaccines, they're the first to use this technology. Why has it taken such a long time? Why was this the first time, was it technically difficult to do?

Margaret Liu
It was technically very difficult to do. The research for developing these vaccines has been going on for over three decades. So even though everyone thinks “Ooh, these were developed really quickly, they're very new”, In fact, the work has been going on for a long time. So, there were many different actually engineering pieces that have to all be brought together to make the mRNA vaccines work. And we're just actually really fortunate that the technology has advanced to this stage in time for the COVID pandemic.

Sue Nelson
And what types of technology were needed then?

Margaret Liu
Well, the first thing was that mRNA itself is actually very, very easily destroyed, there are many enzymes that destroy it. So, once you start thinking about taking messenger RNA, putting it in a bottle, and injecting it, and then hoping that it gets taken up into cells, in fact, that messenger RNA is probably just going to get destroyed, before very much of it is able to get translated into the protein. So, there were a number of different observations and advances that had to be made. So, the first thing was actually back in 1990, was a publication by group led by Phil Falconer at a small biotech company. They were trying to develop these formulations that would protect RNA and DNA. But they were being good scientists, they did controls, which was they use the mRNA DNA without the formulations. So, they could have their control to say, look how much better our formulations are, it actually turned out that the so called “naked DNA and mRNA” worked better than their formulations. So, what they found was that they could inject into muscle, and they could actually get protein made. And this was actually quite surprising, because for both DNA and mRNA, you usually had to do all kinds of things, either formulations, or you have to use some electric shock to blow holes open into the cell membranes, and so on. So that was actually the first step that people said, “oh, maybe we can look at these molecules by themselves”. There were a whole bunch of other steps. So that had to happen subsequent to that. And those who included that it turns out that the messenger RNA is pretty inflammatory. And I think anybody who's had the shot and had side effects, with achiness, or so on, well recognise what I'm talking about. And that's actually a good thing for vaccines, but you also need to be able to control it. So, it's not too inflammatory, too irritating. You want it to be what I call actually the Goldilocks amount, which is you don't want it to inflammatory, but you need it to be somewhat, so you don't want it too ho hum, too blasé. So yeah, has to be just the right amount of stimulation. And then as it turns out, even though that very early work by Falconer and colleagues was using the RNA and the DNA just naked just by itself, it turns out, it actually has taken now, essentially 20 to 30 years to find formulations that really will work to deliver the message into the right cells to make enough protein to be able to make vaccines.

Sue Nelson
It's incredible, really like you say in terms of the time that it's taken and the work that it's had to build on that thank goodness, it all came together at the right time.

Margaret Liu
Absolutely.

Sue Nelson
Oh, gosh, it doesn't even bear thinking about really. So, does this mean because it's fairly, I was going say sensitive, you know, it needs to be kept under certain conditions does that mean that there are challenges in terms of storing the vaccine or how you manufacture them?

Margaret Liu
That is exactly correct. And that's actually one of the challenges that we've seen for using the mRNA vaccines, frankly, not just in poor countries. But even in the rich countries, there are regions that didn't have the types of freezers necessary to keep the mRNA vaccine stable. So, they do need to be kept much colder, actually, at freezing temperatures that most vaccines do not need to be kept at. So that meant that many places just didn't have the right kinds of freezers. And the other thing is, it also meant that they needed to be formulated in just the right kind of what are called lipid nanoparticles in order to keep the mRNA both stable, but also to deliver it to the right kinds of cells. So, one way of thinking about it is, if you ever saw years ago, they used to have commercials for M&Ms for candy-coated chocolate. And the key point of those ads was it would show kids holding chocolate in their hands that would melt and they'd have chocolate all over their hands and their face. But if you coated the chocolate with a candy shell, then you could run around carrying these candy-coated chocolates in your pocket all day long, and they wouldn't melt. So, it's kind of like that, that the lipid nanoparticles have protected the mRNA from getting just totally degraded very rapidly and protected long enough to deliver it into the body and into cells. However, they still need to be kept at these freezing temperatures.

Sue Nelson
All the different technologies that that are required for this, it does show, doesn't it how there is this blurring of a boundary now between medicine, biology and engineering and this field of biotechnology that requires so many different aspects, really, for everything to work together. Have you always sort of taken an interest in the technology side of things? Or have you concentrated on the biology?

Margaret Liu
Well, I think you've actually hit on a really key point that in fact, I have felt just by observing big breakthroughs in science has been key, and that is that. Number one, it really takes disciplines working together. And so that isn't usually just somebody you know, in their own lab who has the insight that does sometimes happen, but you really need to have different expertise and different perspectives. The second thing is that it does seem to me that sometimes the big breakthroughs actually come from people from different fields, exploring another field, and doing so, you know, in the context of a team, for example, but it's often at the interface of two different disciplines. So in this case, you're absolutely right. It's been biology, but that's also included biochemistry, but also sort of the engineering and all of the chemical sciences for formulating the mRNA. So absolutely, that's exactly what has led to the success for these mRNAs was the different people coming together.

Sue Nelson
Does the technology affect the speed of clinical trials, particularly obviously, as many people like yourself are trying to come up with vaccines or during a pandemic, which is not ideal, because preferably, you want to have as many vaccines in your armoury that will work beforehand.

Margaret Liu
So you so you hit upon another key point that has become very apparent in the pandemic in that, first of all, the technology does affect the speed with which you can make the initial constructs. So for example, the earlier technology that made the chickenpox vaccine actually took 28 years to develop. And that's because it was a

weakened strain of the virus. And so people had to just keep growing it and growing it in different cells and over different time courses to try to weaken it. Well, now you can do it faster through genetic engineering of a virus, but it still takes time. Whereas with either an mRNA vaccine or a DNA vaccine, you can basically, if you know the sequence of the virus, and if you know which antigens, which proteins are the key ones, you can go to your lab and design that vaccine pretty quickly and then manufacturer it quickly. However, the other aspect that you touched on there were the trials, how do you actually test the vaccine. And there's where I think it's really important to say that there were not shortcuts taken in the sense that people still did the basic science work, they still did animal studies. And then once you get into the clinic, it's largely a matter of how great the incidence of a disease is. So if you're trying to test a vaccine, and only one person, you know, out of a million gets infected every year, it's going to take you a long time to get enough people to show that the vaccine works. Whereas one of the reasons that the vaccine trials could be done quickly, was because of the sheer number of people who are getting infected in a relatively short period of time. So that's another key issue.

Sue Nelson
And you had so many volunteers as well. I mean, that must have been a boon that so many people were keen to help and take part in the trials?

Margaret Liu
That's absolutely right. One other thing that I do want to mention that I think is really important is that usually, when companies are developing a vaccine, it actually takes a long time, because until a company gets very far along, such as the end of Phase 2, they don't start figuring out how to do the manufacturing for really large scale. So you have to have your manufacturing and process, you know, by the time you're doing Phase 3, but you might not have built a large manufacturing plant. So the other thing that was different was that because governments or the companies themselves, committed at risk the money to go ahead and ramp up the manufacturing capabilities. That meant that it was a financial risk in case the vaccines didn't end up working in Phase 3. But that did not jeopardise anything in terms of the safety of the vaccines, it was simply that they built out all this capacity. And if the vaccines hadn't worked, they would have had all this capacity that they would have wasted money on. But what it did was then it made it possible to immediately start making enough vaccine to use once the efficacy was demonstrated in the clinical trials.

Sue Nelson
Now, we've already touched on a few of the sort of advantages and disadvantages of mRNA vaccines, like the fact that you have to store them at, you know, an incredibly low temperature and not every facility would have that. What would you say was the sort of biggest advantage of these types of vaccines?

Margaret Liu
Well, I think the biggest one, and this applies, in a broader sense to DNA vaccines, but somewhat also to viral vector vaccines, which is that in one sense, mRNA is what people would call a platform technology. So I liken it to being a desert person, to if you understand how to make ice cream, you can go ahead and make different flavours of ice cream, whether it's chocolate or strawberry, or any kind, you understand the basic recipe. So it's pretty much the same thing then with these mRNA vaccines is that although there will be differences depending on the disease, and that's a really big difference, you know, something that works for SARS Coronavirus to may not work for tuberculosis or HIV or cancer, but at least you know, fundamentally how you make it and how you manufacture it. And so that's an advantage to trying to make vaccines for other diseases. But it's also an advantage for the issue we're confronting now, which is do we need to make new vaccines that are more specific for the mutant strains that have arisen?

Sue Nelson

So, these are the variants effectively the variants are you saying all the flavours, different flavours of the same ice cream?

Margaret Liu
Correct. Although making vaccines against other diseases such as HIV or TB is another version of it, it's sort of like you know, chocolate and chocolate mint versus strawberry or something. You can have all different gradations of what you call different.

Sue Nelson
So the potential then of this type of vaccine is pretty impressive. You must be hopeful?

Margaret Liu
It is very potentially broad but I don't want to under emphasise that we keep being humiliated time and time again by these pathogens, by the viruses and the bacteria. Because we think we understand what should be important for a vaccine. And sometimes that just doesn't work. So the huge other big side of the equation is for each disease, whether it's cancer, or whether it's an infectious disease, we don't always understand what type of immunity or even let's say, we think we know antibodies should work. But we're not necessarily sure exactly what protein of the virus or the bacteria or the cancer to target. And that's a big unknown.

Sue Nelson
The technologies we've touched on there, you mentioned lipid nanoparticles, did you also need technologies or a new aspect of looking at what was going on to reduce the potential sort of inflammatory aspects that can happen?

Margaret Liu
Yes and that is something that is a has been a big issue, because while the inflammation per se, can be important, and the reason for that is, our body has two completely different branches of the immune system. One is called the innate system. And the other is called the adaptive system. So the adaptive system is the one we talked about for vaccines, which are the antibodies and the T cells that are specific for that pathogen, but the innate system is the one that's kind of like your burglar alarm system, so that, you know, if somebody, if you have your alarm set and somebody comes in, you don't know anything about the burglar, but what you do know is they breached your defences. And that's what the innate system is like it's something that recognises pathogens, and it starts a lot of activities, whether they are cytokines or activating certain cells. And so, it's not very specific, but it turns out that it helps you, or parts of it help in the development of your adaptive responses. So, some of that innate system helps make your other immune responses, your antibodies and T cells develop better. So the thing about, especially the in vitro manufactured mRNA, the way it's made, and what its components are, is that it does stimulate many arms of the innate immune system. So, there are different ways of toning down that inflammation so that you don't get it to be deleterious, even though you do probably want some of it.

Sue Nelson
And was this area for you, working and researching on vaccines, was that always an interest for you? Right from medical school? Or was it something that just gradually appealed and for your research?

Margaret Liu
You know, that's an interesting question. Because what I've always been interested in, even starting with undergraduate University, before going to medical school was, I was interested in the immune system, and but not just the immune system, but how cells get activated, kind of like, what's the key and the lock that turns

them on, and wakes them up. I think in a sense, that probably stems from, you know, I always liked to do puzzles as a kid, especially those little wooden ones that you have to figure out which particular piece you push your pole and then you can take apart the rest of them. In a way that's essentially what happens with whether it's immune cells that get activated, or clinically, I'm actually trained as an endocrinologist. And those are, you know, like, what turns on your hormones, what do your hormones do then to activate other cells, it's, it's basically the same types of mechanisms as for an immunologist, so, any rate, so I think that that may be part of, to me, it's kind of, I think of them in the same way. And it's a very visual puzzle type of pictures in my mind, whether it's activating cells, or doing puzzles.

Sue Nelson
I know also, I read that you'd attended a leading music school in Paris, playing the piano. So, you've got this musical side to you as well. Does that help with your research? Do you play music to relax or does it aid you thinking about your work or let those puzzles come out? Or is it totally separate?

Margaret Liu
That's a really interesting question because as it turns out, many people in medicine are also musicians. And I know that for me part of it was after taking care of cancer patients, for example, I'd be so sad I just needed to lose myself playing music. So that would be Chopin, playing Chopin, right. But then I love playing Bach, because that discipline for Bach was a way to take my mind off of things and yet have to super, super focus on something that was very mathematical and very precise. So I think that, you know, music has been really an important way, not just as an escape, but it's a way to also still be disciplining my mind, but in a way that was different. And I think that it's actually important to not just do your work all the time. So the other thing I like to do is hike. And I really believe that, you know, when I'm walking, looking at green, green is supposed to help you be creative, but doing that sort of other activity, your brain frankly, keeps thinking about things. So sometimes I'll come back and clues that I couldn't get an a crossword puzzle, often I come back after a hike. And it's like, “oh, that was obvious. Why didn't I think of that before?” and your brain is just kind of kept thinking about these, these puzzles, whether it's a scientific conundrum, or whether it's something, you know, like a word puzzle.

Sue Nelson
And you must be delighted the way things have worked out with the vaccine. In a sort of strange way, although, you know, terrible things have been happening around the world. This is also a very exciting time for you in terms of your work, and what you do and what you've spent your life doing, do you ever feel guilty about that sort of excitement at all?

Margaret Liu
Well, I have to say, rather than excitement, I actually feel two things. The first is to feel relief that the technology had developed. And I didn't work much except some very early work testing out mRNA. But at the time, there were too many technical hurdles. And so we develop actually DNA which is upstream of that. But that what that did do was it helped sort out a lot of the immunologic issues that were also relevant for mRNA. And it also helped set up infrastructure, because DNA is still for the manufacturer, you actually still have to start with DNA for when you manufacture the RNA. And so that helped build up actually, because there was so much interest in the DNA vaccine field, it helped build up in the infrastructure that has really helped the mRNA. So there were, you know, a lot of regulatory issues, safety issues, haematological issues that have benefitted it, even though my work per se wasn't on mRNA. But I would say it's not so much. I'm very glad to have been a part of this work. But it's mostly relief, that the technology is at this point at the right time. However, the flipside is, I'm actually just distressed, that we haven't as a global community done a better job of making sure that the vaccine technologies, all of them are more available to the majority of the world. Because, wealthy

countries, we can sit here and feel like, “Oh, great, we're all safe”. But in fact, you know, we're all part of this global family. And so that's actually a bigger emotion for me is feeling distress that we're not moving faster to immunise our brothers and sisters everywhere.

Sue Nelson
There are also reports of large numbers of people in particular states who are hesitant about taking the vaccine or deny or are totally against it for whatever reason, how does that affect you when you're going about you and your colleagues going about your work?

Margaret Liu
Well, first of all, it makes me sad, because I think that a lot of it has come about because of misperceptions due to emphasis on things like the speed made when you call something “warp speed”, which is what it was called in the United States, the concept is that you jumped over steps. So, it conveyed the wrong information to people who otherwise, you know, that's what they're going on is sort of labels and, and so on. And I think that people didn't understand how there were so many decades worth of work. So, in fact, this is something I'm actually working with the Science Museum to try to develop something to help deal with vaccine hesitancy. And I think that what I would say is that, you know, frankly, as a scientist, I think it's really important to always be sceptical because you always want to test your hypothesis. But what's important then is that you look at the quality of information you're given. And, of course, as scientists were trained to do that we're trained to look at primary data. And so we're privileged in that sense that this is what our life is, is using these tools. And I think we have to encourage people that in their scepticism, that what they need to do is, then make sure that for themselves for the sake of themselves and their families, that they're looking at the quality of the information they're getting, and making sure that they're sceptical of the source of information, not just sceptical about the vaccines, because they don't understand them.

Sue Nelson
And finally, what would be your advice for engineers in particular, who love biology and perhaps want to go down the bioengineering or biotechnology route as a career? Would it be to do medicine or do engineering or to bio engineering - what would you suggest?

Margaret Liu
Wow, that is a interesting question. Because you know, the science just changes so rapidly. So I guess what I'd say is that, you know, my career ended up being hugely different than what I thought it would be, I thought I'd just stay in medicine, practising medicine, doing research, teaching, staying in academia, and the whole area of global health, or, you know, the thought of working with WHO, those weren't things that were part of my internal vision. And yet, they've just been so hugely, you know, rewarding, because I feel like, potentially I can be making a difference. And so I guess what I'd say is, you know, you really want to follow your passions. But you also want to make sure that you don't get pigeonholed too early and say, well, you know, my life's work is to study this one particular, small, you know, enzyme or area, because although that can be important, you need to always be open to maybe the biology or engineering developments. And so, I think, that would be the maybe the one key point is that, we all have to be citizen scientists and so we all have to be, you know, cognizant of everything happening around us, and bring that to our work. And then, likewise, take our work the other direction and say, oh, I've been working in this area, but maybe I can apply the same work to, you know, another area.

Sue Nelson
So it's that sort of be open minded, but also be flexible. And it's that cross discipline as well. Just be ready for ideas from all different aspects and areas of science and engineering.

Margaret Liu
That's right, you've, you've done an amazing job of bringing this full circle back to where we started.

Sue Nelson
Thank you. Well, Dr Margaret Liu, thank you very much for joining me on the Create the Future podcast.

Margaret Liu
Well, thank you very much. I loved your questions and I think you have a really interesting audience, too. So, I've been very privileged to speak with you today. Thank you so much Sue.

Sue Nelson
Find out more about the Queen Elizabeth Prize for Engineering by following @QEPrize on Twitter and Instagram, or visit qeprize.org. Thanks for listening and join me again next time.