TRANSCRIPT: Antibodies, Vaccines and the Current State of COVID-19

Eric Topol, MD:	00:06	I'm Eric Topol and I'm so pleased to have a chance to have a conversation about the pandemic with my colleague, Dennis Burton, both of us being on faculty at Scripps Research. And for all the years I've been at Scripps research, the go to person for me has been Dennis not only is he been leading the field and working on HIV vaccine and you've been, has an extraordinary background in immunology in vaccinology. So Dennis, it's a privilege to have a chance to have an extended chat with you today.
Dennis Burton, ...:	00:39	Well, thanks for those kind words Eric. Great. Yeah.
Eric Topol, MD:	00:42	There's so many questions about the pandemic and immunology is becoming the hottest field of all, because it seems to be what is helping to deconvolute a lot of the mysteries. So before we get into some of the biggest questions in immunology, can you give us your general view of the landscape or where we are right now, now that we've been through several months of this pandemic and it's been hit, the U S has been hit quite hard. Where do you think we are at the moment? And, and where are we headed?
Dennis Burton, ...:	01:14	Yeah, I mean, I think the great hope here of course is a vaccine and I think we've made very good progress. I think that you know, there are several vaccines now that are in the clinic at various stages. I think there's a great deal of optimism that these a number of these will be effective. We don't know for sure how effective and we don't know how long, how durable they'll be, but I think there's a, an optimistic view in terms of vaccines. I think the other question will be how quickly that can be made to for a larger population. So from that point of view, I think things look good. I think that from what I've seen that the clinical care is now getting better and better. So I think there's more better management of the disease.
Dennis Burton, ...:	02:20	I think that antibodies as drugs have now entered the clinic. And I think that there's a good hope that they will do some good things. So I think we're in you know, a reasonably good position. I still think we've got a long, long way to go. And I still think that social distancing and masks and so on, have a huge role to play that we really do have to stick with those kind of behavior patterns. But I think that you know, I, I think that the, the, the pandemic is not going to be with us forever. We're w we can you know, look forward to today's when this is gone, but, but we, but we are going to have to do a lot of work in the meantime.

Eric Topol, MD: 03:17 Right? Right. Well, the optimism is good. We need that to help us get through this. Now, let me start before we get to the vaccine, which obviously a central import, but before we get to that, the immune response to the virus now this is highly variable. We have a large proportion of people that have never have symptoms or don't have symptoms that they distinguish as being potentially a COVID-19. And then we have lethality, at least fortunately in a small percent, but still we've already had likely over 200,000 deaths in the U S already. So this is seems to be a full spectrum, especially emphasize on this asymptomatic or some people call it paucisymptomatic as it's very few symptoms. What is your experience about that with this diverse heterogeneity of response?

Dennis Burton, ...: 04:16 Yeah, I mean, I don't think necessarily that's a completely unusual, you know, I think there always are a large genetic and under the factors that lead into the an immune response, I think here, you know, there are clearly, the immune responses are, you know, there are basically three sorts of immune responses, the innate immune response, which there is a lot between different people in which can really, I think, take care of the virus and the very early stage and you know, obviate too many symptoms. There is the the antibody response, which gang can vary a lot between people. It clearly does in terms of what we measure for antibody responses. And then there's the cellular immune response, which again, you know, can vary. And it's likely that all three of those responses contribute as well as other, as well as other factors, like, you know, underlying problems and so on. So health problems and so on. So when you bring all of those factors together, I think it's not surprising that that outcomes do vary do vary quite a lot.

Eric Topol, MD: 05:41 Well, let's start with of the three parts of the immune response. Let's start with the innate which is somewhat centered around interferons. And what's interesting is that we've already seen some, as you say, people host a defective interferon response that genetically, and that may predispose them to getting severe cases. It's obviously a limited number of reports, but that's certainly out there. We also, I guess, have a sense of the virus itself can help take down the interferon response. So it's here it is the innate first line defense, and it's already got, we have a virus that can basically turn that off. And then we also have this idea of giving people potentially inhalant, but some way interferon early where there's some promising data. Do you think that is a likely this, this interferon, any part of the innate immunity response? Is that something that we should be able to build on in the, in the future to help we don't have a

drug that prevents this, and we know that some people, this is a big deal, at least in the realm of the genomic studies, does that make sense to you or is that really tricky?

Dennis Burton, ...: 06:57 It does, but it, you know, interferons are a very powerful mediator of of responses of antiviral responses and, you know, it can it can in certain circumstances make things worse. I'm not saying COVID, but in, in, in, in other circumstances, in other viruses, it can you know, make things worse. So I think tapping into that on probably needs to do one probably needs to be very careful. We'll probably need some, you know, good animal data in the first place. And then you know, cautious human experimentation.

Eric Topol, MD: 07:44 Yeah. There are a bunch of randomized trials ongoing, but what's interesting to note Dennis is that when the interferon type one interferon was given late, it was harmful so far in the multicenter study in China. And if it's given early, it's like the opposite of dexamethazone when given early, it seems to have this salutary effect. Now, the second area that you touched on, on the humoral response on antibodies, it turns out you've taken antibodies and at Scripps, there has been lots of structural biology work from convalescent patients, monoclonal antibodies. They all aren't neutralizing. That is, they all are potent effective antibodies. Is that correct?

Dennis Burton, ...: 08:33 Correct. I mean, that, that again is true most viral infections so that the antibody system is, is simply set up to recognize proteins that, that, that are coming into the body that are not self. So it cannot distinguish a protein that if an is made to it, it won't, it won't do anything back to the virus. You know, the virus is producing a lot of breakdown, products, viral debris. We sometimes call it, if you may come into bodies to viral debris, that's not going to give you any advantage. You really need to make antibodies to the surface of the virus to stop the virus from gaining entry, into target cells and to get rid of the virus. And those are neutralizing antibodies. We call neutralizing antibodies because they prevent, they neutralize the virus. They stop it, gaining entry, but those are definitely a minority most antibodies that we make most of the time don't do us any good in terms of, of pathogens, but, but, you know, that's, that's that's the way the system works and it's difficult to know how else you could do it. You, you, you simply want to, to, to recognize danger and get rid of it. And sometimes the dangerous, not really there, but, you know, for a virus certainly is,

Eric Topol, MD:	10:08	Well, let's zoom in on the antibodies, because first of all, I think it's important for people to realize that the, a lot of the antibodies that are being produced are not of any functional value and taking down the virus. And so, for example, in the convalescent plasma, it's being used without a randomized trial, you might not predict it may vary considerably from one donor to another as to whether it has neutralizing capacity. Right, right.
Dennis Burton, ...:	10:39	It certainly does. It certainly does. And I think what you would need to do there is to see if you get a better outcome when the antibodies, or the levels of antibody in the plasma that you give to the infected patients, if that correlates. So if you have a higher neutralizing amounts of neutralizing antibodies given to you, when you're infected, do you do better? That's kind of one of the key questions. Unfortunately, I don't think the trials to date, even though they've been done in rather large numbers of, of, of folks are really giving a definitive answer. And that's you know, that's unfortunate. I think we'll probably get an answer quicker from some of the new studies with the monoclonal antibodies that have been isolated and, and mass produced
Eric Topol, MD:	11:42	Right now. That's where a lot of exciting work, much of it, or some of it at Scripps where, you know, atom by atom, there's been structural biology and cryo-EM, and basically mapping these antibodies and the epitopes. And there's lots of different proteins of the virus the spike protein and the nucleocapsid and the envelope. And you can run it through, but what antibodies work the best? What are the most potent antibodies?
Dennis Burton, ...:	12:14	Right? So all the antibodies that are neutralizing that we know about bind or yeah, attach to a single protein, the spike protein. So if you remember the the pictures that we see almost more than once nightly on TV, the large red protein on the surface, that's the spike protein that they kind of liked spikes and that all viruses usually, or many viruses have those spikes the different between different viruses, but Corona virus the, the virus that causes COVID-19, SARS-CoV-2 it has that those red spike proteins, and it's antibodies to those spikes that protect and antibodies against all the rest of the proteins. As far as we can see, they don't do much. And then, and then actually all that spike protein, there are antibodies that the bind that do very well, that are very potent in protection and some that are less.
Dennis Burton, ...:	13:24	So, so it seems that the antibodies that attach to the spike and directly to the site that the spike uses, cause this is the purpose

of the spike. Protein is to the spike protein is going to attach itself to a, another protein on the surface of the target cell called the ACE-2 receptor and the, the the, the, the, ACE-2 receptor binds to a site here. Now, if the antibodies bind to this site, they are the most potent. So and we've seen that we and several different groups have established that over the last few weeks,

Eric Topol, MD: 14:08 And that's the receptor binding domain, RBD?

Dennis Burton, ...: 14:12 Receptor binding domain contains several sites actually for antibodies, but the ones that bind bang on, the ACE-2 site they're the they're the best.

Eric Topol, MD: 14:26 And is there a name for that, or is that just an epitope?

Dennis Burton, ...: 14:29 It's, it's just, it's an epitope. We call it the RBD-A epitope to distinguish it from B and C.

Eric Topol, MD: 14:36 Okay. Now you, as you already alluded to, instead of relying on patient convalescent plasma with a mixed variety of antibodies, some of some of which are not really of any value, but the engineering of these monoclonals based on structural biology, based on a potent neutralizing effect have led to several programs many different companies that are in clinical trials. Now, one of these interestingly is distinct from the others. It uses a cocktail approach because it's a worried that apparently this is a, the Regeneron biotech company. They're worried about escape variance. So could you comment, do we need a cocktail? What are these escape variants?

Dennis Burton, ...: 15:25 So, so this is hotly debated. So this is hotly debated as to whether we will need a cocktail or not. Safest strategy may be to, to, to make a cocktail. The trouble is it's more difficult or more logistical problems. You've got to, you know, if you're going to make a large quantity of one antibody, it's twice as difficult to make a large quantity of two. But you know, if that's what you have to do, that's what you have to do. So what neutralization escape is is that, you know, remember there's the spike that I, that I, I was showing you. So if you now how the antibodies coming on here now, if there's some change here, the antibody can no longer bind and then it no longer works and it no longer protects you. So your kind of insurance policy against that is to have another antibody that binds somewhere else that won't be affected by the change in the virus. And for some viruses that change very rapidly like HIV and influenza you know, that is, you know, really probably a, an almost a

necessary strategy. You would really not try and deal with those viruses without using multiple antibodies, hitting multiple sites because of escape, but for SARS-CoV-2, it's not clear yet how, how much it's going to change.

Eric Topol, MD: 17:07 It's a slow, slowly evolving virus, right?

Dennis Burton, ...: 17:10 It's so far slowly evolving, but it might evolve more quickly once we start putting pressure on it we call it. So, you know, once we start presenting it with the problems of people, lots of people with good antibodies, it may have to change in order to keep going you know, selfish DNA. That's what viruses do. They they find ways of solving the problems presented by the immune system in order for them to survive. And we'll have to see, and there are, there are some concerns that are going with cocktails. You mentioned Regeneron, there are others who are sticking with one antibody for now, and then see what happens. And if there is escape, they'll have backup antibodies.

Eric Topol, MD: 18:07 Yeah, that's really helpful. I like the selfish virus. That's a very important concept. Now, when we get to the next part of the immune system, the T cells, they have been getting lots of play in recent weeks. Uour, our friends at La Jolla Allergy Immunology Institute,uShane Crotty and others have done some nice work. Yeah so what's really fascinating is that some people have at least some preexisting SARS-CoV-2 specific T cell response, that's cross reacting from the, the four common Coronaviruses of common colds that is so the point there is, that's not the same as getting through an infection from this virus. Right?

Dennis Burton, ...: 18:59 Right. So the, what, what they have found is that there are, you know, T cells that have been generated against the the common cold coronaviruses that now have the ability to react against cells infected with, with COVID. And so in principle, they may be able to protect us now, the way T cells work is that the cells have to become infected first. So that's one of the distinctions. Antibodies, well, the very first thing is innate immunity. But after that it's antibodies that are circulating the antibodies that they're in the blood, that proteins they're in the blood, they're ready to go. You know, they'll, they'll, they're ready to go in milliseconds, they're there. And if the virus comes, they can take it out. Bang. T cells require that the virus has infected some samples, so they don't act on the virus.

Dennis Burton, ...: 20:06 They act on infected cells. And so, in a way there's a, there's a delay there, and there's a danger because you've got to wait a

little while you've got to wait until the infection has got going a bit. But nevertheless, that could be a huge advantage to be able to suppress in fact itself. So ideally you would just have no symptoms, but even if you had some symptoms, if these T cells are around, they may be able to great. You reduce them. And in the case of a respiratory virus like this, they could maybe confine the symptoms to those of a cold. So you would have the, you would have the infection in the upper respiratory tract, which, you know, it might be unpleasant, but it's not life threatening and prevent the infection getting down onto your lungs, which would be the the real problem. So, you know, that's what we always ask of a vaccine really, is to prevent disease. And if, you know, if they prevent serious disease, then that's really very valuable.

Eric Topol, MD: 21:24 Well, your distinction is important just to underscore that the antibodies that are potent neutralizing are directly attaching the virus. Whereas the cytotoxic T cells that are taking on the virus are really going after the cell with the virus within it. And this is a really important distinction. Now, it turns out recent studies beyond well, in addition to the one I mentioned same labs and others have shown that some people you can't even detect their antibodies, but you can even asymptomatic infections detect these T cells specifically. And in addition, there've been some patients you've probably seen where they're agammaglobulinemic, they have no antibodies, but yet they have a very good way to fight the infection with a T cell response. So we're, we're learning that there's this variable response where some people are relying more on T-cells, how do they, how do they do that without obviously the people who are born without antibody potential, but how is that happening? That some people just don't ever go through the humoral response or to any significant degree?

Dennis Burton, ...: 22:37 Well, I mean, if they're agammaglobulinemic, then you know, they don't make any antibodies. Usually these days, and for a long time, they will get immunoglobulins given to them. They will get to. So that particular cohort of people no longer exists with no antibodies at all, because you are susceptible to certain viruses and, and you really don't want to have no antibodies. However, it is true that that you know, simply with T cells, you can provide a fair degree of protection. And I think probably what, what a lot of people think is that the best situation for a vaccine is when you combine a good antibody response with a good T cell response, that gives you the, the greatest possibility for controlling the infection. And so probably a number of viruses do that. We to focus on neutralizing antibodies, because

they're like the the, the first line in many ways, but, but we're, we're probably also in many vaccines or inducing the T cell response as well.

Eric Topol, MD: 24:01 Well, and the point you're also getting at is the antibodies are relatively simple and common to measure, whereas the T cell response requiring cytometry and research labs, and certainly not a clinical lab domain. So that's a big part, right?

Dennis Burton, ...: 24:18 Yeah. That's definitely a part, and it's also much more difficult to show that T-cells are, you know, that you might be able to show that you have certain sorts of T cells, but do those T cells actually kill infected cells and that, you know, that puts another layer of complexity on it. And it's, it's, you know, it's still complicated. It's a fact, but you know, with vaccines that are, that work really, really well, we still don't understand all the details of how they work and which is sort of remarkable considering that, you know, vaccines are probably done more to promote human health from a medical intervention standpoint than virtually anything else

Eric Topol, MD: 25:09 That's fascinating, actually, when you think about that, now, that's, that's a good segue into the vaccine world, which we have only barely touched so far, but the vaccines there have been several programs now that are actually already into phase three of almost, or approximately 200 that are out there in some sort of development. Those vaccines have reported in phase two studies and in nonhuman primates. And there's quite a variable response. A couple of them are mRNA vaccines. A couple of them are, you know, different sorts, but some have very, they all have a nice neutralizing antibody response, but the T cell response in terms of the CD4 or the CD8 response is highly variable. What do we make of that?

Dennis Burton, ...: 25:58 Yeah, I mean, I think certain vaccine modalities are definitely designed to be more antibody oriented and others. You know, there are vaccines that have been tried for example, HIV that are wholly T cell oriented but not succeeded. And then there are vaccines that we'll, we'll probably combine antibody and T cell responses better. And it all depends on, on, on, on how the vaccine is formulated in essence. And some of the newer vaccine strategies, the ones that have been very quick. The mRNA from Moderna has gone in. I think that's probably you know, more antibody oriented. There are other vaccines that that use so called viral vectors that use an innocuous virus. If you like to bring in the the the, the, the proteins from the virus, they are probably going to do better in terms of antibody T-cell

balance. But, you know, we don't know, and this is a point worth emphasizing million times, is that with a new virus, a new pathogen there's so much we don't know. But we can't know at this point in time, what is going to be the best protective mechanisms against against this virus. So, you know, having, having a series of different viruses sorry, a different vaccines with different strengths and weaknesses is probably a very good idea.

Eric Topol, MD: 27:52 Yeah, no, for sure. It worked out well for that score, but can we take, can we learn anything from the original SARS? That's what 2003 or so, where we had people still today that have an antibody long lasting, and some people have still manifest T-cell specific response to SARS that is SARS-CoV-1, this is now many, many years later, the structural aspects of these two viruses enough to try to extrapolate that people will get long. And that was of course, without a vaccines, long durable effect?

Dennis Burton, ...: 28:32 I mean, what if that some extrapolations probably could be made the number of SARS, the original saws patients is, is, is not so large and has been not so many have been followed, I think, to be really definitive about that. And any way I think, you know, one doesn't necessarily need to play by the rules of natural infection when, when you're talking about a vaccine. So if you, an, an dramatic example of that is papillomavirus, HPV, where if you look at the natural infection, the responses, the antibody responses are quite low, very low, even, but if the vaccine which is extremely effective, and which, you know, protects now is said to be a cancer vaccine, because it prevents papillomavirus and cervical cancer that vaccine is induces much better responses than the natural infection. So, you know, it, it, what, what we can say is that probably natural infection, if you just looked at Coronaviruses as a whole, you would say that natural infection induced rather quite strong neutralizing antibody responses, but they weren't very durable and they didn't last very long. We don't necessarily need to play by that rule for a vaccine. The way the vaccine is set up, could induce first of all, much higher responses. Secondly they could last much longer. We'll just have to, we'll have to see.

Eric Topol, MD: 30:22 It was really important. The idea that you could get a vaccine that works better than how humans would respond on their own is a critical point. Now, the other issues about vaccine is the worry factor, not so much that we'll have vaccines that are safe, but they'll have these untoward responses of antibody enhancement and things like, you know, immune complex

disease and serum sickness. Can you, are you worried about that?

Dennis Burton, ...: 30:53 Not, not particularly, not, not, not to say that one shouldn't you know, do appropriate trials and and eliminate those possibilities. When one, should, you don't want to jump to, you know, vaccinating 10 million people immediately you, you, you do want to do do things in stages. The, there, there are two types of enhancement as it's called antibody mediated enhancement. One type is associated with antibodies binding to particular cells. And then getting into those where the antibody binds to the virus naturally helps the virus get into a certain cells. And that type of a fact has really only been described for certain viruses of which Dengue viruses are an example, they call Flavi viruses, Dengue, yellow fever, Zika West Nile. Those are viruses of, of that type. And there really does seem to be the possibility of antibodies under certain circumstances, making things worse.

Dennis Burton, ...: 32:18 But those can be avoided if, if, if the conditions are set up correctly, that's one kind of concern for for COVID, there's no indication at the moment that that mechanism works in vivo. There's no clear indication, but, you know, folks look at lots different studies and they do experiments and, and, you know, you'll get a little bit of an indication here that may be, this could be something. And, and so, you know, some level of caution is reasonable, but, but overwhelmingly, I would say the evidence does not suggest that this will be a problem so far, but keep remembering this is a new pathogen and we don't know everything. We really don't. So that's one mechanism. The second mechanism is what you mentioned particularly which, which has been seen in the 19 50/60s, which was that if you induce with your vaccine induced too many of the wrong type of antibody, then you can get what's called, as you said, immune complex is formed between the virus and the virus proteins and the antibody.

Dennis Burton, ...: 33:39 And they can get deposited in bad places like in tiny vessels in the lungs, and that can lead to damage to the lungs. Now again a good vaccine won't do that. And we are aware of that problem. And I think that it's highly unlikely that that will turn out to be a problem with the current vaccines. So, you know, some caution, you know, some humility before the fact that this is a new pathogen and, you know, and we can do all the studies we like in test tubes and in model systems, but we do need to see what happens in people and,umonitor them carefully and,uand, and, and move in stages and, and go for it.

Eric Topol, MD:	34:32	Now, let's say we've got one of these vaccines it's passed its phase three. It's now approved for use next year, sometime, perhaps are we going to vaccinate everyone? Or only if you've not had a prior infection that is, if you've already been through this and you have antibodies, would you still have a vaccine?
Dennis Burton, ...:	34:55	I think we'd have to know what level we'd have to know more. We'd have to know, you know, what level of antibodies provide protection. And you know, if, if those folks are immune now to the virus who already had the virus and how long they are immune for so the, the, the questions that would have to be answered before you could say whether people were infected previously, need to be vaccinated.
Eric Topol, MD:	35:27	Yeah. I mean, overall, it's estimated that at least 13% of Americans have now been through an infection, whether they know it or not. So it's not a trivial percent as you start to give them a vaccine that could, if you gave someone who has had an infection, a vaccine, would that potentially be more of a risk for that individual?
Dennis Burton, ...:	35:48	I don't think so. I think you would, again, have to, you know, you'd have to look at the immune parameters and and, and, and, and, and, and take things cautiously. But, but I, I think that, that wouldn't be right.
Eric Topol, MD:	36:04	And what about if somebody, when the neutralizing antibodies come out and they get those, and they last for some, several weeks or maybe months, would that be an issue about giving those people a vaccine?
Dennis Burton, ...:	36:17	It might it might for the time that the, the amount of what is, was circulating, so you would have to vaccinate them once the antibody levels had dropped, but it wouldn't, but they would be protected by the passive antibodies for the first phase, and then you would vaccinate them and then they would be protected by the vaccine. So they wouldn't, but it would be a consideration.
Eric Topol, MD:	36:43	Yeah. So, you know, Dennis, nobody's been talked to about this stuff yet. This, as far as I know, I try to follow the literature pretty closely. I haven't seen people talking about if you've had an infection or you ended the vaccine, if you had the neutralizing antibodies, and when you're going to get the vaccine, these are practical, important issues that haven't even been confronted

Dennis Burton, ...:	37:04	Are important tissues that, you know, and, and, and probably a lot of them need more data in order to, you know, make informed decisions.
Eric Topol, MD:	37:13	Now you've been working on the HIV vaccine for some time and you probably, well, you know, more about vaccines than anyone I know, and people say, well, you're, you're optimistic. As, as most people in the, in the vaccine expert world are that there's going to be a successful multiple vaccines likely, but can you also help people understand why this is a different challenge than HIV
Dennis Burton, ...:	37:40	Right. Yeah. I mean this, this virus in many ways is quite straightforward. In fact, it you know, you get good neutralizing antibodies from infection, and if you immunize animals, as far as we've seen, and now people, you can see that you get pretty good neutralizing antibodies. There may be concerns about how long they last, but usually we can deal with that. Or I mean, worst comes to worst you've vaccinated every year, but there are ways to deal with it. For HIV, the great problems are that first of all, the virus is highly variable. So you know, what do you vaccinate against? There are hundreds of thousands of different strains out there. There are hundreds and thousands of different strains in the single person, never mind out in the wide world. So you have find those few parts of the virus that are its weaknesses, its sites of vulnerability.
Dennis Burton, ...:	38:42	If you like on that envelope spot on that spike structure, you have to find a few places that antibody can get in. And that's challenging now that particular problem hasn't been solved over the last few years. So we have found the weaknesses of the virus. But now those weaknesses are, we have to be able to take advantage of them. And that requires very precise immunogen or vaccine design candidate, vaccine candidate design. And it really, you know, if your normal situation is, if this is your spike, your antibody can come in like this or this or this, and all of these may well work. But with HIV, you've got a very narrow mark. You've got to come in just like that because all of this other areas are blocked. And that is so that means you've got to design something so that the antibody system just responds to that. And that's hard. And that's meant that we've had to learn a lot about about design of proteins, about persuading, the immune system to behave in the way that we wanted to. And but we've made a lot of progress and you know, a an HIV vaccine based in this kind of a rational, precise approach, it's coming, but it's hard. And it's, you know, it's, it's on a longer time frame.

Eric Topol, MD: 40:26 I know you like big challenges, so it's just right for you now. Dennis, the structural biology has really come into its own in terms of the pandemic. And obviously as you are alluded to, for understanding HIV that 3D capability, you want to comment that, you know, years ago, and people were making vaccines, they didn't have any structural crystal structure of of a virus or pathogen of the antibody of anything. So doesn't that really kind of reset or capability in many respects?

Dennis Burton, ...: 41:00 It does. It does. And that was sort of revealed when I said rational vaccine design. It's not that originally vaccine design was irrational, it wasn't, but it was much more empirical. So and, and what what you dealt with were, were pathogens for which the, the pathogens really haven't evolved lots of fancy mechanisms to avoid antibodies. They didn't need to. So, you know, you take measles, you know, measles will jump from one person to the next boom, boom, boom, boom. And it doesn't care about the antibody response you make to it because it's already moved on to the next person. It doesn't care. HIV, It's got to sit around maybe for years and years before it can jump to the next person it's got to coexist with your antibody system. So it has to find all sorts of ways to avoid being neutralized by antibodies. So it's evolved all sorts of mechanisms. The classic one that everybody knows is variability, lots of different strains, but it also has other mechanisms, this so-called sugar coating. So this spike protein that we talked about, how some lots of sugars. So, you know, it's, it's a it's, it's just a much more difficult problem to deal with the, the pathogens that, that you know, have to wait around to jump.

Eric Topol, MD: 42:43 And in fact, as you mentioned, yes, just yesterday, it was a paper which is one of the first I've seen where it gave the 3D structure of, of these glycans and you know, really looking at how they mask the virus, spike protein and the epitopes and the interactions here are so darn complex. And I have to say, I didn't appreciate the value of structural biology nor the velocity of its contributions until 2020. This has been incredible, incredible to watch. Now I do want to get into one other topic with you because I could talk to you all day. This is fascinating. I'm learning so much, but one of the areas that still totally unknown and it kind of is reminiscent of something we talked about with a potential vaccine response that is, you've been hearing this term long COVID and the long haulers.

Eric Topol, MD: 43:36 And so it turns out a significant fraction of people who get infections, even mild infections, not just the severe ones, even young people who are perfectly healthy, in fact, typically more

in women, but interestingly, they linger these symptoms and these symptoms include not just fatigue, but also joint pains, chest pains, lots of different symptoms, often debilitating difficulty breathing, and they can't even go on. They can't even walk a block. And these are people who were, you know, basically some of them athletes, some of them, you know, incredibly healthy. So what do you think no one has done any immunologic studies to date, which is amazing that I know of. What, what do you think is the explanation for this very troubling problem?

Dennis Burton, ...: 44:28 Yeah, yeah. You know, I don't know. Honestly, I have very little idea whether it's some immunological basis or not. I mean, I think you're right. I mean, obviously it's, I mean, I guess it's just emerged, you know, in the last two, three months or so these, these problems, the realization that these are longer term problems. But you know, I mean, I think there are now a lot of measurements that people can do on immune responses. It's much more possible to find defects in immune responses and see if they are, they may have no bearing whatsoever on, on, on, on these long COVID symptoms, but they certainly could be investigated by quite sophisticated tools now.

Eric Topol, MD: 45:21 Yeah, we really, we need to see those studies. What's interesting is that whether some respects, this could be auto-immune or some respects, it could be that the virus, some of these people are still PCR positive for months. And whether that means that there's some virus particles that they're reacting to, not the virus per se there hasn't been a documented re-infection but there is certainly people that have viral load of particles of, of some nucleotides for some period of time, or is it, you could call it debris, whatever could that be? Could you be having any chronic reaction to particles of virus?

Dennis Burton, ...: 46:04 That's a good question. I suppose technically it's possible. I mean, I suppose technically it's possible. I mean, I think what you're referring to, as you say, I don't think it's clear whether those are infectious virus or it's you know, defective particles that are still causing some sort of inflammation. I'm sure there must be folks working on these problems already. Presumably, but I haven't.

Eric Topol, MD: 46:31 Yeah. I talked to Akiko Ishikawa at Yale and she's starting to work on it. Of course, as you said, and emphasized, everything's so new and we're just starting to learn, but I think over the months ahead, we'll see these types of immunologic immune response studies to help sort it out. But it's a very troubling

thing that, you know, when you started in early in the year, we didn't know that there still would be people here many months out that are really in tough shape, you know now the virus story, just to close up with if I can sum up you're pretty upbeat about things. And you also gave caveats many caveats. The lack of the fact that we, the many things we don't know, we need to be humble. Humility is a, is a key thing and open to all sorts of unexpected things that might crop up. But, but the fact that this a relatively straightforward virus to develop a vaccine and we have smarter tools than we had before, and these are very encouraging. So I am actually feeling much better talking to you today. I hope our listeners will as well. I also just want to say, you know, how proud I am to get to work with you and the team here at Scripps who are just doing a bang up job, everything has been so covert centric and this year to just scale up everything we can do to help. And I'm so proud of the team here and to be on a faculty with people like you and our colleagues. I'm just thrilled about that.

Dennis Burton, ...: 48:09 Oh, same here. I mean, all the work that we do, you know on, on HIV is a, is a, is a huge team effort. You know, we have the structural people Ian Wilson, Andrew Ward, we have immunogen designers Bill Schief, Rich Wyatt, you know, we have it's such a team effort and you know, virtually the whole HIV team switched from HIV to COVID and you know, it's, it's, you know, the, you can see the, the value of all our efforts on HIV over the last 20 years has really been hugely valuable in order to move quickly on COVID.

Dennis Burton, ...: 48:57 And that's not just at Scripps. I mean, his scripts has been very strong, I think, but other institutions as well, you can see the efforts that have gone into HIV have made the response to this new virus a much more rapid and much more deep and meaningful. I think.

Eric Topol, MD: 49:19 That's terrific. Well, Dennis, thanks so much for sharing. I know I've pumped you with for information very hard, but I really appreciate it. Thank you.