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CONVERSATIONS WITH MIKE MILKEN

A Special Episode: Curing and Preventing COVID-19

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Mike Milken: Welcome to Curing and Preventing COVID-19. It's been a long journey for all of us during this period of time beginning in February when Dr. Jonathan Simons and I began, as a team, to reorient our activities towards COVID-19, and at the same time maintain the clinical and translational research activities of the Prostate Cancer Foundation. And today we will have a session covering how the biomedical community has responded to COVID-19.

One of the most interesting findings as we began to look at the data related to work that we had done at the Prostate Cancer Foundation by Dr. Peter Nelson with a report in 1999 and hundreds of follow-up research areas under relationship to TMPRSS2. And the fact that if you were on androgen-deprivation therapies, suppression of testosterone it discovered when we looked at the data in Italy, that very few people died who were on this therapy. And as this work developed in R&D – and over 400 researchers had worked on it – it appeared that it was testosterone which had the ability to create TMPRSS2 that effectively served as a key to open the door to your lungs.

What is the link between cancer and COVID-19? One of the simple ones was to understand the cytokine storm and many of the immunology efforts that have fired up your immune system causing over action of your immune system, causing side effects and potentially death.

And so, it's like calling up the Army and the Marines and the Navy and the Air Force and the Coast Guard. And so Podcast 50, which covers the cytokine storm, but focuses both

on TMPRSS2 and a small biotech company that had recently received Phase Two approvals for lung cancer were focused on this issue.

I'm going to turn it over to Dr. Howard Soule, and he will lead our discussion today. Howard?

Howard Soule: Thank you, Mike, for that a truly outstanding introduction to an absolutely unprecedented time in all of our lives, and really the history of the world. We pivoted our oncology science towards COVID-19 in late February, early March. We also were aware of the co-receptor for the virus called TMPRSS2 that Mike mentioned. This molecule plays a part in the earliest steps of carcinogenesis turning a prostate cell into a prostate cancer cell. Early on in our funding many years ago, a young scientist at the Fred Hutch named Peter Nelson had actually determined when he first cloned TMPRSS2, collaborators pointed out that this was part of the influenza viral entry mechanism into pulmonary cells. So, the first thing we did as we always do at our foundation is we created a couple of very large knowledge exchanges in the virtual space on TMPRSS2.

So we're going to go much broader than TMPRSS2 today. The first person I will introduce is Dr. Joseph Vinetz from Yale University. Joe is studying repurposing a medication camostat that is used in Asia to treat acute pancreatitis, but this drug is known to inhibit TMPRSS2, and clinical trials are getting kicked off and this is a program that's being funded by a generous donations to the Prostate Cancer Foundation. We're so glad to have you with us this morning. So Joe, why don't we start out with the story of camostat and TMPRSS2, and how that clinical trial is developing?

Joseph Vinetz: I'm a physician scientist and my whole reason for what I do is to be able to understand the science for the good of people. And so last March, I had everything canceled on me. I was supposed to give an academic seminar here and do a meeting there. And then in New Haven at Yale New Haven Hospital, we got this enormous onslaught, which was just a bit delayed from New York City, not to the scale that New York had it, but really that went and tested the metal of every physician, nurse, healthcare provider in the whole state of Connecticut, including the Yale health system. And so, our group of 40-odd clinicians in just infectious diseases, we were all called on board to do COVID-19 consultation in the hospital.

We saw thousands of people over those few months from March until May, almost 500 people in the hospital at the max, with a couple hundred people on ventilators. We were all frustrated because all we had was hydroxychloroquine, which I was doubtful, and some of my colleagues were doubtful of. But clinicians just do practical things. So we tried it out and didn't do much. We did some other immunomodulatory treatment and that seemed to be pretty good; tocilizumab, the IL-6 receptor antagonist, that seems to block a lot of the inflammatory progression. But I was frustrated because we could really

do nothing specific for COVID-19. And so, reading the literature, a very formative paper was published in Cell by Hoffman in a group out of Germany that showed that a TMPRSS2 inhibitor, camostat, that blocked entry of SARS COVID-2 in vitro assays.

People who thought it was interesting didn't want it to progress to a clinical trial because it was too much work or too difficult. And I basically was working in my office seven days a week and got an approval from the FDA for an investigational new drug application for camostat. This is a drug used in Japan for pancreatitis, but is not licensed in the United States by the FDA. And there is all sorts of complicated regulatory stuff. But we were able to convince the FDA that a biologically focused clinical trial, using camostat would be a good thing to do.

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> **Yale School of Medicine**

And as we got all of the regulatory approvals in place, because Connecticut so well-behaved, our patients essentially went away and we had virtually no COVID-19 outpatient that would be suitable for enrollment in an outpatient clinical trial. So all of the early focus clinically was on hospitalized patients, but it seemed to me that a pill that could prevent the progression from infection to severe disease, which happens in maybe 5 percent to 10 percent of all infected people, maybe a magic pill might be able to prevent that. And so that was the guiding principle behind hypothesis generation, figuring out how to make a proper clinical trial based upon appropriate enrollment criteria, such as a new positive test, an active infection, actively replicating virus. A lot of biology goes into a clinical trial like this. And so, we opened up actually in mid-to-late June; we had a few patients and then we stopped because we had, first of all, no new patients, and second, those few patients who would be eligible didn't want to be in a placebo-controlled trial. And actually another issue was we couldn't get people into our COVID biosafety-restricted clinical sites. We had a lot of obstacles to overcome for this trial.

And so we've been lucky that the saliva-direct test that Yale developed – Nate Grubaugh in his laboratory – a quantitative PCR test to look at the effect of the drug. So the inclusion criteria are people with a new COVID-19 infection within three days, and then they're either getting placebo or camostat, and then we compare the amount of virus in a nasal pharyngeal swab or saliva or both. At four days compared to day zero, and then we compare that between placebo and a study drug groups. And this is the only way – the gold standard – to find out if a drug works

The SARS-2 coronavirus, with the spike protein, this trimeric protein on the surface, binds to the surface receptor called ACE2, which is involved in blood pressure regulation in the body. And once the virus binds to ACE2, it then is susceptible to being processed by TMPRSS2, again, the protein that the Prostate Cancer Foundation supported discoveries led to in camostat is a searing protease inhibitor. It's a certain class of protease and camostat blocks that protease activity to activate the virus for getting into the cell. This is a repurposed drug already available and manufactured in Japan, and it's super safe. It's been used for 30 years. And I started this out quite naive, really. I didn't know how to go from an approved drug in another country to getting it into people in the United States. And it's a whole new set of challenges. And so where we are now is we've got camostat at higher doses than the typical label allows – the FDA suggested and approved that – and that's now starting in people. We already have a few people who did well. There's a small paper published out of Germany where we're talking nine patients, five of whom received hydroxychloroquine and four of whom received camostat. Camostat led to rapid symptom relief while hydroxychloroquine essentially was a placebo. And so there's some indirect evidence that camostat works at least in that moderately severe group. And now we are testing it, starting at Yale, but we have a series of external sites to expand this clinical trial to. Some very exciting news, once we get the phase two study going, the NIH has expressed significant interest in leading to a 2,000-patient outpatient trial.

Howard Soule: Joe, thank you very much for that. I would like to next introduce Dr. George Yancopoulos from Regeneron, who will share with us the evolution and status of the monoclonal antibody cocktail against SARS COVID-2 that his company is fast tracking in the clinic today. George?

George Yancopoulos: Well, thank you, Howard. It's a privilege to be involved in your guys' effort here. I thought that before I talk about our antibody cocktail approach, since it's already come up, this notion about repurposing drugs and also the concept of cytokine storm came up, and since we were very involved in these sorts of efforts as well, I thought I would just very briefly start with that before sequewaying into our antibody approach. But, in terms of repurposing old drugs, I think that we all have to understand that science is very hard, and particularly clinical science is the most difficult, I think. And most things we have to understand fail, particularly retrying old drugs to cure new diseases.

And I really commend Joe doing as he called it, the gold standard, to test in clinical trials drugs to prove that something that people think might work actually does work. And Joe mentioned that he actually thought, as did many, many others that anti IL-6 drugs that work in cytokine storm in another setting, might actually be working in COVID-19 patients; particularly in the most severely ill, those on ventilators and so forth. And in fact, they were actually clinical trials, but not the gold standard sort of trials that Joe is

doing, but that are not controlled. They were done in China and Italy using either – there are two approved IL-6 receptive drugs, one from Roche Genentech and one from our company. And they tried these drugs and they claim that they were miracle drugs. We realized how important this possibility was, so very early on our organization immediately committed to testing our anti-IL-6 receptor blocker. We committed hundreds of millions of dollars, and we did actually the first rigorous gold standard Phase Three trial in COVID-19, and we actually showed that blocking cytokine storm with these IL-6 receptor inhibitors did not provide profound benefit. Our negative results in this area was subsequently confirmed by Roche Genentech testing, their IL-6 receptor blocker. So that little intro, I just wanted to get across how hard it is to do clinical science and particularly the field of repurposing old drugs to treat new diseases like COVID-19, and how important it is to do exactly what we did and what Joe is doing now – to do these rigorous gold standard clinical trials to really understand and prove whether a drug is providing false hope or whether it really can make a difference, and to what extent that can really help patients.

Now moving on to what we're calling our antibody cocktail approach, I thought I should get back to basics and just describe what the body normally does and how it deals with viral infections, such as the flu and COVID-19, and why we think instead of repurposing old drugs, developing targeted-specific new drugs that do exactly what the body normally does might be the best chance to really fight this disease.

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- George Vancouplous
Regeneron

So, when you get a viral infection, it could be the flu, or it could be COVID-19, the body's immune system responds by generating what I think we've all heard about – these antiviral antibodies that bind and kill the virus. These antiviral antibodies clear the initial infection, and in some cases they can last a lifetime protecting against future reinfection by the same virus. There's some issues and controversies about this regarding COVID-19, but I think a lot of this is proving to be true and will still be true despite exceptions. Now vaccines are really an important approach and they build on what the body normally does, which is why vaccines can be so successful. They literally trick the body to make a similar immune response to what it normally does to the real virus; that is, when you're giving a vaccine you either give something that is the dead virus or a weakened virus, or a very small part of the virus, such as the COVID-19 spike protein. And when you give this vaccine, you're trying to

elicit long-lasting antiviral antibodies to protect against the infection that you've artificially raised by tricking the virus using this vaccine approach. Now, some vaccines work really almost perfectly. They can protect a hundred percent of the people and can last a lifetime such as the measles vaccines. Some do much worse, and can only protect a fraction of the patients and only last a short time.

And one of the big issues and problems and challenges with vaccines is that some of the highest-risk individuals – that is the elderly and immunocompromised – those are the people who often don't mount their own immune response and response to vaccines very well. They don't respond to the virus very well, which is probably why they get so sick and they have such a higher risk of death. So those very people who don't respond to the virus and attack it very well, often don't respond to a vaccine. Now, we all, I think society, we desperately all understand we need a vaccine, and we're all hoping that the Moderna efforts or efforts at other places really produce really useful and protective vaccines. But even if they do, we may still need to protect those who do not respond well to the vaccines, such as the elderly or the immunocompromised, or to actually treat those were already infected.

So, no matter what we do, this scourge is going to continue, and there's going to be people who are not going to have access to the vaccine, they're not going to take the vaccine. And once you're in already infected, it's too late to take a vaccine. You have to take the vaccine weeks in advance of when you would be challenged with the virus.

So what can you do? Well, at Regeneron over the last several decades, we've pioneered making fully human antibodies and antibody-like drugs outside of the human body; that is we can grow them in large bioreactors and we can highly purify them, and we can give them back as a new class of biologic medicines. And some of our drugs that we develop this way to treat diseases ranging from blindness to asthma, to heart disease to cancer, have been some of the most important biologic drugs that have been approved over the last 10 years.

We recently took this approach of being able to make fully human antibodies outside of the body and applied them to viral infections. We started with Ebola. And unlike vaccines, when you inject these into patients, they provide immediate protection. It's like having taken or already been vaccinated, but with the most effective possible vaccine. We can give antibodies to levels that are thousands of those that the body can normally generate on its own in response to the virus or to a vaccine.

And so the hope is by giving these very high concentrations of antiviral antibodies, you can not only prevent infection like a vaccine, but they can also be used to treat already-infected individuals. And Ebola was actually the first example of Regeneron developing our antibody cocktail approach for infectious disease. And in fact, we hope that it'll prove to be the first approved antibody cocktail approach for any viral infection disease and the first approved Ebola treatment, where it saved the lives of people both in the

early stages of infection, even people in the late stages of infection as shown in a clinical trial that was carried out in the Congo by the World Health Organization.

So what have we done at Regeneron in terms of this approach with regard to COVID-19?

Basically, we used exactly the same technologies that we use to create our antibody cocktail against Ebola, which we did in nine months going from an initiation to clinical trials. We selected our antibodies from a very large collection of antibodies, and we believe we selected the most potent antibodies available, and our antibodies we've tested them on to use ones that are active against all naturally occurring viral mutants described to date. We chose to develop an antibody cocktail culture consisting of two antibodies. This notion of using cocktails, combinations, is really based on the fundamental realization that was made back in the days of HIV, and it's been subsequent shown to be true for other viruses, that combination drug therapies can prevent viral drug resistance by requiring simultaneous mutation at multiple genetic positions.

We reasoned and have now proven rigorously that the same occurs when you're using antibodies use you need multiple antibodies. So, our antibody cocktail we've shown potently prevents infection in non-human primates, can result in what they call sterile immunity, and can likewise also treat infection in non-human primates that have already been infected. Obviously, as I said, I think we need the whole ecosystem; we need all the efforts that are going on; we need to continue to test repurposing of drugs, even though the anti-IL-6 approach has not proven effective. Hopefully, camostat or other approaches that are going to be testing older drugs might work. We're going to need vaccines to create as widespread herd immunity as we can, but we're also going to need drugs that are targeted against the virus that can provide immediate protection and also treat those who are already sick.

So we have multiple clinical trials ongoing with our antibody cocktail, both for prophylaxis or prevention, and also for treatment. Our treatment studies include both outpatients, those that Joe described those that are in the early stages of infection that we're hoping to prevent from getting seriously ill, but we're also trying the sickest patients in separate clinical trials, those that are in a hospital and on ventilators and have little hope. Our efforts of course, are all supported and being done in collaboration with BARDA, the Department of Defense, the National Institute of Allergy and Immunological disease, and recently announced a major partnership with Roche Genentech. One critical thing about these antibody approaches is that they are much harder to make these antibodies than for example, vaccines. It's another reason we need vaccines; you can give them much more broadly to many more people.

But these antibody approaches, as I said, can be very complimentary can work where the vaccines have failed. But they're much harder to make; it's harder to treat as many people as you would want. And, we're very impressed that Roche Genentech, which

did not have this sort of effort on their own, realized or decided that we had the most-promising antibody cocktail approach out there and they decided to partner with us. And because they like us are a very large bio-manufacturer together, we've tripled or quadrupled the ability to provide or hopefully to provide this, if it ends up being effective, to the patients who need it by dramatically increasing the manufacturing capacity of the effort through this collaboration with Roche Genentech. That in summary is where we stand in what we're doing with our antibody cocktail approach.

Howard Soule: Thank you, George. And thank you for creating an R&D culture that allowed people to do what you guys were already doing really well for many, many other human diseases and pivoting on a pin – this is a monumental achievement of milestone, and we thank you for that very much.

So, I want to get to the vaccines now with Dr. Zaks. Tal is now the Chief Medical Officer at Moderna, a company that unless you've been asleep for nine months, you would know that they are producing and testing in Phase Three, one of the first vaccines for COVID-19.

You guys also pivoted with record speed in creating a vaccine, which you're in the middle of right now, as are a number of other companies. So we want everybody's vaccine to work. We want everybody's antibody cocktail to work. Why didn't you tell us about the experience at Moderna, where things stand.

Tal Zaks: Thank you, Howard. And thanks Mike for inviting me today. Joe and George actually set the ground quite nicely for understanding what it is we're trying to achieve with our vaccine. So I'm going to spend a few minutes just explaining the basic of our technology, because I think once you understand it, you understand why we've been able to move so fast in this instance. But you're right, the pivot for us back in January, and I give up my boss Stephan, our CEO a lot of credit, he was already on the phone to the NIH, even before that sequence was known because we had been working with the NIH for a number of years now, recognizing the potential of our platform to react quickly. And so in a way, we were well set to start this race. Of course for a small biotech company that's investing everything it has in an existing pipeline, to shift so rapidly so many resources over to this was not a simple decision. But, I'm really glad we made it in that we made it at the time that we did.

You can think about our drugs as information drugs. Every cell that makes protein, the information on which protein to make is encoded in this transient message, what's called messenger RNA. It copies just that piece of genetic information from the DNA, which is the same in every cell, but every cell is different because every cell has different MRNAs that lead it to make different proteins. And so once you can get an MRNA into a cell with an instruction set of what to make, you can then coax that cell to make the protein in vivo, in our body. And so we've kind of turned the biotech paradigm a little bit differently.

The central dogma of biology is that DNA makes MRNA and MRNA makes protein. That's true of every living organism. And if we can get that intermediary, the MRNA, into our body to make a therapeutic intent protein for a medicine, a vaccine or therapeutics, it's got a lot of advantage because all of our drugs then are actually the same. They all start just with a code, and if you change the code, outcomes a different protein. So we had already been doing this for infectious disease vaccines for a number of years, as I said, because we saw the utility to react quickly because the process by which to make this messenger RNA, it's not made in cells like recombinant protein technology, it's all made in an accurate solution. And so you can make it relatively quickly and you can condense it. A large bioreactor for us is 30 liters, so it's, it's relatively small to get the MRNA that you need. Now, the trick here is to get the MRNA into the cell and convince the cell that that MRNA, once it's inside, it's kosher. Now, why is this so difficult?

The most frequent types of viruses are RNA viruses. And so evolution has evolved many mechanisms for us, both as unicellular and then multicellular organisms, to reject something that looks like a virus. Because there's nothing more scary to a cell than a four nucleic acid coming in and trying to take over its machinery. Now, after a number of years and a lot of investment in science technology, we've actually figured out how to get that MRNA into cells and have the cells think by and large, this is kosher, I should go make protein out of it. And so now if we encode that spike protein, right, the thing that the virus makes that allows it to get into chip into cells as Joe had described, and we use it in a vaccine; so we inject it with a needle into a muscle, it gets into our lymph system, it goes into our immune cells and then the body starts to make that protein inside its immune system. And the immune system goes, hold on, I've never seen this protein before. This is something foreign. And that's what triggers our immune system to start to make antibodies against it.

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> **Moderna**

And the beauty here is that our vaccine doesn't have the virus. There's nothing permanent here. There's nothing that replicates here. This messenger, RNA, is transient within a day or two it's degraded by cells into food and it's completely gone. And what we've done is focus the attention of the immune system, just on this spike protein. In fact, we've never had the whole virus in our labs anywhere. We don't need it. This is all

based just on knowing what the information is for the sequence required to make the message to make the protein.

The beauty of this technology is once you've proven it works once, it's likely to work again and again and again and again. And in fact, this is the 10th virus against what we now show with this technology, out of 10 times we've tried, that we're able to generate neutralizing antibodies in early studies. It's a relatively young technology. We only went into the clinic about less than five years ago. And so our most advanced trials have been Phase Ones and Phase Twos, but we had a good basis to understand, to expect this to work. And as it relates to antigens, the spike protein is actually relatively simple. Of all the things we are trying to recognize to get the immune system to recognize, this one is pretty well understood, and it's another reason why people could start making vaccines so quickly.

Most of the other vaccines that you see are all using the same spike protein to try to elicit a neutralizing antibody against it. The earliest data have actually been published by George and his group to demonstrate that it's actually the neutralizing antibodies that matter. You know, people talk about T-cells and a whole bunch of other stuff, but at the end of the day, the part of the immune system that's critical here is indeed these neutralizing antibodies. Using this technology to generate neutralizing antibody against this spike protein is what makes us confident that this is going to work.

The reason we've been able to go so fast is when you went to make against the spike protein, we had already had a good collaboration with the NIH. And so in fact, this Phase One trial that we've spoken about is one that they have run. So this is all actually not work done by us. And I give our NIH a lot of credit for stepping into the breach here early on. But it's this ability to generate these vaccines very quickly is what allowed us to start that clinical trial so fast. In fact, it was 63 days between the time we actually put the sequence in production and the time the first subject was dosed here. Now we've done even better than that. The reason we've been able to go so fast as an aside is because we've actually been using this technology for a number of years now to try to generate a personal cancer vaccine.

So, we sequence people with cancer: we look at their cancer and we try to generate a vaccine that's specifically tailor made just for that person, right? So an individual, each vaccine is an N of one uniquely. And so we have to produce just that vaccine in small quantities just for that one person. And that's an effort that's been going on in collaboration with Merck for a number of years. So we're already had this infrastructure how to have a quick turnaround time it's enabled by the technology and we were able to get started fast. But the critical piece here is that that same technology enables one to scale up manufacturing relatively rapidly. So we had started as we put this into production. We started clinical trials. We have already started to scale up production, and so relatively quickly, we then use the data from the Phase One; as soon as we had safety, we started Phase Two. And as soon as we had a sense of what the right dose is,

we went into Phase Three. So this was sort of an accelerated development, if you will, we leapfrogged from phase to phase to phase so that we were able to start Phase Three in collaboration with the NIH, testing it in 30,000 people.

What we know today about our vaccine is as follows: first, we've been able to show in Phase One trials that indeed we can elicit these neutralizing antibodies. In fact, we can get them to levels that are higher than those that you see in people who've been sick with COVID-19. And I think that's critical because we believe, and so far, the data suggests that if you've been sick once you're not going to get sick again, at least in the next five, six months. I haven't yet to see a case being described where somebody was ill and then they become ill again. Now it doesn't mean that your ability will last forever. I think its early days and we don't know the duration of protection here, but certainly in the early months we expect this to work. I mean, that's how basic immunology works at the end of the day throughout evolution.

The fact that we can get it to levels that are higher than what you see in people who've been sick, and I think George has described eloquently their proof that indeed you want to get as high as you can have these neutralizing antibodies; that is what makes me optimistic that indeed will be able to prevent disease in our large Phase Three trial. Now there's another important element here which George mentioned, that many vaccines lose potency in older adults. And we know that the older you are, the more susceptible you are to significant morbidity, as well as mortality. We've been able to show with this platform, and this is not I believe by chance, that indeed we're able to induce the same level of potent immunity also in older adults. We've described just this past week data in the 56 to 70 and above 71 year olds that indeed the same level of antibodies that is still higher than what you see in convalescent plasma. And as far as I know, that is a unique ability of our vaccine from those that have been described to date to maintain that level of immunogenicity, even in older individuals. We're able to prevent viral replication in the lungs while we're able to elicit these neutralizing antibodies, and I think that gives me optimism that indeed humans are not going to be different at the end of the day, and we'll be able to demonstrate that this vaccine can indeed protect all of us from COVID-19 disease.

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- Tal Zaks
Moderna

I think in the coming months, you'll expect data from us and potentially some of the other vaccine companies that have also started Phase Three trials that will conclude

conclusively demonstrate that these vaccines can work. I hope all of them succeed because I don't think a single company can carry the weight of what's needed to protect all of us and all those who need it. I think many of us have already started manufacturing at-risk to large quantities, and my expectation is the winter may be tough. I don't think vaccines will be available yet but I think I'm hopeful that at the beginning of next year, we will start to have both data and sufficient vaccine supplies to be able to start deploying it to vulnerable populations. Thank you.

Howard Soule: Thank you, Tal. Assuming some of the early vaccine trials are positive, how long would it take to gain herd immunity in society?

Tal Zaks: That's a great question. It depends on three factors. The first is how fast can we get supplies out there? And I think, realistically, if you look at what the U.S. government has contracted from the leading manufacturers, I expect by the middle of 2201 it could be possible. Number two is, how many people are actually going to want to take the vaccine? The biggest thing that concerns me in the last several months, as those of us who believe in science are toiling away at translating science into medicine, I have started to turn my personal attention on how you translate medicine to politics, in the sense that people out there are skeptical. We're living in an era of polarized public discourse on almost every venue, and that worries me in terms of people's concerns and acceptability accepting what science has shown as it relates to the utility of the vaccine.

If only half the population takes the vaccine, obviously it's going to take longer to get to herd immunity if ever, because it implies that the rest of the percentage required to get the herd immunity will unfortunately come through natural infection. And I think the last element which we will see is how potent are these vaccines. The FDA has set a bar for 50 percent. I think that's good, but quite good enough. I'm hoping that we will have vaccines whose efficacy is somewhere north of 75 percent or 80 percent. We can get to herd immunity with a vaccine that's only 50 percent effective, but I think we'll get there faster if the vaccines are more potent. And so, it's a mixture of those factors and the way they will play out, I think, in the beginning of next year that will drive herd immunity over.

Howard Soule: For both Regeneron and Moderna, what does quote failure for a clinical trial look like? Is it just efficacy or something else? What surprises emerged in prior clinical trials from each company? How does each company handicap the success of its current trial for COVID?

George Yancopoulos: I think Joe started addressing it in his presentation. He described how, first of all, if you're looking for where the pandemic is raging, that's a moving target. So when we did our initial cytokine storm trials with our anti-IL6 receptor drug, where we repurposed that, we did that all in the New York City area. We had that same infrastructure in place, and then just as Joe described, by the time we were testing our

antibody cocktail trial, the numbers were way down and we had to find and open up a whole new series of sites in different locations.

There's also serious issues, and these have been covered in articles about our efforts and Lilly's efforts and so forth, for some of the trials you have to be able to identify that the patients are recently infected. Or you have to identify whether they have already had antibodies and so forth. So testing, just the logistics, the operational issues, become problems. So, we hope that we have been able to deal with satisfactorily, constantly dealing with all these operational logistical challenges, and that all we're left with is the efficacy challenge. Will having a very high level of antiviral antibodies in your bloodstream really either protect you from infection or cure you if you're already sick and will cure you no matter how sick you are? We're hoping that once we've continued to deal with the operational, logistical challenges that all we're left with are these efficacy challenges. But unlike with vaccines, our efficacy challenges are not only in showing that we can prevent infection, but can we successfully treat people at early stages? And also can we successfully treat people even at the latest stages? So there's a lot of efficacy bars and thresholds that we're going to try to meet.

> **"SARS Cov2 only lives in humans, and so if you break the transmission cycle for a few weeks, it theoretically would be gone from the human population. I predict that, and I don't want to play politics, but I think it's going to be primarily gone and that a vaccine will be useful for eradicating those last vestiges."**
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> - Joseph Vinetz
> Yale School of Medicine

Tal Zaks: I think for us, defining the efficacy is obviously the critical point. I think the concern I have is how long it's going to take, because it's a case-driven design, and we need to get to a certain number of cases. And there's a paradox here: the worse the transmission out there, the better it is for the vaccine's ability to demonstrate. If suddenly it all went away because everybody wore masks and didn't get near anybody else, we wouldn't have any cases and we couldn't tell whether our trial was successful or not. We'd have to wait for a very long time where it could be moved. So that's, that's probably my main concern and the way we overcome it is just to do a very, very large trial and try to go into areas where we know transmission is currently occurring and is expected to continue at least to some level.

I think the second element has to do with safety and tolerability. I'm less worried about safety per se, as I am about the perception out there where each individual kind of believes where their risk benefit lies. So what do I mean by that? It turns out that if you're currently activating immune system and we see it after the boost, not after the prime, but after the second shot, people get a bit of flu-like symptoms that evening. You can get some aches and pains, low grade fever, and a headache it's by and large gone the next day, and I think the risk benefit is there in that that level of discomfort warrants being protected from COVID-19. That's not going to be a universally held a belief, and some people are going to say, well, I'm healthy. I feel good. I don't want to feel crappy for an evening to be protected. And it's a bit of a yin and yang here because, you know, if we titrated dose where the side effect profile is much lower, we actually end up with fewer antibodies. That's a function of your immune system getting stimulated. So that's where I'm really curious to see where the Phase Three data pan out in terms of that reactive genicity profile and how it translates to protection from disease and antibody levels.

"There are two approved IL-6 receptive drugs, one from Roche Genentech and one from our company. We committed hundreds of millions of dollars, and we did actually the first rigorous gold standard Phase Three trial in COVID-19."

- George Vancouplous
Regeneron

Howard Soule: To Joe Vinetz, what does COVID look in the future? If you look out two or three years, there will be a number of vaccines, a number of antivirals. How will you figure out the sequence of these treatments and prophylaxis methods? This is not unlike the complexity that an oncologist faces treating a cancer patient; a lot of good drugs, don't exactly know how to sequence them. What can we learn from that and do this better for infectious disease?

Joseph Vinetz: So thanks for the question. It's a great question. What we have seen now is COVID-19 has become really super endemic and has spread in a very fine granular way across all populated areas of the United States and indeed the world. I can tell you that in our very remote study sites in the Amazon, there's COVID-19. There's COVID-19 in rural areas of Iowa and North Dakota and Idaho, etc. So we're in this era now, it's not in the population centers, it's kind of everywhere. So that's point one. Point two is that SARS Cov2 only lives in humans, and so if you break the transmission cycle for a few weeks, it theoretically would be gone from the human population. We even know that 97 percent to 99 percent of people who are infected don't have active culturable virus two weeks later. So theoretically, we should be able now the first point of hyperendemicity and second point of the fact that the virus only lives for our limited

time in people, I predict that and I don't want to play politics, but I think it's going to be primarily gone and that a vaccine will be useful for eradicating those last vestiges.

In malaria, we have control, elimination and eradication. So, the first step is control. The next is elimination from our region and the third step would be eradication. There's a lot of lessons that we can apply from multiple other infectious diseases, contagious diseases, rapidly spreading diseases towards the eradication. I bet you that in five years it's not such an issue. I don't think it'll be even a common infection. I'd even go on a limb here: I think because of our social distancing and mask wearing and hand-washing that we're not going to have a bad flu season at all. I shouldn't say that, and everybody should get their flu vaccine and continue our COVID precautions. But I think that between vaccination, possibly coming up with a therapeutic antiviral drug that this, virus is going to be gone from our population. But it's not going to be fast; it's going to take a couple of years. That's just based upon my gut feelings and that's sheer speculation.

"We greatly underestimate the response of the government in this area by investing billions of dollars in many of these vaccine efforts and antiviral efforts, to not only encourage people to work in the area, but to create an environment that they will manufacture the product before you know if it works so it's available."

- Mike Milken

Howard Soule: Thank you Dr. Vinetz. Mike, do you have any final comments before we close this really wonderful and thought provoking panel?

Mike Milken: Yes, Howard and I just want to add on a sense of optimism. One of the greatest companies built over the past few decades is Regeneron and its commitment. It didn't have to choose to go in this area, but its leadership you heard today sent it in the area and they're not alone. One of the very first podcasts we did in April was with Alex Gorsky of J & J, the world's most valuable healthcare company by market cap. Talked about that they were working on a vaccine, they were going to put it out at no profit in conjunction with BARDA, invest a billion dollars between them and BARDA, and they hoped to be putting it into human beings in January of 2021. The technology to build hundreds of millions of doses is available and is underway. We greatly underestimate the response of the government in this area by investing billions of dollars in many of these vaccine efforts and antiviral efforts, to not only encourage people to work in the area, but to create an environment that they will manufacture the product before you know if it works so it's available.

I think we're all being judged today. Every single one of us, and the question, what can each of us do? And as we look back in 2021 or 2022, in many ways, we'll be judged on what response we took to change the course of history. We, from an educational

standpoint, put on this session today, so you could understand what some of the world's greatest companies and some of the world's greatest researchers are doing. As we listened to the presentation today from these companies, as George pointed out, these antivirals and cocktails work and they work potentially at different levels. And I just want to remind there is no vaccine that works for HIV AIDS, but today two thirds of all the people in the world who've had HIV AIDS live in and sub-Sahara, Africa, and we now have a 95 percent to 98 percent possibility with modern medicine to prevent the movement from the mother to the child in childbirth with AIDS. The world has changed. Moderna, why are we rooting for them particularly? If this works, this way of getting your body waking up to create its own antibodies against, maybe this will be the technology we use for all future viruses that might come down the path.

And lastly, the repositioning of a drug that Joe has been working on. The sheer opportunities that it can prevent serious side effects, if not prevent you from getting the virus. And it's been around for 30 years, the same as many of the ADT drugs. So I just want you to take away today that science is moving and today you had an opportunity to listen to people that are changing the world. I want to thank our panelists for their commitment and diverting their own lives and their companies and organizations to solve the COVID-19 crisis.
