Interview with Dr. Robert Malone

IB - Good morning, Mr. Malone, it's an honour to have you here and to have this exclusive interview for IppocrateOrg. Nice to meet you!

RM - Nice to meet you too, Irina! And thank you for the opportunity to have a conversation, and also to share information with your viewers.

IB - Thank you. So the first question is, **you're considered the father of the RNA technology applied to vaccines. Is this definition right for you? And what is your personal history?**

RM - So I think that that's a fair moniker, label. During my graduate work at the Salk Institute, I had a series of inventions; each involved other people, but I was the driver through those. And then I left the Salk and joined a small startup company at Vical and had some additional inventions. And then there were invention disclosures made – these are formal processes – and **a large number of patents were filed that covered both RNA and DNA vaccines with the self-assembling lipid-nanoparticle technologies for delivery, as well as covered the use of RNA alone without added lipids.**
And the patents covered … and there was reduction to practice. This occurred mostly … the reduction to practice of the immune responses occurred at Vical. So it was an industrial environment. And I was there as a technician working for a few months while my wife finished her bachelor's degree. So it was actually a very brief time I was at Vical, and everything happened within those four months, that was important, really. Those patents were issued, you know, and then there was follow-on work with others that joined Vical afterwards, that reduced those to practice and demonstrated the protection in a mouse model framing for influenza, and other people reduced to practice demonstrating the cellular immune response at Vical. This was all under the corporate umbrella. And that information, they didn't write it up as manuscripts … it was outside of the focus of the company. It was not the business plan. Vical was set up to work on antiviral compounds with a contract with Burroughs Wellcome for liposomal deoxynucleotides for AIDS, and calcitonin analogues, hence the name Vical. So

this was this was a SkunkWorks operation they had set up, that led to all these patents that covered almost everything that's being done right now. And they were blocking patents. They were sold to Merck. This is when Murray Salomon was still at MerckVaccines. And Merck made a decision that they were only going to pursue DNA, not RNA; they thought RNA was too difficult to manufacture. But they successfully kept out others, other companies, or really they also sent letters to me, as an academic at that time, telling me that I should not work on any of the things that I worked on when I was at the company. And they successfully prevented other companies from entering the field for the 20-year lifespan of the patents. They didn't actually get anything to work in their hands, they made a series of bad judgments in my opinion. But you know, that's the way it is with industry; that is when the pharmaceutical company owns the intellectual property, they will actively exclude others from working on it. And that's just the way things are; and whether they succeeded or not in exploiting the technology was out of my control. So the key patents came about, and the discoveries came about, kind of through two tracks. One was that I was developing, trying to develop, methods for asking questions about retroviral packaging. Retrovirus exists as an RNA, and then becomes a DNA in the cell due to reverse transcriptase, but then is produced as RNA and packaged to form virions as RNA. And at the time, retroviruses were the leading technology for gene-therapy applications, which is what I was passionate about. And I wanted to, as a graduate student, better define this packaging process and the interaction of RNA structure and function in sequences with the packaging proteins. So to do that, I had to develop a system to make large quantities of RNA and deliver those RNAs into packaging cells that make all of the proteins entrants, so that I could ask the questions about packaging and RNA function.

I was also working under the mentorship of a postdoc named Dan St. Louis, who was working on classic retroviral gene-therapy approaches. In his case, he was infecting cells in culture, mouse cells, with a retrovirus expressing a protein that would be potentially therapeutic for a paediatric condition. And he found that, when he infected those cells and then transplanted them back into the mice, the mice would only express the protein for about three weeks. This was a problem; no one could understand what was going on. They thought that it was a gene-expression

regulation problem. And I'm the one that figured out that actually what was going on is the mice were meant for generating an immune response against the protein, against the foreign protein. This was heresy at the time, because it meant that the whole gene-therapy paradigm was flawed.

Because the foreign genes associated with an attempt to correct inborn error of metabolism would be recognized as foreign proteins and the cells expressing them would be attacked. So this meant that the whole idea of gene therapy was problematic, because the immune response at the time that was heresy, that was not known, people didn't believe that, there was much derision, and the usual kind of gaslighting. But that's turned out to be the case. And that's what's really restricted gene therapy. Only, you know, very few applications have been developed and it's been very difficult to do so. But my insight was that we could take this problem and turn it upside down, we use the expression “make lemons out of lemonade”, that we could take this problem and make it so that at least we could use the technology for vaccines.

So that was one of the key insights that led to this whole thread, and it was about 1987-1988 when that happened.

Then there was all this work with RNA and the structure of the RNA, and proving the structure of the RNA was correct and had all the right elements, and developing the system for manufacturing, which is basically still used, but it's just scaled up. And there's been some refinements in that in terms of things like the cap structure, nuances, inside-baseball stuff, as they say in the States. Probably they don't talk about baseball in Switzerland.

IB - Maybe, I don't know, I don't follow sports so much … so ...

RM - Okay, yeah, neither do I. So insider details that, you know, have subtle impacts on the efficiency. And the basic idea of … people get it wrong, these aren't liposomes, you're not entrapping the RNA into liposomes. That idea of putting RNA into liposomes, where the liposomes are like a balloon, and the RNA is on the inside, that turns out to be really, really, really inefficient, both in terms of delivery and in terms of encapsulation of the RNA. And RNA is a very expensive biomolecule to make.

So the core technology for the lipid part, the packaging part, is that the RNA is negative, and these fats, ketonic lipids, quaternary means, initially, are positive and the two are just driven electrostatically to associate. And

so you mix the two and they self-assemble into a particle; a particle is not a liposome. It's a lipid nanoparticle that has an RNA string in its core, and then it has lipids wrapping around it. And it just self-assembles in an aqueous solution. And it makes the whole thing very easy to do. It's very, very efficient. So all of that tech is still used. You know, there was a series of events where I, being at the Salk Institute, at the time I was there, there was half a dozen Nobel laureates, some of the greatest scientific minds in molecular virology and biology were there. And I would get advice now and then from senior scientists that would say, “Hey, Robert, you should look at this thing, or you should look at that thing”. So back then, we didn't have a PubMed, you couldn't go and type in and say, you know, well, what are all the articles that relate to this or that or the other thing? So it was a kind of a random walk through the literature. And there's some people at the Salk, Tony Hunter, notably, that are just brilliant. And they're like walking Wikipedia, they just know so many things. And so Tony made a couple of the really essential suggestions. “You know, Robert, why don't you talk to this person?” or “Robert, why don't you look at this new paper?”, whatever. And it was that and another person that was very influential was Marguerite Vogt, who many people credit as the woman who really did the work that Renato Dulbecco got the Nobel Prize having to do with cell culture. And so just it was so an amazing place. And I had many people supporting me and suggesting me with ideas. A series of things happened where I was teaching - helping to teach – embryology course, on a campus. And for embryology, you have to be in the course. The course is a lab course that I was helping with. And I had to prepare frog embryos for the students. And at one point, I had many extra frog embryos, we call them tadpoles in the United States, baby frogs, but tiny. And so I had somebody leftover, I thought, “Well, why don't I try some of these with the lipid RNA complexes?”. And, surprisingly, that worked. And it also worked with DNA. And then subsequently, the next step in embryology course was to examine chick embryos. And so I was preparing chick embryos from fertilized eggs, and transfected those with the DNA. And that was clearly positive. And at that point, there was just an explosion of fighting between the University of California and the Salk Institute, about … it was, of course, all about money. And people thought that they were going to get rich, and that this was going to become a Nobel Prize, and, you know, very important and a big breakthrough, and people

were coming to me saying, “Well, you have to collaborate with me”, “No, you have to collaborate with me”. And there was all this fighting, and my mentor has a history of being a little unethical about things. And we don't need to go down that. And so I was I was caught in all this. And I ended up having a nervous breakdown, and ending up with a diagnosis of post-traumatic stress disorder from the university physician. And I had to get out of the lab, I couldn't stay there, which is why I took a Master’s instead of a PhD. **The irony now is that the work that I did then has given rise to this whole new field.** And I got a Master's for it, and what's even being discussed is that, you know, it potentially qualifies as a candidate for a Nobel. I knew at the time I was doing something important, and I knew that the idea of using RNA as a drug and RNA as a vaccine was revolutionary, but it was so far ahead of its time, that it had created this funny mixture of people wanting to own it, and own the patents, and also people being very derisive and “Oh, no, no, this, this isn't important at all”. And you know, “It's absolutely not practical, and there's no way this is ever going to lead to anything”, and all that kind of stuff. So it was a fascinating thing. And, like I said, I had to leave, my wife had to finish her bachelor's. So I joined this little startup company called Vical. And eventually it became the focus of the company. Merck failed. They gave the patents back. Merck leadership quit Merck and became leadership at Vical and they still couldn't get it to work. And after 20 years, the patent expired, the money ran out, the company failed. And then all these other companies like, for instance, CureVac had started to build a company and then ran into a bunch of lawyers attacking them. Well, most lawyers were from Vical defending my patents. And, you know, it wasn't until those expired, that CureVac could move forward commercially, and BioNtech could move forward commercially. **Now all this controversy comes around because Katie Karikó, and I guess one of the founders of CureVac, both promoted themselves as Nobel Prize candidates, and got a lot of press, and of course Katie is the vice president of BioNtech,** and also a professor at University of Penn, which holds the patents on the incorporation of pseudouridine. And those organizations apparently have heavily promoted her as a candidate. And she's been in the press and, you know, done the tours. My wife eventually got kind of aggravated because of stolen glory, basically, other people taking credit for what I did … I

don't discount what they did, but they felt the need to take credit for … you know, and say that they were the ones that came up with all these ideas.

The irony is that, in Katie's first paper, on RNA, she actually mentions me in the acknowledgments. She had contacted me, and I tried to help her. And I introduced her to some people in the RNA world and I gave her some suggestions and I introduced her to another scientist that was in my group that I created at Davos and I invited her to a meeting that I organized in Annapolis, Maryland, and I just tried to help her, but then, you know, she decided for whatever reason that it was in her interest to promote that these were her discoveries and her ideas initially, and, you know, people are going to do what they're going to do, and this kind of thing happens so many times in science. But what matters is not then, in my opinion, it's now. And since then I've done many other things.

I was in the field of in-vivo electroporative delivery that gave rise to Inovio: also this came off of my bench. We have multiple patented ketogenic lipids, some of which are marketed by Promega and many other advances since then. And then since 2000, after the anthrax attacks and the 9/11 attacks in the United States, I started focusing on bio-defense and in working much more closely with the US military, in developing rapid-response bio-defense capabilities. And that's much of what I've done since then.

I was very involved in working closely on behalf of the military and bringing forward the Public-Health-Agency Canada vaccine for Ebola during the West-African outbreak. And I got Merck involved, we now call that the Merck Ebola vaccine; it’s the only licensed Ebola vaccine. So I was central to that.

I did a big drug repurposing effort for Zika, and in that case, I did that closely again with the Department of Defense.

Many of the agents that are discussed for this current outbreak, we’d identified. I still think that ivermectin probably has significant activity against yellow fever. But that's never been tested in the field. But that company went broke, bankrupt, because **there wasn't any interest on the part of investors in repurposed drugs, because you can't make money on off-patent drugs; this is the thinking.** So that was a lesson. When this outbreak happened, I got a call from an intelligence officer of the United States who was in Wuhan, China, during the fourth quarter of 2019. And this is a guy that I

published with in the past. And he called me in the first week of January and said, “Robert, this virus looks like it's a major threat, and you need to get your team spun up again.” So I did a threat assessment and came to the conclusion that again repurposed drugs were going to be the best short-term option for preventing disease and death or reducing it. And so that's what we've been working on ever since. I was brought into this whole vaccine controversy about the safety and the other effects, kind of through a side road because of this historic association with RNA vaccines and the technology platform. And also, I wrote a paper about the bioethics of emergency.

I work very closely with FDA and other agencies in the US government and have for many years. I know the person that wrote the initial emergency-use-authorization justification at the FDA. So, you know, I am kind of an insider. And I understand the government, but I don't directly work for the government. So that allows me to speak more freely than many of my colleagues. I was just on the phone to one of them just up until the moment when your podcast started, who's a very senior person at Defense Threat Reduction agency, talking about what their plans are, and the new initiatives that are coming down, based on our success. **I think we're about to go into the clinic with three different clinical trials with the combination we've identified of repurposed drugs, and, oddly enough, these are off-patent drugs. We believe that there's good efficacy and reasonable safety for both the outpatient and inpatient environment for the combination of famotidine, which is marketed in the United States as Pepcid, so this, yes it is a stomach-acid drug, but it is one of the most potent inhibitors of the histamine h-2 receptor.** It's actually a second-line drug for stomach acid, but that's how it's marketed. **And the other agent is celecoxib, that's sold in the United States as Celebrex and it's the only specific cox-2 inhibitor, which is another inflammatory pathway, that’s sold in the United States. It's also generic. And we also find that adding Ivermectin on top of those two provides some additional benefit, particularly in lymphocyte recovery.** So our work has been very methodical, based on rigorous structure analysis of mechanism of action, and originally grounded in computational docking, so very high-tech stuff, computer-based, but then on clinical data, and this vaccine thing, that's probably why you want to talk to me about in my opinions … yes, I'm trained at Harvard, and have a fellowship

in clinical development, regulatory affairs, epidemiology, all that kind of stuff, biostatistics, and through my other training, and I have years and years of experience in clinical development. And I'm a kind of an outbreak specialist, I've been doing this, you know, since the very first days of AIDS in so I have perspective on things. I've spoken at the World Health Organization, had many meetings there.

So people seem to find this cluster of experience where I understand the government, I understand outbreaks, I understand technology platforms, I understand adenoviral vectors also pretty well, and I follow that closely … so there seems to be something about my style that is causing people like you to want to have podcasts with me. And my wife says, "The government should be paying you because you just sit here hour after hour on these podcasts, trying to educate people and help them to understand", but that seems to be something that's needed. So I'm doing my best.

IB - There's so much information that, I mean, someone like you, who has an overall view of everything is the best person who could tell us what's going on and tell us about these vaccines, because today things are not completely clear. So it is important for everybody to hear your opinion since you're one of the inventors of the RNA technology applied to vaccines.

So I know that you know our Association also and you know our protocol that has been followed by our 150 doctors of medical assistance. What do you think about our protocol as an expert?

RM - So regarding your protocol, Irina, one thing is something very similar has been used all over the world, and many physicians are finding this to be useful, this approach that your group is using, useful particularly in outpatients, particularly if administered early. And the problem has been worldwide, that the agents that have been developed or tested like Remdesivir, or Dexamethasone … Remdesivir most of the world agrees is not very potent or effective. In the United States, it's still the only approved agent, and I think this has a lot to do with certain influential people's advocacy, and not to mention Gilead's revenue. But Dexamethasone is actually, if you read the Recovery Trial

data, very carefully, particularly the supplements (and they've never actually published the full study, only interim studies, they published two interim-study analyses, and never a final-study analysis), if you read those carefully – and we have a paper out that should be getting published fairly soon, that has a lengthy analysis of this, among other things – Dexamethasone is only demonstrated to be useful, to the extent that it is useful, in a very small subset of patients that are on high-flow oxygen or intubated, and within certain age ranges, and even by gender and race. And so when you put all those things in, and you look at how many people have actually demonstrated, you know, what specific little slice of the population, has demonstrated benefit from Dexamethasone, it's very, very small. And it took a very large study to even demonstrate that. And they had to do some age corrections and other manipulations of the data. So the truth is that the data supporting Dexamethasone is pretty restricted.

Some others use, in addition to your protocol, various other steroids, anti-inflammatory drugs. The problem with the steroid component of those treatment protocols is that it can be a broad-spectrum inhibitor of lymphocyte function, so immune function, and I don't think that's a good idea. Personally, I think that it can be useful in the short term with the cytokine-storm kind of problems, but may not be useful, may create an environment in which the patient becomes more likely to develop the chronic symptoms, the long COVID. That's still not proven, but I think it's a risk. So your protocol is one that is best administered, I think most would agree, very early. And I think that's the key to keeping people out of hospital. If you think about it, the expense and the death and the severe disease, it only occurs in a very small subset of people. And there's been so much emphasis on the hospitalized population in drug development, and almost no emphasis on clinical research in the outpatient environment; yet if we can treat people early, they never develop those long, severe problems. **They never get the deep lung damage. You know, I'm sure you know, Irina, generally speaking, lung and heart don't recover their scars. And so if we're having things like cardiomyopathy, you know, and heart damage and lung damage, those people are never going to be the same and I speak from experience.**

I got COVID, so I got infected and developed significant COVID disease at the end of February when I was attending a Boston conference on drug discovery.

And I went through a period where I couldn't walk up a hill, I'd had to stop, I couldn't breathe, I still don't have the stamina, you know, I'm a person that does carpentry and manages a farm and I'm very reactive. But even in giving these podcasts now, I have to speak a little bit more slowly and take a little more breathing. Because my lung capacity isn't what it used to be. So this is not a nothing disease, even though I didn't die, right, and I didn't end up in hospital, so it's not the influenza, I guarantee, and back then we had nothing. That's actually how I discovered famotidine. I was treating myself with drugs that we'd identified using the computer. And so, but that treatment was tentative and partial and, you know, we didn't know anything about some of these other agents at the time. And so I got more lung damage. It would be nice, you know, it would be a good thing for me, I'd love to be able to have contributed to helping people not develop what, and go through what, I've experienced, but I think your protocol is consistent with what's used worldwide.

IB - So this early-therapy approach works. And we we've showed this, we've tried to spread this information in order to save a lot of lives. And we have the proof that these therapies work. And today, we also published an English manual that you can find on Amazon, in order for people to know that a cure exists. Why do you think, Mr. Malone, that the governments don't officially apply these early therapies?

RM - I don't know the answer to that, and it's a paradox. I think many people all over the world asked the same question. It just doesn't seem to make sense. In the case of ivermectin, just for example, we had an odd situation where Merck came out with some very strong statements that ivermectin was not safe and was not effective. It's odd because it's a Merck drug. We have 40 years of safety. And any drug dosed at sufficiently high levels will be toxic. We call that the therapeutic window. So long as you're within the therapeutic window, ivermectin is a very safe drug. And so, there's the appearance of financial conflict of interest within the industry. Merck no longer manufactures, or they manufacture but they don't market, ivermectin. So, even though it's a drug they invented forty years ago and they got the Nobel Prize for it, or one of their scientists did, and it's been

used all over the world, it's generic now and it's on the World Health Organization essential-medicines list, so to say that this drug is toxic is absurd.

Yes, one can, for instance, here in the States, you can buy ivermectin formulations made for cattle. And they're in very high concentration. And yes, if you were to drink those, it would be toxic. And I wouldn't give cattle ivermectin to my dogs or my horses either. I give my horses ivermectin once a month to prevent their worms. And it turns out the dose that is approved for my horses is precisely the human dose. It's 200 micrograms per kilogram. So you don't give the same mass that you give to a three-quarter ton horse to an 80-kilogram person, but you know, just for body weight, it's the same dose. So Merck came out with these statements.

Pfizer is apparently developing a drug that's very similar in mechanism of action to ivermectin now, **and they're promoting it as their candidate for treating COVID. And now Pfizer officially says that we won't be able to overcome this pandemic with just vaccines. They think that we need to use vaccines plus the Pfizer drug. So, yeah, so fascinating … gently put … So there are financial interests here. And Merck is of course promoting its own, advancing its own, antiviral drug that it purchased from Ridgeback that they purchased from Emory that was developed actually by, funded by, my colleagues at Defense Threat Reduction Agency. So Merck is now saying this is their drug, and they're promoting, you know, as a direct-acting antiviral. The problem with direct-acting antivirals is that they are likely to develop resistance, the virus is likely, you know,** we learned this from AIDS, whereas a lot of these agents like ivermectin probably is not a direct-acting antiviral when it's used at the doses that are safe in humans and **these other agents that you're mentioning are all designed to treat the disease, not the infection, and the disease and the infection are separate.**

So I don't know why governments are… there's the appearance that their response has been influenced by the pharmaceutical industry, and I know there in Switzerland you never have any problems with pharmaceutical industry, except that it's a major source of revenue.

B - I think it's worldwide, I think it's worldwide, you know …

RM - Just so … and it would seem that Pfizer is being particularly aggressive.
I've learned from colleagues just last night in Israel, that the Pfizer terms for their contract to get access to the vaccine early are such that Pfizer gets access to all the data, and that the adverse events that are occurring are actually available to Pfizer, but not available for public disclosure. So, when we hear that there's no adverse events being reported in Israel, well, that's actually by law, by contract, that they're not able to disclose those adverse events, and that the terms are such that they won't be disclosed for a 30-year period. **So Pfizer is being very aggressive in protecting its interests. I don't think that they're in the interests of the world at all. And so maybe there's some undue influence on governments by the pharmaceutical industry, causing some of this … I think that's one hypothesis. Another is that there's just a massive groupthink going on.**
And maybe the United States is responsible for that, in some ways, because we've had various thought leaders in the senior positions in the government, stake out positions that only the vaccine should be promoted. And so I don't know what else to say. I mean, most of your viewers can come up with as many hypotheses as I can, and probably more. There are many conspiracy theories. And I try really hard to avoid conspiracy thinking.

IB - Of course, no. I think the same but you know, today, if you just have an alternative, you're considered someone that, you know, doesn't believe in science, but it's not a matter of science. It's a matter of interests, economic interests, business, it's a lot of things.

RM - Yeah. But I disagree with that. Yes. So the reason why these things are being suppressed is not a matter of science, I agree with that.
I am increasingly convinced by the opinions of Geert Vanden Bossche in the Netherlands that the policies that we're pursuing globally right now are highly counterproductive and that we need to move back to a position of vaccinating the people at highest risk and expediting making protocols and drug treatments for early-stage disease available and very aggressively implementing those.

I think he's right, that we're at risk of selecting vaccine-escape mutants because of the vaccine campaign.

IB - I have one last question for you. Since you're one of the top experts on genomic technology for vaccines, what are the strengths and the weaknesses of this technology applied to vaccines?

RM - So, thank you for that question, I'm glad to have that question… it's rarely asked. So this whole idea of using gene therapy for vaccination purposes. At the time, most of the attention in vaccinology was on generating antibodies, and in many cases, it still is. You may recall with the early rollout of these vaccines everybody was talking about their neutralizing-antibody activity. Okay? Well, it turns out that those neutralization assays using pseudoviruses or live viruses, are actually poorly predictive of efficacy, they're measuring something that doesn't really correlate with protection, which is always a problem in vaccinology. Just to give a little more context to that, if one can define a “correlate of protection”, something that if you measure this laboratory value that means that you're protected, and if you don't reach a certain level then you're not protected, that's the best situation in vaccines for development, because then we can just run the lab assay. We don't have to wait until you get challenged by the virus or not. So that's the case with influenza vaccines; we have correlate of protection. It was assumed that the antibodies were a correlate of protection for these vaccines, but they're not, and this is often the case with vaccinology. Because the immune system has these two: it has the innate immune response, that's kind of this primitive, primordial, nonspecific immune response that exists, it's not really truly non-specific, but it's things like interferons and other things, molecular-pattern-recognition receptors, and those kinds of pathways; then we have the B-cell responses (we think of the antibodies) and we have T-cell responses. Now T cells are also involved in managing B-cell responses, so it gets really complicated. But one branch of the T-cell response is cytotoxic T lymphocytes. And these are the killer T cells that go around and search out cancer cells and kill them. And they also search out cells that are infected with virus and kill those, because those cells that are infected with virus are really the little manufacturing facilities that the virus uses it, it parasitizes ourselves – that's what a virus does

– and it makes our cells become virus-manufacturing facilities. So the viruses are kind of like the Borg: if you are a Star Trek fan, you know, they will assimilate you eventually, right? They take over your cells and make them do what they want them to do. So you need not just having antibodies that attack things on the outside of cells, but you need things in your immune system that can go and attack the cells themselves. And traditional vaccines have not been very good at making immune responses that elicit effector T cells. The whole idea behind … you know, when I got past the "Aha, we can do this with gene therapy", then that was the next question: so, why is this a good idea, right? Why would it be better? Because using a gene-therapy strategy more closely mimics the virus infection, without having viruses all develop these special little tools that they use to pick the locks in our immune system, that's they're under such amazing evolutionary pressure and so they develop methods through signalling. And SARS-CoV-2 does this too, through NF-κB and other pathways. They develop methods to influence how our cells respond, to turn off the normal protections that cells use to keep from being infected by viruses. Makes sense?

And so the idea is that we use a gene-therapy technology to put the gene in for one or more key antigens, but not put in the parts of the virus that cause our immune system to be downregulated and not respond effectively, and that, by expressing the proteins in the cell, as opposed to just having them on the outside of the cell, we can get both B-cell and T-effector-cell responses, so a more complete immune response, and, mimicking the infection without having the parts of the virus that are manipulating the immune response, so we can get a more robust, effective immune response. That's the logic. And to make that work, you have to make sure, for instance, that the antigens that you're expressing aren't the very proteins that are manipulating the immune response. Unfortunately, spike is one of those proteins.

And, you know, so the challenge with all of these things is to make sure they're safe and effective, and pure and all that. But that's the reason, the logic, why a gene-therapy-based strategy makes sense and, in particular, the difference between, say, an adenoviral-vectored vaccine, which is a DNA cold virus, it's putting the gene of the other virus all the way into your cells in the nucleus where the DNA resides, versus an RNA strategy. The logic – this was the basis for the

whole excitement about RNA as a vaccine, the “aha” moment – is that RNA gets degraded fairly rapidly, whereas DNA will stick around for a long period of time: adenovirus vectors were made to produce lots of protein for a long period of time for gene-therapy purpose.

RNA can be dosed more like a drug, it's more kind of like a long-acting drug, relatively long. You dose it, it gets into cells, in theory, it's degraded within a few hours, it produces proteins while it's there; those proteins may last for days or months, depending on the nature of the protein in the cell, but the RNA part itself is there for a fairly brief period of time, and then it gets degraded. So if there's a toxicity, it's not there in your body for a really long time.

You know, with a classic gene-therapy strategy, like a retrovirus vector, the only way that you could fix somebody that was having a problem would be to somehow go in and cut out all those cells. And you can't do that, because it goes all over in your body. So that's a kind of a risk with the classic gene-therapy vectors.

And the idea of the RNA is that you can dose it more like a drug, it produces its effect for a few hours, and then it's gone. So then if you want more, you can have another dose. That's the logic why potentially, if you're a pharmaceutical company, that's a great idea, because they like redosing because every time they get their little, you know, they get their Frank, or 100 Frank, or whatever they get for that drug. Right? Every time it's dosed. So they like the idea and it has advantages for safety, but it's a very expensive molecule to make, and, you know, these aren't cheap vaccines, that's why they're not really so useful for large outbreaks in emerging economies.

You know, they were intended more as a specialty product, rapid response which you can give, like if you want to contain an infection, when it just starts. They might be more appropriate for that. But for large-scale deployment across the world, that's turning out to be an expensive and difficult process. Have I answered your question?

IB - Yes, I just want to know, and what about the side effects of these vaccines?

RM - So **the side effects get complicated. We generally right now have two categories of genetic vaccines, right? we have the recombinant adenoviral-vectored one, so that's Oxford Sanofi AstraZeneca is one of them, Johnson&Johnson is another one, and then we have the mRNA vaccines, and the two that are available worldwide, you know, in selected countries are the BioNtech one that Pfizer promotes, and the Moderna one. Focusing for a moment on the adenovirus-vectored ones, those are generally designed to produce large amounts of protein for long periods of time,** so sustained expression, and yet the immunogenicity seems to be lower, and in some cases the efficacy seems to be lower. Not clear to me why that's happening. That's counterintuitive. It may have something to do with the nature of the vector and the complications associated with it and the immune response against the vector itself, because that's also a virus.

So, in general, those vaccines seem to be provoking some of the symptoms sooner. The signal has been detected of the adverse events of thrombosis, that's blood clotting, and some of the autoimmune diseases like Guillain-Barré syndrome seem to be showing up first in the datasets associated with the adenovirus vectors, so that's consistent with them making higher levels of protein for a longer period of time which is what you'd expect. And you'd expect that, if that same type of adverse event was occurring in the RNA, then it's likely that it's not due to the platform, but rather the thing that's being produced, and they're all making the same protein, and by the way, that protein is present in the virus that causes the disease, so that's why we're using spike. So we've got spike in the virus, we've got spike in the adenovectors, and we've got spike in the mRNA. The spike in the virus is known to be cytotoxic, directly cytotoxic, to affect ACE-2 receptor activity, to open the blood-brain barrier, to cause us a large amount – the information comes in, you know, every week or every month of more risks associated with native spike. So the pushback is: is the vaccine toxic just because the native protein is?

And so people have said "Well, they've engineered the vaccine to be less toxic". Well, that's not actually true. The mutations, two amino-acid mutations are put into the spike protein, typically, to keep it in the open conformation rather than the more closed conformation that it develops after it binds to its ACE-2 receptor, and

that's used to inject the genome of other parts of the virus into the cell, okay? so spike is a knob that sticks up, it has three identical components, they assemble into a trimer, they each have interfaces, they have edges, and they move around, they're flexible. And so these mutations are there to keep them more open, thinking that the antibodies to the pocket are the ones that are going to be important; and so to make it more immunogenic they did this. It turns out that those aren't the most important antibodies; the most important antibodies are the ones that are up at the edge, and at the junctions, okay? Those are the ones that are blocking the infection and disease.

But **they didn't know** that at the time and they also didn't know **about all these toxicities, so we can't really blame them, except that they kind of rushed it and they didn't challenge each other and think very hard. But that's what happens.**

So there appears to be toxicities that are similar across all three platforms. Now, in addition, the RNA is untested. The lipid component, especially (remember I said that the lipids are positively charged and they bind around the RNA and they coat it) so the lipid component hasn't really been used – these new synthetic fats haven't been used in humans a whole lot before. And at least the Pfizer data package from their common technical document, that is their briefing document they give to the regulatory agencies, shows in a very limited number of rodent experiments that this lipid seems to accumulate in the ovaries. It's about 12%. And so there, may be, you know … and it goes to other places in the body and accumulates there, bone marrow and spleen and liver and others. So we can't say that there aren't problems that are associated with the lipid component, because there just haven't been the studies to show whether that's the case or not. So I think to be honest you have to say that the adenoviral vectors have been tested in multiple other viral vaccines. And we have those data. So we know what the problems are with adenoviral vectors. This kind of profile of blood clotting and autoimmune disease that we see coming out has not been seen with those other vaccines as much. So it seems that it's not adenoviral-vector platform problem. Now, we're also seeing, in addition to the thrombocytopenia, that's low blood platelets, and thrombosis, that's clotting and that includes deep venous thrombosis,

that’s big clots, as well as micro-coagulopathy, that’s little tiny clots in your small vessels, we have these signals of autoimmune disease, and there's also antiplatelet antibodies among those. We don't fully understand what the autoimmune disease spectrum will be, because that's going to take years to figure that out. We have the problems of the cardiotoxicity, so this is the cardiomyopathy and pericarditis. Those are also seen in the disease itself.

They could be triggered by this micro-coagulation in small vessels, that could be a cause. There are those that say that these problems are really relatively trivial, and they go away. Like I said at the start, damage to heart and lung doesn't go away, it just scars. So the children that do develop these problems, their hearts are never the same. They will develop scarring where this has happened, and that's just the truth of it. It may be that they don't show, you know, they still run around as much as they did before, but that doesn't mean that their hearts haven't been damaged permanently. There are many other things that are showing up at low frequency. And this is hard to detect and resolve whether they're vaccine-associated or not, because the nature of how we're capturing the data and the self-reported systems aren't very good for allowing us to come up with a rigorous assessment. So there's various signals, including the female reproductive health signals, having to do with, you know, alterations in periods, menstruation, and perhaps worrisome. Many women have experienced this. It's not officially recognized, yet women after woman after woman says “Yes, I've experienced this”. There are women that are postmenopausal that have started bleeding, that's often considered a sign of cancer, that may or may not be cancer-related in this case. Another one that's coming up is reactivation of latent viruses, so shingles is one example that's very obvious. It seems to be triggered by this. There are many others. There's some concern in terms of reproductive health, spontaneous abortions in the first and second trimester that's not proven yet, but it's a risk right now. So the databases don't allow these to be characterized well, but one that many virologists and vaccinologists have been most concerned about is antibody-dependent enhancement or vaccine-generated enhancement of disease.

This does happen with some vaccines. Historically, it has happened quite a bit with prior coronavirus-vaccine development both in animals and humans. The period of time where that would be most likely to manifest, to show itself, is in the waning phase of the immune response.

We now know that the durability of these vaccines is only about six months so that means that that term durability refers to how long does it provide protection. So that looks like it's about six months, certainly with Pfizer.

And so, if antibody-dependent enhancement was to start showing up, and there are some signs in some of the data like from Israel, that that might be the case, then you would expect it to start showing up about six months after full vaccination. So we have to watch for that right now.

And we should know in the next two to three months whether that is really manifesting as a significant problem. To date it does not seem to have been, so maybe we're going to get lucky. So there's a brief overview of adverse events and risks.

There's various physicians that are doing the study where they measure, they do a blood draw in the laboratory assay called D-dimer that detects fragments from blood clotting, the coagulation cascade. And so they will draw D-dimer levels before vaccination and after vaccination, and there are many that are claiming that about 60% of patients show elevated D-dimer after vaccination, so that suggests that the vaccines are triggering this micro-coagulopathy problem, and that would probably be due to spike if that's happening.

So, it's still evolving picture. The observation is made by many practicing physicians, particularly ones that are focusing on the chronic COVID symptoms that we call long COVID, that many of the symptoms that are being reported at lower frequency in the vaccine recipients are very similar to these chronic symptoms that are seen after COVID and so the hope is that the same drugs can be used to treat one and treat the other. But again, that would be a sign suggesting that the native spike, the spike protein that's involved, that is being produced in your cells, using these genetic-vaccine strategies may be the problem and so now we talk about second- and third-generation vaccines.

The other bigger risk is one that's been highlighted by Geert Vanden Bossche, I think I mentioned him earlier, which is that universal vaccine strategy, where we deploy vaccine to everybody all across the world, just based on fundamental basic virology, is likely to generate vaccine-escape mutants and result in kind of an arms race between us and the virus, where the viruses are driven more and more evolutionarily to overcome the ability of the body to mount an immune response against certain spike epitopes. And there's ways that viruses do this through glycosylation, or other modifications, to make it so that they can hide their weak parts, it's like putting on armor. So it's a metaphor that works for the Swiss: I know that you have long been skilled in the production of armor. And so we have the Swiss Guards, right? But so I think that's a good metaphor that the virus can learn to arm itself to escape the immune surveillance caused by the vaccines.

And if that happens, because all of us will have been trained, immunologically, to have the same response against the same focus protein, once the virus learns to escape that particular immune strategy, then we all become very susceptible to a new mutant. And that's a big worry.

So a good argument can be made that a more intelligent strategy is to deploy drugs, to blight vaccines to the people that are most at risk for disease and death, like the elderly and to not vaccinate the majority of the population so that we don't have this selective pressure. This is how our immune systems are designed really, because we have a lot of genetic diversity in our major histocompatibility-complex molecules. These are the ones that control how we each mount an immune response. So your immune response can be very different from mine without vaccination. With vaccination, yours and mine are going to be similar. So, you know, this is arguing about the big picture of us as a species, as opposed to us as individuals. And I think there's a lot of merit to what he's saying.

The problem is that it you know, this is kind of advanced virology and epidemiology, and it's really hard to help public-health figures and government officials to understand this.

You probably don't have children yet. So there's a saying if you give a three-year old a hammer, everything becomes a nail. And we're kind of like that with vaccines sometimes. And Geert is arguing persuasively that we need to be a little

more sophisticated and just use the hammer where we need it, and don't use it on everything.

IB - I agree with you, absolutely. Thank you a lot, Mr. Malone for this interview. It's been an honour to know you and to hear your words.
And I know you will have a conference in Rome in a few days.

RM - Yes. Really looking forward to it.

IB - Okay. And so I hope to meet you again soon from alive.

RM - Okay.

IB - Thank you and have a wonderful day.

RM - You too. Bye bye.

IB - Bye bye.