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# CONVERSATIONS WITH MIKE MILKEN

## *A Special Episode: Potential Breakthroughs in COVID-19 Research Coming from Cancer Research by the Prostate Cancer Foundation and FasterCures*


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**Mike Milken:** Thank you for joining us today. This is our 50th podcast and it's quite different from the others. We will have eight others joining us today to discuss the efforts of people who have worked in cancer research over many years and how that work relates to the COVID-19 crisis.

We're going to focus particularly on one potential therapy and work done by the Prostate Cancer Foundation over the past several decades and another example of a biotech company that has interacted with *FasterCures*. That is our goal today as we begin the 50th broadcast on how we're going to accelerate solutions for COVID-19 crisis. The focus of our previous podcasts was to give everyone an opportunity to listen in and be part of a conversation that I was having with a CEO, a Nobel prize winner, or people running government agencies, and trying to look at this crisis from every

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***–Mike Milken***

angle, from the largest employers in the United States and leaders of the largest technology companies to those who run hospital systems.

We've spoken with those responsible for the leadership of the pharmaceutical and biotech industries, those in finance about what was happening to the economy and to former heads of the FDA to try to give you a 360-degree look at what people are doing, to bring an end to this crisis. We have to remember that 50 percent of all economic growth that's occurred in the last 200 years can be traced to advances in public health and medical research. One of our great advantages is the enormous investment made around the world over the past decades in medical research, basic science, translational science and clinical science. Today, you'll hear about potential opportunities to produce a vaccine in less than 12 months, many of which have already gone into human beings. We'll look at antivirals, antibodies and other things that have safely gone into humans.

I will introduce you to two leaders that I reached out to three months ago. Esther Krofah, who runs *FasterCures* and then Dr. Jonathan Simons, whom I challenged as the head of the Prostate Cancer Foundation to look through everything that has occurred in our cancer work that safely went into human beings over the decades. You will hear from eight leaders who have been focused on COVID-19 for the past three months and promising opportunities that might lead the way to bring this crisis to the end.

*CaP CURE* was formed in 1993 as an outgrowth of my personal activities from the 70s and 80s to accelerate medical research. The CA stood for all forms of cancer, P prostate cancer and CURE all life-threatening diseases. More than 15 years ago, it was separated into two parts, one *FasterCures*, which Esther runs and the Prostate Cancer Foundation (PCF), which Jonathan Simons leads.

So, Esther, I'd like to start with you. Please give us a brief overview of the mission of *FasterCures* and what has happened over the past three months.

**Esther Krofah:** Well, thank you so much, Mike. As you mentioned, *FasterCures* was established to accelerate the development of medicines and treatments and what we needed to do in the medical research continuum to ensure that medicines were getting to patients as quickly as possible, and that nothing is standing in the way. So in our normal day-to-day jobs, that's what we work on. One of the areas that we have turned our attention to is tracking the development of treatments and vaccines. We're now tracking over 330 different efforts toward either a treatment and or a vaccine. In fact, as we look across all that is happening from a research perspective, a lot has already gone into clinical trials. Over 81 different candidates are in clinical trials. We expect to see many more over the coming months, and on the vaccine side, we already see 10 vaccine candidates that are in clinical trial.

We have established eight pathways to direct the scientific investigators that are coming to us. On average, we get about three to 10 new ideas every single day and we've established direct collaboration with the VA (Department of Veterans Affairs), with NIH (National Institutes of Health), with BARDA (Biomedical Advanced Research and Development Authority), with CEPI (Center for Educational Performance and Information), with the Gates Foundation, as well as large and small biopharmaceutical companies that have platforms that can establish and accelerate lab work in response to this virus. So Mike, there's a lot that's underway.

***"We're now tracking over 330 different efforts toward either a treatment and or a vaccine."***
***–Esther Krofah, FasterCures***

We've directed a lot of our efforts toward the regulators or those partners that I've talked about and working in partnership with our Milken Institute centers, whether the Center for Public Health, the Center for Strategic Philanthropy and others. We've also been able to work directly with the philanthropic community and with the CDC on contact tracing efforts and others and we'll continue those discussions as we go on.

**Mike Milken:** Thank you, Esther. I also want to thank your family, your children, and your husband for allowing me to call you morning, noon and night on this, and I appreciate your entire team's input.

Jonathan, one of the things I reflected on today is UCLA being represented, the Fred Hutch, the University of Michigan and UCSF. When I think back to my first visits to those institutions in the early 1970s focused on many of my family's serious health issues and our first funding in breast cancer, they are a great representatives of our academic institutions and their ability to accelerate research. You and I were in South Africa and Johannesburg at a medical conference that we were putting on together. On the way back it just dawned on me that the world was about to change, and when you got back that Thursday, your world changed also. Thank you for joining us today. And I'll turn it over to you.

**Jonathan Simons:** Well, thanks Mike. It's a privilege for my colleagues and I to be a part of this amazing series you've put on that has educated thousands and thousands of people in real time. And the headline for our portion of this is that cancer research may have already provided incredibly important clues to understanding the COVID-`9 virus. Cancer researchers in the prostate community have swung into action and redeployed and under five weeks in an extraordinary

way, which we'll get to later. At little later I will introduce professor Matthew Rettig. Dr. Rettig is a professor of oncology at UCLA, leader of their prostate cancer clinical trials program, but is also the chief of the David Geffen program at the West LA VA. He's a leader in our Veterans Administration prostate cancer precision oncology clinical trials network.

One of the messages today is how important the Veterans Administration clinical trials program will be to accelerating the testing of new drugs. The VA is the largest health system in America, and has the best electronic database that will allow us actually to accelerate the testing of new medicines, vaccines and actually speed FDA approvals for new anti COVID-19 strategies. We think our partnership with the Veterans Administration for precision oncology puts us in a great position.

***"In Casablanca, Rick … says, 'of all the gin joints in all the towns in all the world, she walks into mine.' Well, of all the 80,000 proteins in the human genome, COVID-19 walked into the Prostate Cancer Foundation cafe."***

***–Jonathan Simons***

So we have this extraordinary group of cancer researchers and cancer fighters and they all have something in common: they're contributing very actively to the fight against COVID-19. In *Casablanca*, Rick is sitting there and looks up and Ingrid Bergman comes into the cafe and he says, "of all the gin joints in all the towns in all the world, she walks into mine." Well, of all the 80,000 proteins in the human genome, COVID-19 walked into the Prostate Cancer Foundation cafe.

As we're going to discuss, the SARS COV2 virus breaks in and infects a lung cell and multiplies, basically by turning a door handle to get into the cell. That door handle was identified by a group in Germany. It's called TMPRSS2, and is a gene that's involved centrally in prostate cancer. This German group, basically only six weeks ago, ruled in that every death – all quarter of a million deaths so far on the planet from COVID-19 – had to occur by the SARS virus getting into cells in the body through this prostate cancer protein. The TMPRSS2 gene is made in men and women. We think it's in every cell in the body, but men are two or three times as likely right now to die of COVID-19 as women.

We believe that TMPRSS2's ability to open the handles on the door is influenced by testosterone. So if you have a Y chromosome and you have normal testosterone in your body, you literally have more TMPRSS2 on the surface of some cells. It's a really important question that needs to continually be tested, but the opposite is also true. If you lower testosterone with drugs like Lupron, we know you lower the amount of TMPRSS2. For both men and women who get infected, and both men and women who succumb to COVID-19, the virus got into the cell through a key hole called ACE2. Basically putting a key into a lock and turning the door handle. So, the TMPRSS2 protein is absolutely central to understanding how this virus kills human beings. There have been

958 research papers on prostate cancer and TMPRSS2 written since 1999 when Professor Peter Nelson made the first research report. We have an extraordinary FBI dossier, so to speak, on the TMPRSS2 protein that allows us to have many really interesting ideas about how you could stop the virus from getting in in the first place. If you can make new kinds of medicines or redeployed existing medicines, you might be able to reduce the amount of TMPRSS2 in your lung and your respiratory track.

You Mike, you along with several other philanthropists supported in 1999 Lee Hood and a very young professor Peter Nelson to go out and look at every gene that might be overexpressed or abnormal in prostate cancer. So I was going to ask Pete Nelson, who discovered TMPRSS2o in prostate cancer, to tell us a little bit about the biology of TMPRSS2. And then we'll evolve the story to how you might use FDA-approved drugs for prostate cancer to slow down or stop the spread of the virus. Then we'll move on to how we could in real time make even better TMPRSS2 drugs and bring forward very quickly out of the cancer research community, a whole new class of anti COVID-19 medicines in record time. So with that, Pete, would you talk a little bit TMPRSS2?

**Peter Nelson:** Thank you Jonathan. And thank you Mike. It's really a pleasure to be here. I'll get into the TMPRSS2, but I thought first it's useful to just display a little bit of the breadth of work at a typical cancer center that has rapidly pivoted to understanding and studying COVID-19. And we're not unique by any means at Fred Hutch and the University of Washington; I think you've seen a major pivot in cancer centers across the U.S. I would just say the cancer research community has a tremendous background in understanding the immune system, which has clear relevance for COVID. And a lot of this work comes out of preexisting cancer research. We know a number of drugs or molecules already approved or in pretty far-advanced testing could now be redeployed for COVID testing. The example I'll give you of TMPRSS2 really tells you how disparate areas of science really can convert.

In oncology, we've often used prior work in developmental biology, genetics and physics. But in this case, we're seeing prior and ongoing research in cancer that has an impact on COVID. So, as Jonathan mentioned, this lifecycle of the current COVID virus depends on two proteins that are produced or expressed in the lung. One of these is TMPRSS2, and the other is ACE2. We were quite interested many years ago in TMPRSS2 because it's well known that prostate cancer is highly dependent on testosterone or androgens. From work supported by the Prostate Cancer Foundation decades ago, we and others were trying to identify the genes that were turned on or turned off by testosterone in the prostate that could drive prostate cancer growth. During these studies, we identified this gene TMPRSS2 as being highly produced in the prostate gland and was turned on by testosterone.

We actually identified an inhibitor, a drug that would block the TMPRSS2 activity. A few years later after we published this work, we were contacted by a group in Germany who had a clue that TMPRSS2 may be important in influenza transmission. The important key here is that the transmission or the infectivity of influenza is actually quite similar to now. What we see with COVID infection. We had made a mouse where TMPRSS2 was completely deleted by genetic engineering and we sent these mice to the group in Germany, and they proved that mice that were deficient in TMPRSS2 were not infected by influenza. They also showed this was very important a few years later for the SARS virus that at the time was of great concern for another pandemic. Fast forward to this last year, this same group demonstrated that TMPRSS2 and the ACE2 protein were both very important for the current COVID-19 pathogenesis, which then opened up opportunities to try to target or block TMPRSS2 activity to see if you could either prevent or at least attenuate the virus.

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***–Peter Nelson***

This gives you a nice example of the serendipity of two fields coming together to understand that in many of these viruses – and influenza which we shouldn't lose track of because it's also a major health issue in the U.S. and worldwide –hijack or use very similar mechanisms. The things we may develop for COVID-19 could also have very important ramifications for other viral diseases such as influenza. The real key question, which I think Dr. Reddick and others will get into, is whether TMPRSS2 is also regulated by testosterone in the lung, which could explain possibly some of the male/female disparities both in infection rate as well as the disease severity.

**Jonathan Simons:** Our colleague Andrea Alimonti in Italy in the midst of the Veneto-area catastrophe, was in the Mike Milken way collecting all this big data on patient outcomes when they were off shift. Dr. Alimonti was aware of all the TMPRSS2 research and asked the following question: what if testosterone in a man will make more TMPRSS2, then what about prostate cancer patients who've been given Lupron to slow down and stop their cancer by lowering their testosterone to exceptionally low levels? On May 7th this year, the world got rocked again in cancer research because while all cancer patients do worse with COVID in Northern Italy, there are still more women than men were infected

but far more men than women died of COVID-19 pneumonia. But if you were on anti-TMPRSS2therapy, which is hormone therapy with Lupron, that takes the testosterone in a man down to an exceptionally low level, one-fifth of men, matched for everything else, died of COVID-19. Andre and his team's hypothesis is that if you're on medicines that lower your testosterone low enough, the TMPRSS2 in your lungs has been reduced to the point that the virus can't spread as well or take off.

Matt, do you want to talk a little bit about the breakneck speed of taking two decades of science straight into the clinics in America? Matt represents the first clinical trial in the world to our knowledge to ask a randomized controlled trial about targeting TMPRSS2.

**Mike Milken:** Jonathan and Matt, as we transitioned to you, I just want to mention one element that might be useful for philanthropists and others around the world. It was more than 20 years ago that we had come to UCLA and I had asked Jerry Levy find us the 10 most-promising scientist investigators, creative individuals in bioscience at UCLA, to address our CaP CURE (now the Prostate Cancer Foundation) board meeting. We didn't care if they had worked in prostate cancer, but we wanted new and fresh ideas. And in that group was yourself, Matt, Arie Belldegrun, Owen Witte and Charles Sawyers, and it changed the world of cancer research and changed the world of prostate cancer research. So Matt to you.

**Matthew Rettig:** Thanks so much Mike and Jonathan for inviting me to speak to this really critical and important discussion as a cancer researcher and specifically a prostate cancer researcher, I knew about Dr. Nelson's and actually Dr. Chinnaiyan's work – you'll hear from Dr. Chinnaiyan in little bit – about the role of TMPRSS2 in prostate cancer. I do work in the lab as well as in the clinic and have research programs in both environments. When I heard that the SARS COV2 virus, the virus that causes COVID-19, needs this TMPRSS2 protein to get TMPRSS2 into lung cells – that struck me as an opportunity. You've already heard that TMPRSS2 is required for the virus to enter the lung cell. If viruses don't get into cells, they die. The virus is a parasite. So it needs to get into the cells in the first place to harm the host. TMPRSS2 is the gatekeeper and we hypothesized that if we can shut down TMPRSS2, then we can shut down the infectivity of the virus.

It's really that simple and it wasn't a huge leap to come to that hypothesis, given all the prior work that Dr. Nelson, Dr. Chinnaiyan and others had done in the realm of TMPRSS2 in prostate cancer. So the key question that I think still remains is whether or not in lung tissue TMPRSS2 is regulated by androgen, the male hormone environment. There's a lot of correlative evidence that that is the case. That was enough for me to

hypothesize that we ought to target TMPRSS2 by targeting the male hormone environment. We designed a clinical trial to that effect and this clinical trial is treating sick, COVID-19 patients who are hospitalized. There are various illnesses sufficient that they require hospitalization and we asked the following questions: "If we give them a drug that is well known to the prostate cancer world that temporarily suppresses the male hormones, can we reduce the severity of the disease? Can we reduce the mortality? Can we decrease the hospitalization duration of patients who are suffering from COVID-19? That study is underway and it would not have been possible without the Prostate Cancer Foundation and its collaboration with the VA.

> ***"If we can shut down TMPRSS2, then we can shut down … the virus."***
>
> ***–Matthew Rettig***

So you heard about the serendipity between prostate cancer research and COVID-19 through TMPRSS2. There's another serendipity and that relates to the PCF-funded prostate cancer network within the VA. It turns out that these sites are actually sites where there's a high burden of COVID-19 in Los Angeles, Seattle, Brooklyn, Manhattan, the Bronx, etc. So the infrastructure to conduct the clinical trial was already in place. We were fortunate; it was just pure luck that we had this opportunity to repurpose not only a drug for prostate cancer, but also the clinical trials infrastructure that was supported by the Prostate Cancer Foundation through the VA.

This has enabled us to accelerate the development and execution of the clinical trial, which would not have been possible without this fortunate coincidence in terms of the science and the infrastructure to execute clinical trials.

**Jonathan Simons:** Matthew actually accomplished this as the national leader in under three weeks. It's the fastest science-to-medicine-to-man clinical trial certainly in the VA's history, but I would challenge it's probably in American healthcare.

**Matthew Rettig:** Thank you Jonathan. Designing and getting a study approved at multiple sites usually takes on the order of 10 to 12 months at a minimum. Our ability to get this study designed and approved for clinical application in just a matter of weeks represents the combination of the collaboration between PCF and the VA. This is a

rigorous clinical trial where patients are randomly assigned to temporary hormone suppression with the drug called the degarelix, which goes by the brand name Firmagon. It rapidly suppresses male hormone levels, so male hormone levels are reduced by about 90% within 24 hours. Patients are randomly assigned to getting that drug or a placebo and the patients are randomized in a two-to-one fashion in favor of the active drug. We're planning on enrolling 200 patients. The goal is to enroll all 200 patients within 90 days and we would need about another 30 days beyond that for the follow-up and some additional data analysis. We are doing an interim analysis, which means that midway through the study we're going to see if there's such a benefit that we need to stop the study unblended and give the real drug to the placebo patients. This hopefully will be done very rapidly and the VA has been very nimble actually in its ability to not only get this study open, but potentially include additional VA sites as needed depending upon how quickly patients are accrued to this study.

**Jonathan Simons:** The Prostate Cancer Foundation is going to convene, as soon as the data is out there, one of the largest Zoom calls of experts in infectious disease, as well as in TMPRSS2 biology and drug development, because the trial is designed fundamentally exactly like remdesivir. If the study is promising, if lives are saved, and significant patient benefit is observed, we could immediately try to scale throughout American healthcare and around the world because every pharmacy with in a hospital has degarelix. And there are other ideas about how to further target the androgen receptor or target testosterone. In HIV research we got glimmers. Our current HIV medicines aren't the ones that first showed promise, but our current HIV medicines for patients that are not going to die of HIV include protease inhibitors, which are basically a class of medicines against exactly the kind of target TMPRSS2 is. So it's game on for anti-TMPRSS2 antivirals until we can completely exclude the possibility that there's patient benefit.

**Mike Milken:** Matt, what I heard is there's a potential if this trial is showing very strong results that we might know in 45 days, as soon as a month and a half, which would bring us to the end of June 2020. We look forward to how we could help accrue patients faster. To my knowledge, you have more than 30,000 or 40,000 patients in the VA system that we're interacting with who've had prostate cancer. As we search for those that have COVID-19, and look at what occurred with our colleague in Italy, we're talking about an 80% substantially less burden than what occurred in their development of the disease in a reasonably large sample. So it gives us a great deal of hope on your work, Matt. Thank you. Jonathan, back to you.

**Jonathan Simons:** Arul, I thought I'd ask you since you're leading one of the most important efforts in the world against TMPRSS2 right now, what's your lab up to and what are you guys thinking about at the University of Michigan based on the last six weeks of all this TMPRSS2 science?

**Arul Chinnaiyan:** Thank you Jonathan, as well as Mike for inviting me to this teleconference. As you had alluded to, my lab has begun studying COVID-19 primarily because SARS Cov2 utilizes the two proteins mentioned earlier ACE2 and TMPRSS2 in animal models as well as in in-vitro studies. These have been shown to be clearly involved in SARS Cov2 infection and replication, and as you've mentioned, it's certainly very intriguing and somewhat serendipitous that the gene TMPRSS2 is part of the gene fusions that we discovered through prostate cancer foundation support where TMPRSS2 is fused upstream of a cancer driving gene called URGH and is found in upwards of 50 percent to 60 percent of prostate cancers.

What we have been doing at the University of Michigan is looking very carefully at both animal models as well as patient samples, as to what cells actually express TMPRSS2 in the lung, as well as what cells in the lung express the androgen receptor. They are expressed together to basically allow for the hypothesis that androgen receptor could control TMPRSS2 in lungs. We're using what I would call microscopic methods or insight to analysis as well as single-cell sequencing to really look at individual rare populations of cells to see if these two genes, androgen receptor and TMPRSS2, are expressed in the same cells to support the hypothesis that TMPRSS2 could be regulated by testosterones in lungs. That's where we've been primarily focused on, and like Dr. Reddick and others, we are exploring ways that we can begin to employ these therapies in a clinical trial.

These various different next-generation, anti-androgen therapies such as enzalutamide, apalutamide and daralutamide are among a host of potential anti-androgens that have been developed in treating various diseases of the prostate, including prostate cancer, that could potentially be repositioned in the context of COVID-19 disease. The last thing that I'd like to mention that in addition to the fact that the androgen receptor could be controlled by TMPRSS2 in the lung cells. The other important aspect to mention, and I think this was alluded to earlier, is that testosterone or androgens have a major impact on the immune system. Androgens are generally immunosuppressive where they suppress the immune system. So it will be really

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***– Arul Chinnaiyan***

interesting to see what anti-androgens do in terms of the immune system in the context of the cytokine storm that's seen with COVID-19, that would it actually suppress those effects or potentially further amplify those effects? So I think that's another unclear question that we need to explore. Not only the fact that whether TMPRSS2 is testosterone regulated in lungs, but what are the impacts of testosterone and androgen on the immune system. And that's certainly been some of the molecular basis of the differences between males and females in terms of testosterone's effects on the immune system. As you've probably heard, the state of Michigan has been hit pretty hard with COVID-19, so our cancer-related research labs are completely shut down, but we've been able to obtain permission to work on COVID-19-related research. We have about 5 percent to 10 percent of the lab really focused on exploring the ideas around how TMPRSS2 is regulated in lung cell; I would say about five to eight individuals.

**Mike Milken:** Jonathan, as I listened to the discussion, it seems to me that the (Stewart) Rahr VA-University of Michigan collaboration, we should start immediately or try to figure out how it could fit with Matt due to the number of people that have come down with this disease in that area. We've talked about the (Len) Blavatnik program in New York at the VA or the (John and Daria) Barry program in New York at the VA. Also, it seems to me we ought to try to launch this immediately at the University of Pennsylvania with its VA? And so it just seems to me as we've discussed the (Stephen) Cloobeck effort and VA and Fred Hutch that we ought to launch this at all of the centers. And also as you know, Jonathan, as well as anyone in the world, the mutations found in prostate cancer that you've discussed are found in more than 70 other cancers and the links between mutations in breast cancer and prostate cancer today, we know are now strong. And now that we know we can accelerate multiple trials simultaneously with Laura (Esserman), let's introduce Laura.

**Jonathan Simons:** Laura, Archimedes said, give me a lever and I can move the world. Laura Esserman is one of the leading physician scientists in breast cancer and Laura and her colleagues have created this fulcrum for a lever for faster ways to get more important information to develop new treatments for breast cancer, which we think are a critical part of the modeling for multiple COVID-19 clinical trials. Laura, I thought you should share with the viewers a bit about what you're doing against COVID-19 using the paradigm of I-Spy, by starting really by explaining to citizens what I-Spy is.

**Laura Esserman:** As a surgeon. I like to really try and think about what is the most critical element. And when I think about why people are dying, we looked at the people with Stage 2 and 3 breast cancer reported very high risk to die early of their disease. You really thought, okay, this is where you really need to focus. Drug development tends to start or stay in the metastatic setting. And unfortunately we're not very good at

treating people. We've done a reasonable job of prolonging lives by weeks and months, but we haven't really had a major impact on curing. And what we thought about doing was really trying to focus on these women at highest risk to die and move drug development to an earlier stage to take women at high risk for early recurrence. Change the order of therapy so you have an early endpoint, figure out whether you're on the right track. You treat first. Not only do you find out whether or not the drug you're using is working in preventing metastatic disease, you actually are improving their surgical outcomes. But it also keeps you from treating everyone the same.

In medicine we tend to get guidelines and then treat everyone the same, but in fact the era of personalized medicine requires that you understand how each person responds. So the whole idea here was to try and figure out how do you shift drug development, move it earlier, get an early endpoint and get that started. That's what we did with I-Spy 2. And so we have now 20 sites and we have a Bayesian adaptive platform design where we can test multiple agents at the same time. You learn as you go. This idea of double blinding and then looking at some point down the road – you want to be fast and efficient, learn as fast as you can that as something is working. You learn early if it's not working, you drop it.

> ***"Instead of being on cancer time, we're on COVID time, which I think is Mike Milken time. It's seven years crunched into five months."***
>
> ***–Laura Esserman***

Our whole model is collaborative. We started it with the FDA, Anna Barker, Janet Woodcock, our advocates with the pharma community, clinicians and researchers. We have this Quantum Leap Healthcare Collaborative, which is our sponsor and our not-for-profit honest, trusted broker that manages the trial, bringing in Silicon Valley management science to the table. The COVID-19 pandemic is a crisis primarily because the pulmonary toxicity causes this high associated mortality and we not only have to solve this problem for SARS Cov2, but for other future viruses and pandemics. This virus could mutate and we'll need to have something right there. I do not think that the economy is going to recover until we solve this problem because people aren't going to feel safe going out. So we have to prioritize finding high-impact treatments, reduce mortality and time on ventilators independent of these vaccine efforts.

It turns out that everything that we're doing is easily translated into this field, but instead of being on cancer time, we're on COVID time, which I think is Mike Milken time. It's seven years crunched into five months. I think this idea of taking a pragmatic real-world evidence-based adaptive platform trial and a learning system so you can find agents with a big impact, speed time to recovery and drop mortality and harness that infrastructure, the human and intellectual capital that we built over the last decade. So the whole idea of the trial is that you come into critical care. Now the ICU is no longer an ICU. Everyone

can get on the trial and you'll be assigned to one of up to four drugs at a time, but you can have this rolling list of agents, agents that come from ideas about TMPRSS2.

There are some amazing drugs out there that are being repurposed. We're partnering with the COVID R&D consortium. It is amazing how the industry has come together to save lives and their livelihoods to say, here are the immune modulating agents or the antivirals that are coming up and we're going to make them available and we're going to find a way to get them forward. In my 10 years, I've never seen this amount of collaboration. It's really extraordinary. We can put these many drugs in. We're looking at time to recover. We're not looking for little bits of change so we don't have to double plan. There's a lot of things that you don't have to do. You're looking for a big impact. And so our modeling and a lot of in a Bayesian adaptive design, one of the key things to do is to model and do simulations.

***"The era of personalized medicine requires that you understand how each person responds. So the whole idea here was to try and figure out how do you shift drug development, move it earlier, get an early endpoint and get that started. That's what we did with I-Spy."***

***–Laura Esserman***

And our simulations show that in about even with four agents at a time with 50 people a week, you would probably see in about six weeks whether or not a drug is working and the chance of having it be a graduate is very high and making a mistake and dropping something that's not working is good, but this way you're not looking for little things. You want to find those big things that really matter. And the only other thing that I would say is that we put this trial together, start to finish in four weeks. We've just submitted it to the FDA, did it around one o'clock last night and working together 15 to 20 sites could probably test 10 agents in four months. A lot of this of course depends on the pace of the virus, but if we could find three and four agents that dramatically reduce the time to recovery and death, it would make a huge difference.

And I think one of the last most important things is, if something is working, we can leave it in the trial, validate it, and if that gives you that same signal, you can move it to the backbone, so you can automatically build in this idea of building on your engine and it's going to be combinations that work here. The last thing I think everyone needs to think about is there are many, many exciting things that could work, but you got to focus on those drugs where there's sufficient capacity to scale so you can rapidly move to treating worldwide or at least across the nation and across the world. That's really what's going to solve this problem for us.

**Mike Milken:** Thank you Laura and thank you for your enthusiasm.

**Laura Esserman:** Well, there's no shortage of that.

**Mike Milken:** Jonathan, this has outlined a completely new way of doing trials on multiple agents simultaneously and getting decisions. I think one of the things we're going to learn from this, no different, whether it was NASA or other challenges, is that the way medical research is done in the future is going to change. Time is going to be suppressed and we're going to find new ways to get answers quicker. I'd like to now transition to Esther Krofah.

Esther, as you pointed out, there are more than 300 antibodies, antivirals, immunology agents, vaccines and other approaches that you are monitoring and updating on a daily basis appearing on Milken institute.org. One of the areas that bridges from cancer (to COVID-19) that I challenged both you and Jonathan on was this idea that your immune system is smarter than you. This was an element that Nobel Prize winner Jim Allison put forth when I first met him more than 25 years ago. What happened in cancer: was it turned off, was the cancer disguised, was it weakened and how can we deal with that immune system? And much of the successes in cancer in the past few decades have had to deal with what is now called the cytokine storm, the over-energizing of the immune system. As you and your extensive team are looking at these things daily, could you now bring one of them to the forefront as a representation of when they got approval two business days later they were interacting with us?

**Esther Krofah:** That's right Mike. We're approaching almost 80,000 deaths in the U S and the question that you've raised that we raise on a daily basis is, “What is safe and can go into humans as soon and rapidly as possible?” When we're getting dozens of ideas a week around compounds that are proven to be safe, that have patient benefit, that can lower the mortality. The questions we ask are, “what's standing in the way? What do we need to do? How can we accelerate those efforts into clinic and into patients directly? One of those opportunities organizations came to us as you mentioned by this company in North Carolina, BioMarck, that had previously studied a compound for COPD for ARDS (Acute Respiratory Distress Syndrome) non-small-cell lung cancer. The received data reached out to us over the course of a weekend and in two business days we had a phone call with that company to learn more about their efforts and we've spent quite a bit of time with them to learn about what do we need to do if this is safe and can potentially help patients to quickly accelerate their efforts. So Ken, what, why don't we start with you.

**Kenneth Adler:** Thank you very much Esther and thank everybody for inviting us to this podcast. We actually, as you pointed out, have developed a drug originally developed to address cancer, which now could be used to treat COVID-19 patients. We discovered about seven or eight years ago related to cancer, a potential target in cancer cells called MARCKS protein, which is involved in cancer progression and metastasis. We developed a drug to block its function in cancer. It's an inhaled drug and we actually completed a clinical trial in lung cancer and showed that it was effective in blocking cancer progression and metastasis.

At the same time that these studies were going on, we also noticed that when we were doing studies with animal models in my laboratory that this drug also blocked in the lung inflammation and the cytokine storm that occurred in another disease entity that's called acute respiratory distress syndrome, so abbreviated ARDS and that is a deadly disease. It's fatal and probably close to half of the patients that get it and the United States. We thought that this drug, since it blocked the inflammation and the cytokine storm which characterize ARDS, we thought it would be useful possibly in that disease. We did an FDA-approved clinical trial in human patients with ARDS that was successful. It decreased deaths by over 40 percent in our population and it was shown to be totally safe in this patient population.

We finished this ARDS trial in March. This is the same time that the COVID pandemic came along and it turns out that this disease ARDS is what is responsible for mortality for the deaths in most of the COVID-19 patients. They progressed from viral pneumonia to ARDS and that is what they die from. They have to be put on a ventilator, and I think you've seen the results of treating COVID-19 patients with intubation with a ventilator and it's not very efficient.

> ***"This could be a way of keeping these patients off the ventilator and saving countless lives in the process."***
>
> ***–Kenneth Adler***

COVID-19 patients are being treated with high-flow oxygen, nasal oxygen. There's a period of time when they're treated with the high-flow oxygen where they could be possibly kept off the ventilator. I'm not sure what the exact percentage of patients that progressed to a ventilator are, but I think it's still fairly high even with the high-flow oxygen. So if we could treat those patients at that time with this drug, which we know prevents the inflammation and the cytokine storm, this could be a way of keeping these patients off the ventilator and saving countless lives in the process. We're very excited about using our drug to treat COVID-19 patients. I'm going to pass the baton here to Dr. Rajin Ahuja, who's the chairman of the board, and I think he can tell you more about these clinical trials, both the one we just completed on ARDS and potential new ones for COVID-19.

**Rajin Ahuja:** Thanks very much Ken. And of course, thanks Mike for letting BioMarck join this podcast. I would like to say that, yes, I do remember Esther that phone call. It was my first call, if you will, right outside of the rest of my partners at BioMarck with you and your crew. I thought that we have something very unique. When I started with the company seven, eight years ago, the company had the COPD data. It was very promising. It was Phase 2. It hit four primary endpoints. Clinically significant is a big study. It's 170 patients and it was at that time when Ken came and said, look, you just finished doing a lot of animal data with respect to lung cancer and also with respect to what's known as ARDS and an orphan indication. So we said, look, let's just pause real quick on the COPD. We know that the product works in man. I mean, we've proven that with these results, but let's shift and move forward with oncology and also with ARDS. After a few years of research, we didn't know that we wouldn't have such promising results in ARDS right in the middle of the world's pandemic. As we all know, these COVID-19 patients are dying from ARDS.

> ***"It's a very competitive industry, but the whole world is working together to solve this, and it's a really dramatic shift in the industry from such a competitive environment to cheering each other on. We really want somebody to help solve this and we look forward to being part of that."***
>
> ***–Rajin Ahuja***

We strategically shifted and now we've tried to gear up to move forward on that. Laura's campaign would be an excellent next step. What we need to do as a company is to drive this forward. We're reducing mortality in ARDS by over 40 percent. We've demonstrated that we have over 300 patients dosed with our product with minimal to no side effects. So we're a very safe compound to be treated in this disease state. We've had numerous calls from several pharma companies and in having discussions with them, when you wrap up the call, it's always wishing each other luck. It's a very competitive environment. It's a very competitive industry, but the whole world is working together to solve this and it's a really dramatic shift in the industry from such a competitive environment to cheering each other on. We really want somebody to help solve this and we look forward to being part of that.

**Mike Milken:** Raj, thank you and I want to thank everyone for joining us today. The theme of collaboration when CaP CURE was formed, at the very beginning – and once again C stands for all cancers, P for prostate cancer, and CURE standing for all life threatening diseases. Our representatives today from the Prostate Cancer Foundation which took over the CaP and *FasterCures* which took over the CURE, were built on this very concept of collaboration. Whether it was the very first Cancer Summit in the mid-

1990s whether it was The March with more than a thousand organizations participating, which ultimately led to President Clinton signing into law the doubling of the NIH budget and the tripling of the National Cancer Institute budget; whether it was the Center's activities in Lake Tahoe and our medical research retreats, or whether it was the efforts that brought the National Center for Advancing Translational Science to the forefront with the Innovation Summit in Lake Tahoe so many years ago. And lastly, whether it was the Celebration of Science bringing 1,200 people together in Washington DC to reaffirm the United States' commitment to bioscience. All of these are underlying with the concept of collaboration.

***"It is this hard work and teamwork. It gives us great hope that we'll see a solution to this virus, whether it's an antiviral, whether it's immunology, whether it's antibodies, or whether it's a vaccine in the near future."***

***–Mike Milken***

Lastly, there's a very famous phrase. I used it myself starting in the 1970s and that was, "the harder I work, the luckier I get, the better prepared I am, the more successful I am." And judging by this enormous collaboration as seen just recently with Gilead offering companies the right to make their product, which has just been approved by the FDA, without royalties; companies opening their patents, working together, and not only doing that, but working together and providing insight and data. Each bioscience company all over the world we've interacted with – more than 100 of them – each rooting for each other to find a solution to the coronavirus. It is this hard work and teamwork. It gives us great hope that we'll see a solution to this virus, whether it's an antiviral, whether it's immunology, whether it's antibodies, or whether it's a vaccine in the near future. Thank you all again for joining us today.