

## **Transcript of CC Conversations: Facing the Pandemic**

*This webinar was held on July 16, 2020.*

Phoebe Lostroh: I want to say welcome to everybody who is here. We'll be waiting a few more minutes for anyone to connect to the meeting. We're monitoring the number of participants, and when we get to the right number, we'll begin the webinar. So stay tuned.

Phoebe L.: Welcome, everyone, to the CC conversation on facing the pandemic, we are just providing a little bit more time for all of the participants to join, so just stay tuned and we'll be beginning in just a few minutes. Thank you.

We expect the webinar to begin at about five minutes past the hour, as we wait for more participants to have the opportunity to join us. See you in a few minutes.

Hello, and welcome, everyone, to the CC conversation on facing the pandemic. My name is Phoebe Lostroh, I'm a professor in the department of molecular biology and I have taught courses in virology and molecular biology and microbiology at Colorado college since 2003. I'll be the moderator for today's conversation, and it gives me great pleasure to introduce our participants. So before I intlus them, I just want -- before I introduce them, I just want to say that this is not another college town hall on the nuts and bolts of the college's plan for the fall semester. Instead, this is a conversation about aspects of the pandemic that affect everyone beyond the border of the Colorado college community.

So our speakers today include Tia Tummino, who is from the class of 2016. She has a degree in neuroscience from the Colorado College and served appears the paraprofessional in the CC Department of Psychology for the 2016-17 academic year. Currently Tia is a Ph.D. candidate in pharmacoscience and pharmaco-- at the University of California where she primarily works on merging in circumstances lico, in vitro and in vivo methods for the discovery of nonopioid pain therapeutics. She was motivated to find a way to adapt her scientific skills in the age of COVID-19, teamed up with biosciences institute coronavirus consortium to understand how SARS-CoV-2 highjacks human cells and applied chemo informatics methods to identify novel drug candidates.

Phoebe L.:

We also have with us today, Sonlatsa Sunshine Jim-Martin from the class of '94, she was raised on and lives on the Navajo Reservation in New Mexico, she received her bachelor's degree from Colorado college and is working on a master's degree in social justice and community organizing, her experience includes working with public education, Indian education, human resources management, Navajo Nation social services, nonprofit management, Navajo Nation HeadStart, Navajo Department of Health, public health and community outreach. She provides Native American community engagement as a consultant. She advocates for the reform of systems to promote public health equity in rural indigenous grassroots communities. Currently she's returned to work for the Navajo Nation coordinating with 110 local chapter governments in three states. As a manager with the Navajo Nation division of community development, Jim March hin has been cysing -- Jim-Martin has been assisting with the COVID-19 emergency operations and response since the beginning of the outbreak in March 2020, Jim-Martin is a wife and mother of four daughters, an indigenous food are grower, indigenous woman leader and social activist.

We have with us Dr. Margaret Liu from the class of 19 # 7, renowned in the field of gene based vaccines, immunotherapy and global health, obtained MD from Harvard Medical School, BA in chemistry assume cum laud and honorary doctorate of science degree both from Colorado College, completed internship and residency in internal medicine and fellowship endocrinology, board-certified internal medicine and endocrinology and metabolism, received NIH physician scientist award, pioneering research includes bispecific antibodies that activate T cells for cancer therapy and DNA vaccines, which earned her the moniker of mother of DNA vaccines, which are in numerous human trials for vaccines, gene therapy and I am notice therapy for cancelling autoimmune diseases and allergy, one of the leading technologies for making a coronavirus vaccine and most recently served earms the president of the international society for vaccines from 2015 to 2017.

In addition to these three presenters we also have Brian Young and Lesley Irvine from the college with us, so that they can answer any questions that arise relating more directly to the college, so Brian is the vice president for information technology and the chief technology officer and chairpz the college's prevention working group which is charged with developing and I am plip meaning prevention protocols for the safe return to campus, it is the sole campus entity responsible for acquiring all the needed supplies and materials such as masks, hand sanitizers, sanitizer dispensers, pleks glarks temperature checking areas and others, Lesley Irvine is vice president and drek tofer athletics, co-chairs the college's campus life and co-curriculars working group which determines activities that will continue in person and which will be virtual, its also developing supports for an expected increase in demand for mental health services.

Phoebe L.: But now we'll really turn our attention to these three panelists from off campus who have joined us, and we have asked Tia to go first, so she's going to share her research about COVID-19 with us and I will be monitoring to wawp for questions. So after Tia, we'll have Sunshine present and then Margaret will present. Thank you. Tia, take it away.

Tia Tummino '16: Thanks, Phoebe. Can you see my slide?

Phoebe L.: Yes, we can see your slide.

Tia T.: Agreement of I just wanted to check. So thank you so much for that nice instruction, Phoebe, thank you for inviting me to be here, I'm really excited to chat with you guys today a little bit about drug repurposing in the age of COVID-19. Just to start off, I wanted to show a screenshot of this project that I have been fortunate enough to work on, we published it in April, it's called a SARS-CoV-2 protein interaction map reveals tarkts for drug repurposing. Oh, sorry, I was supposed to go here. But I wanted to show you the screenshot just foint out the amount of people who worked on this project with me, it ended up being over 100 scientists in multiple couldn't nents, so it was -- multiple continents, so it was a really great opportunity for a lot of different scientists with different backgrounds to come together to try to tackle this problem using their own unique skill sets.

So I will go through the main goals of this project first. So the first goal of the project was really to understand how SARS-CoV-2 highjacks human cells. The reason we are interested in this question is because viruses don't have many proteins and they don't have their own machinery to be able to replicate without getting into a human cell, taking over the human cells' replication machinery and using that to replicate and infect new cells and new hosts.

So we wanted to understand exactly which human proteins are being targeted by SARS-CoV-2 in order to accomplish this goal. And this really was the idea led by Dr. Nevan Krogan at UCFS, he has really pioneered this research in other areas of infectious diseases, including HIV, HCV, Zika virus, tuberculosis and many other infectious diseases.

So kind of with this information in hand, then our second goal became to leverage this knowledge to identify drug repurposing candidates. This work was led by lot of different professors, including my PI, Dr. Brian Shoichet, as well as Dr. Shokat professors of pharmaceutical chemistry at UCSE, we wouldn't be able to do it without our collaborators Dr. Garcia Sastre and Dr. Vignuzzi.

Tia T.:

How does this SARS-CoV-2 -- we turned to understanding proteomics a powerful approach to understanding viral biology, you take a virus protein, which is called a bait protein, and it's shown here in green, you can attach it to a tag of some sort, which is shown in red and then you can put it into a human cell and allow it to interact with a human proteins that it likes to interact with. You can then break up the cell, pull out the tag, and along with the tag will come your viral bait protein as well as the human proteins, like blurks purple and yellow guys shown here.

And Nevan and his team got the idea to do this shortly after the SARS-CoV-2 genome was published, so here is an image of what the genome looks like, it's about 30,000 base pairs long, and it's broken up into three main groups of proteins. We have the nonstructural protein shown in blue, NSP1 through 16, we have the structural proteins shown in red, and there are four of those, and then we have accessory factors. And really, of all of these proteins, the most known and most well studied is the S or spike structural protein. So if you've ever seen this image of the SARS-CoV-2 virus, then you may be familiar with these red guys hanging off the surface, and these are the spike proteins that are known to be involved in viral recognition by human cells as well as viral entry into human cells. But one of our goals for this project was to understand who in the human cell are all of these other proteins interacting with and can we use this information to find new drug candidates. So the results of this method look something like this, we call it a protein protein interaction map, and what you can see is these viral proteins shown in red diamonds in the center and then they are connected by lines to all these human proteins around the edge, and these make up the protein protein interaction networks. And if you're interested in kind of playing around with your favorite protein, you can go to this website up at the top of my slide. We were really interested in find that as I nengsed before, a lot of replication machinery came out of this protein protein interaction network. So for example, we found things like DNA polymerase proteins, proteins involved in transcriptional regulation, protein quality control and the folding of proteins as well as RNA processing. So armed with this information, we now have the ability to leverage it to identify drug repurposing candidates. So I wanted to just start by talking about what is drug repurposing. Drug repurposing is the idea that you can start with an FDA approved drug that is already approved for another indication, for example, cancer, and you can use it for a new indication such as COVID-19. So I pulled these data from this website, the redo project, and they get their data mostly from places like clinicaltrials.gov and they showed that there are 885 repurposed drugs in clinical trials for COVID-19 right now and that makes up approximately 64 percent of all COVID-19 trials. And the reason COVID-19 is so well suited to a drug repurposing campaign is really because of the fact that we are looking to find a molecule that can be anti-viral and efficacious as quickly as possible.

Tia T.:

I pulled this figure from this older Nature Reviews drug discovery paper, I'm sorry the quality isn't quite as good, it's as good as I could get but what it shows you in this first panel is that if you start with a typical drug discovery campaign where you start by finding a target you care about and you take it all the way to FDA registration, that takes on average about ten to twelve years, but if you start with an approach like drug repurposing, it takes only between three and twelve years on average. And this is mostly due to the fact that you have already taken that molecule into safety trials in humans and have proved that it has quite favorable pharmacokinetic properties so you don't have to redo those challenging clinical trials, you really only have to demonstrate that it's efficacious. So given that drug repurposing is a really great approach to try, we tried to apply this to our protein-protein interaction map, so here the map is in the background and laid on top of it are the drugs that we predicted with cheminformatics that can modulate these human host factors and you can see that we have very structurally diverse molecules that cover a large range of these viral protein interactions. So given all of these molecules in the really short time frame that we were working under, we tested as many of them as we were able to in anti-viral assays to see if they could potentially be efficacious. So I will walk you through the assays now. We did four different assays, two of them were in New York and two of them were in Paris, so what you can do is you can take a plate of cells and these are in this case these are African green monkey cells which are able to be infected with virus, you can treat with your drug that you're interested in, you can add in your virus, and then once you've allowed the virus to replicate, if at all possible, then you'll fix your cells and put them through these assays. The four that we looked at are staining using an antibody to quantify the amount of viral NP protein that's around, you can also quantify the concentration of your drug that allows for only 50 percent of all cells to be infected with a TCID<sub>50</sub> assay, you can quantify the amount of viral RNA that's around with RT-PCR or you can quantify the number of infectious units using a plaque assay, I won't show you all the molecules we looked at. If you're interested, please feel free to look at our paper. I'll just show you two examples here.

So here we have Sotatofin a clinical candidate in cancer and on the right is Hydroxychloroquine which has been talked about a lot for drug repurposing for SARS-CoV-2 and it's an FDA approved anti-malarial compound and on the y-axis we have the percent of NP<sup>+</sup> cells that express NP protein, and what you can see is for both of these molecules as you increase the concentration of the drugs, the amount of NP protein quantified by this red line goes down. So these are the type of outputs that we were looking for. But really I just wanted to end by giving a quick summary of some take-home messages from this research, which is that understanding how the virus hijacks human cells really positions us to identifying new anti-viral therapies.

Tia T.: And this is just one example of drug repurposing that has been used, but it's a really good short-term strategy for finding new therapies and allows us in this particular case to learn what human interactions are necessary for the viral survival. If you have a molecule that's anti-viral and you know which human protein it's targeting, then you can work backwards to figure out how to stop viral infection. And finally, going forward, de novo drug discovery efforts can be utilized to develop targeted SARS-CoV-2 research, it's a little longer of a road. Thank you, we have hundreds of people working on this project, it's been a pleasure to be part of it and I'm happy to answer any of your questions.

Phoebe L.: Thank you so much, Tia, that was very clear and very interesting. So I would encourage anyone who has questions for Tia to type them into the Facebook or into the Q & A now. We have people monitoring the questions so that we can get back to those questions after all the speakers have had a chance to make their presentations. Okay.

So with that, we'll turn our attention to Sunshine's presentation. Let's wait for her to appear. There she is. Are you ready, Sunshine?

Sonlatsa Jim-Martin '94, P'19: Yes. Can you hear me?

Phoebe L.: We can hear you. Yes. Go ahead.

Sonlatsa J.-M.: Thank you. (Speaking language other than English) thank you so much for this conversation so thank you for coordinating the call, I really do appreciate the speakers and the information that is being shared. I want to first introduce myself and let you all know a little bit more about me. My name is Sonlatsa Jim-Martin and Sunshine is my nickname and it is the name I did go by at CC. I am an alumni from the class of '94, and I want to just share a little about my introduction and just share my formal relations as a member of the Navajo Nation to any of the viewers from my nation and then just as a way to introduce myself appropriately.

My name, again, I shared (Speaking language other than English).

I did introduce my clans in the Navajo language and I introduced who I am to my relatives who may be listening or watching this call. I am a manager with the Navajo Nation division of community development, and I do have an active role in addressing our current situation with the COVID-19 emergency on the Navajo Nation, which we call the -- in Navajo, it's called the big cold, or the big cough, and it has been very challenging, soiled like to just share my presentation as far as what we are experiencing and what I've been involved in on a community level and emergency response level.

Sonlatsa J.-M.:

We're still in the middle of it, so my phone continues to have messages coming in, we have continued emergency calls going on throughout the day. I am in four months into this emergency swaaption on the Navajo Nation, on March 14th our Navajo Nation president and leadership called an emergency declaration for the tribe, and for those of you who are not familiar with the Navajo Nation and I think this is really important to understand, we do have three states that we do encompass for our citizens on the Navajo Nation, so I'll share just a quick map that shows the extent of the area we cover for our Navajo Nation citizens. We are within the states of Arizona, New Mexico and Utah, and we do also have some citizens still in the lower corner of Colorado. So it is really a huge undertaking in terms of the response that we had to manage and are currently managing. Just to give you another idea of the size of our government, I'll share another map that shows that we are comparable to the states of Massachusetts, New Hampshire and Vermont. So if you think about those states combined, we really are covering a huge land base to address the needs of the Navajo people during this pandemic, and that has been the biggest part of the challenge is the infrastructure and the response for a land base that large and functioning in three states on the reservation has been very complicated and continues to pose challenges that we've never needed to consider or address before during this pick. As you can see on that slide, we do have 13 grocery stores, large grocery stores that really feed the Navajo people, and so that just gives you an idea of how little resources there are and have been during this pandemic. Our hospitals and clinics on the Navajo Nation are in three states, several counties and also the jurisdiction on the Navajo Nation has been complex from working with the federal government to working with the state governments and then within our own Navajo Nation having 110 local governments within our communities. So it is very complex and the health system, the healthcare system is disconnected. This is just from many years of disconnect within our health systems.

So the journey that started on March 13th for us was really from our Navajo Nation Department of Health, our own Department of Health leaders, our public health leaders, we're monitoring the world situation with the COVID-19 outbreak, and based on continued conversations, continued meetings with the Centers for Disease Control and the World Health Organization, the information that the Navajo Nation leadership was getting was helping to guide us in terms of preparing for this virus as it deam into the United States -- as it came into the United States. The virus did get into discussions around I would say February of 2020, where we had a working group that was monitoring the situation in New York and also on the West Coast in Washington State, and then from there, based on the numbers increasing around the United States, the Navajo Nation with consultation with healthcare professionals and public health leaders decided to close the Navajo Nation under a declaration of emergency.

Sonlatsa J.-M.: With that, March 13 we did close the Navajo Nation, and on March 17th we had our first positive case on the Navajo Nation, which did come into the area of Arizona, which is the Chilichimbuto area near Kayenta, Arizona -- Kayenta, Arizona, and that was when we were activated for emergency response. The.

The Navajo Nation has the health command operations center established, which is the emergency operations center for the Navajo Nation for this pandemic. Unlike any emergencies we've on the Navajo Nation, which were really more natural disasters, floods, wildfires, those kinds of things, we did respond through our Navajo Nation Department of Emergency Management, but because this was a public health crisis, the emergency operations center was set up through the Department of Health and our health professionals set up the health command operations center. The first two months trying to contain the virus was very heartbreaking. It was really tough for the Navajo Nation. We were not prepared, just like many other states, and the capacity for the Navajo Nation to handle the virus through our fractured healthcare system was really difficult, so we did have to do our best to work on isolation and containment in the Kayenta area, but with our Navajo people continuing to travel and visitors continuing to travel through the Navajo Nation, the land base was just very difficult to get us to contain the virus in one location, so we started to get multiple outbreaks in various areas of the Navajo Nation.

So I'm sharing with you a map of the current situation, and you can see that right now from March 17 getting our first case positive for COVID-19 in the area of the Kayenta, we are now in July, four months later, and we have many cases of COVID positive across the Navajo Nation. We are currently at 8,370 positive cases on the Navajo Nation who are citizens of our nation, and you can see through that breakdown where those numbers are in connection with the three states. We also, unfortunately, have reached 401 deaths -- I mean, we're at 405 nowrk as of today. 405 deaths on the Navajo Nation from COVID positive.

Initially, with emergency planning and response, we were anticipating possibly 100, and because the pandemic has moved across our land base so fast with limited resources, limited healthcare staffing, healthcare facilities, just reaching every community member in all the rural and remote areas of our land base, we were not able to contain the virus, and so the fact that we are now at 405 deaths is really hard for the Navajo Nation.



Sonlatsa J.-M.:

We are now seeing that the virus is being contained better. We have a team at the health command center that I have transitioned from since we do have an excellent group that is working now as a unified command structure, which now is including all the healthcare providers across our land base and includes the Indian Health Services, it includes the healthcare corporations, it includes the county public health entities in all states, and it also is working directly with public health entities from the Navajo Nation who are currently working on case management, contact tracing, also isolation centers and also assisting Navajo citizens with self-isolation and providing isolation kits so that they can -- providing isolation kits so that they can self-isolate near their homes. We do have many partners, many organizations that have contributed to assisting us. We work with the CDC representatives and also FEMA response teams.

We also have a lot of nonprofit organizations that have come to the aid of the Navajo Nation so that we can do our best to contain the virus and provide more case staffing. Many of our healthcare providers are going on to four months and there have been relief teams provided to assist the clinic and the hospitals, but also with our public health and first responders, we do see a huge need for more support to continue to contain the virus. This goes back to again the Navajo Nation has had many social medicine issues historically, and I believe that the reason we are still in the middle of containing the virus is because of the historical issues that our government has had to face, our people have had to face in our own infrastructure development, also through mental health and public health structures and the capacity to staff and a workforce to provide support to that. So there are multiple reasons I think that we do have issues in the overall response to the COVID-19 -- response to the COVID-19 on the Navajo Nation. I am looking at the positive side that we do have citizens who are participating in wearing masks all the time in public, we have stay at home public health orders, which our citizens are following more and more, our leadership at the known has instituted curfews and weekend lockdowns to help us contain the virus and also for businesses on the Navajo Nation and even travel through the known it has been restricted and limited, so they are closing every evening for nightly curfews, and then we do have 57-hour weekend curfew lockdowns.

So that has been helping a lot, and more and more we're able to support our citizens on the Navajo Nation. Unfortunately, the border towns and the cities and states around our nation are seeing an increase in COVID positive cases and a lot of that is a result of opening too early or not being able to contain the virus in those states through their health systems. So we are concerned that if we don't see a decrease in the states around us, that we might have to have a second wave of COVID positive cases rising on the Navajo Nation.

Phoebe L.: Yes.

Sonlatsa J.-M.: So that's pretty much what we are doing, and we have a Navajo Nation epidemiology team that works constantly out in the field. We have community health representatives who are community health workers who are the backbone of reaching out to Navajo citizens in the rural and remote communities, and our tribal leadership doing everything we can to continue to isolate the COVID positive cases through testing and then also through working together to get this information out to our citizens. So with that, I'll stand for questions, and again, I want to thank the coordinators for this call and CC for having this discussion.

Phoebe L.: Thank you. Thank you so much for that presentation. You have received many questions in the chat and in the Q & A, and so has Tia. So I'm going to give Margaret an opportunity to talk and then I will probably get to ask each of you just one question, so I'm going to be sorting through the questions and try to figure out the best question. Thank you so much for sharing your expertise, and we will now hear from Dr. Liu. Take it away.

Margaret Liu, M.D. '77: Thank you very much, Phoebe. I'm really honored to be able to speak and love to be back in touch with the CC community. So I'm going to be talking to you about some of the advances that have been made in terms of vaccine development -- in terms of the vaccine development. What I would like to do, though, is to emphasize that the first thing we all can do, while we are working on developing vaccines, is to try to protect yourself now by whatever you can do for masks, for distancing, and avoiding interactions with people as much as possible because every interaction is a risk, even if you think you're being careful. And unfortunately, some of the issues are very built in, they're systemic in terms of the people who are most at risk because of our economies and various the issues people in specific groups such as the Navajo Nation. But I do want to make the point, don't wait for a vaccine to save us, do what you can now.

Let me just start by reminding you that there's basically two specific immune responses that we're most interested for vaccines. On the one hand are antibodies, and these are proteins, these little Y-shaped proteins that can directly kill viruses. But the other side that hasn't really been talked about a lot for coronaviruses are T cells, and there's a form of helper T cells that help make antibodies, but the kind I'm talking about now are specifically killer T cells or cytolytic T cells.

Margaret L.:

These can't kill a virus directly, but if you look at the bottom at what is a cartoon of infected cell, what happens is a virus infects the cell, and basically takes over the machinery of the cell. It invades it and starts to making this cell produce new viruses, new progeny virus. So what killer T cells do is they actually kill infected cells. So this is another cell type that hasn't been focused on but may, in fact, as some data is indicating, play an important role for coronavirus infections. Tia has already given an important explanation about the key protein that is a spike protein that is the one that is the surface part of the virus that then binds to human cells, to a receptor call the ace 2 receptor. So most of the vaccine efforts are trying to make antibodies that bind to the spike and therefore basically code it and prevent it from binding to the cellular receptor, so they can help prevent cells from being infected as well as then helping basically to kill the virus.

I'm going to tell you about the five main types of vaccine technologies that are now in clinical trials. So the first one is just where you take the virus and you kill it. You inactivate it. And an example of this is the way that most flu vaccines are made for influenza vaccine, so it's a tried and true technology. A recombinant protein is a way you can use recombinant DNA technology and you can use this for -- it's been used a number of times, such as for the hepatitis B vaccine. Now, a neuroapproach but that has been used successfully is where you take a virus, but in this case not the coronavirus, and you take out at least one of the genes from this other vier, and instead you -- other virus, and instead you put in a gene for for example the spike protein for example of coronavirus and so you use this viral vector sort of like a Trojan horse, and an example of this is the Ebola vaccine and one of the real advantages for using potentially for using a viral vector is that you may not need a booster dose which of course would be useful to try to get immunity up more quickly

The last two technologies are very new technologies in the sense that there are actually no human vaccines for either one of them. The DNA vaccine, which is the one Phoebe mentioned that my group had pioneered has been made into several veterinary vaccines, including a west Nile virus vaccine for horses, and it's basically just a ring of DNA where you put in the gene coding for whatever pleen urmt, like a -- whatever protein you want, like a spike protein, and mazingly enough you can actually just deliver this into the muscle and the muscle cells start making your spike protein, so instead of delivering the protein, you deliver the gene for the protein. But the DNA doesn't last a long time, it doesn't integrate, so it just makes a vaccine and then it disappears itself

M veteran a newer technology -- mRNA is a newer technology, and this one has never been approved for vaccines or drugs, so it's promising but we don't yet know if it will work

Margaret L.:

This is a slide taken from the journal Nature and it's just to show you how many different sorts of different vaccines are being developed using these different technologies. So you can see that worldwide people are focusing on a number of technologies. So I'm just going to talk through just really briefly and give an example of how these vaccines, these different technologies would work. As I mentioned, whole inactivated viruses are used for a number of vaccines. The challenge here partly is that in order to make the vaccine that you're going to kill before you give to people, you have to grow the virus. So it's a potential safety issue for the manufacturing plant. You have to devise a way to grow up the quantities you need safely. It's not a safety issue once you've made the vaccine, but you have to design your manufacturing plant the right way. So there are four of these in clinical trials right now and actually two of them are already in Phase III studies, which is the last phase before approval, and I'll show you exactly how that process works. The issue is that what people don't know is that when you make this virus, you may make immune responses against a bunch of other proteins on the surface and maybe when you kill the virus, you may change the way the protein looks. So people aren't sure whether or not this will work for any given pathogen even though we know it works for certain pathogens. Recombinant proteins I mentioned are made by recombinant DNA technology, so what you do is you actually just in a cell in a tank basically, you can get yeast cells or insect cells or plant cells to produce these proteins. And in this case of course people are mostly focusing on the spike protein. You then purify the protein, but you have to also give it with what's called an adjuvant to stimulate an even more powerful response. Now, what's interesting about it is you can see in this picture that I've shown just individual proteins, but in fact, one of the companies called Medicogo that's in clinical trials is actually making not just the single protein, but what they've done is they've made what's called a virus-like particle so it looks like the virus but it's empty on the inside because there's no gene, so it can't cause an infection. But because it's shaped like a particle, usually these particles are much more immunogenic than single proteins. The other interesting thing about what they're doing is they're actually making this in transgenic plants, so they basically can just grow the plants and then they purify the protein out of it. And this can be very appealing because you can actually just, you know, grow a lot of plants, so it's a potentially very powerful way when you have to make lots and lots of protein

Now, a recombinant vector vaccine which is what I mentioned has been done for Ebola as an example can be made in two ways. The first is that you take out enough of the virus' own genes so that it can't replicate at all. In another case, what you do is you simply replace one gene but the virus can still replicate. So these are actually complicated to make, but because people have made them in experimental systems and have tried them for a number of vaccines, for other diseases, these actually were among the first to go into the clinic.

Margaret L.:

So you've heard about one in China that's actually already being used in the military. They didn't go through the whole process of phase 3 studies, but they felt the results were so good in Phase II that they are using it to protect their military. The Chadox vaccine being made by Oxford and another company are in Phase III now and they say they'll have results by September. By way of disclosure, I'm actually on the scientific advisory board for the Oxford group and have been for about 15 years and we've looked at this in many many clinical trials for other diseases. I mentioned that the VSV vector is the that Merck licensed for Ebola so there's hope the same technology will be effective. What's interesting about these newest technologies is instead of having to use either a protein or killed virus, you actually can just use the DNA or the RNA and as you recall DNA is like a blueprint from which messenger RNA is made, which then is what the protein is made from. So surprisingly enough, it turns out that you can actually just inject these and they can then result in the protein being made. So these are really fast to make, which is why you probably heard the DNA vaccine company said in three hours they made their vaccine. What they meant was they could design it in three hours because all they had to do was put together the right sequence. The DNA technology is known to be very safe because it's actually already been approved for three veterinary vaccines and have been in thousands of patients. So one of the appeals of this is this is actually a very generic technology, and so I'm actually work with the WHO right now because they've already issued guidelines for countries that don't have an FDA for how to manufacture this, but we're revising the guidelines in lieu of the Ebola virus -- sorry, in lieu of the coronavirus pandemic right now

So RNA is one of the vaccines you've heard a lot about, again, it can be rapidly made. The key the issues this, because there are no approved vaccines or drugs, is that we don't yet really know whether it will be efficacious, even though there's now been some positive data in the first 45 patients who received this vaccine. It tends to be a little toxic in the sense of causing inflammation, and so the different companies have done a lot of work to make the mRNA itself not be inflammatory while still stimulating immune response. So these are two of the leading candidate in clinical trials

So I just wanted to explain the process. So even though right now there are 140 candidates being worked on in the laboratory and 23 candidates in clinical trials, you can see that every vaccine has to go through different phases of clinical testing, and phase 1 is the safety and getting some idea, do you have an opinion get immune responses. The second phase which is where some of the vaccine rs in right now actually goes into different populations. So in phase 1 you go into normal healthy people, but generally aged 18 to, say, 50 or 55. By the time you get to Phase II, sometimes you can go into either older people or unique populations that may have certain risk factors.

Margaret L.:

And it's not until you get to phase 3 where you are doing tens of thousands of people that you can really understand whether there's efficacy. So I wanted to actually highlight this process because I see that one of the questions already to Tia was about showing laboratory evidence that it looked like that the Hydroxychloroquine did appear to help work somewhat in the laboratory for the coronaviruses, but the problem is that, in fact, usually when you go from the laboratory to phase 1 and then phase 1 all the way through approval, you actually find out that there are problems along the way, and that's what's happened actually with that disease is that there's a lot of cardiac toxicity so people have heart arrhythmias and so on, and things that work in a lab experiment don't work when they get into humans

On the other hand, if something doesn't work in the lab experiment, you don't want to take it into humans. So this is why you always start and that's your initial hurdle that a drug or a vaccine has to overcome

So the-ish urpz that I just wanted -- so the issues that he just wanted to emphasize is that it's not known if a vaccine works in healthy young people will it work in older people or will it work this different populations who have different risk factors, such as diabetes or maybe even just genetically they're different or they live in different geographies and so they may have different parasite loads, for example. Another key question is how long will immunity last? And one of the reasons this is a big challenge is that natural immunity to coronavirus infections is not particularly long lived, and this has been studied mostly because criefts are one of the viruses that cause the common cold, and it's well-known that people can get reinfected even though they've had good immune responses to the first time they get infected. And then there's a question of can the virus evolve and in fact some of you probably read about how there is now one major mutation that is taking over about 70 -- it's now responsible for about 70 percent of the virus that's been sequenced. It appears it's possible that this virus makes the coronavirus more contagious, but it doesn't seem to worsen disease severity, and to date there's no clear impact of this on the proposed vaccine strategy. But as you know, this is an issue for the flu vaccine because every year we have to make a new flu vaccine because of mutations

I just wanted to mention that there are some potential other therapeutic and prophylactic immune interventions that don't involve vaccines, and you've probably heard about taking plasma or immunoglobulins from people who already had the coronavirus and using that. There are monoclonal antibodies that specifically neutralize the spike protein, and then one of the things that is being talked about but actually hasn't been done that I personally think should be studied, which is that you know for a number of diseases like rabies and tetanus, people have taken immunoglobulin from people who are already infected and then they just administer it IM kind of like a vaccine except that you have to keep readministering it.

Margaret L.:

But this is something that could potentially be given to healthcare providers to protect them before a vaccine is made, so this would need to be studied

I want to end on a note of hope, which is that most of us, even I, don't really remember the polio epidemic are but you can see there are almost 60,000 cases of polio in 1952 and this terrified people, they kept their kids out of school, they wouldn't let them go to the beach, it was just like now, because people ended up either dierks often being paralyzed and being on a rech ray torpedo which at the time was an iron lung. There's -- respirator which at the time was on an iron lung. There's one man alive who has been on an iron lung for it must be now 60 or 70 times from this time period because he didn't want to move to a more modern respirator for various reasons but you can see how the incidents plummeted after the vaccine was introduced so that now we don't worry about polio except for unfortunately there are some people who refuse to take their immunizations. What I wanted to show you was this was what happened when polio got introduced into the world and the same thing happened, the problem was you can see by the time lines, this didn't really happen until 30-plus years later so this gets at one of the issues that Sunshine has raised, which is that we really need to dreads systemic inequities and the systemic problems for any either therapeutic or vaccine that we develop, which is that we need broad, equitable, affordable access to vaccines worldwide so we don't just want to stay, well, the people who are rich can afford it. This is an issue that isn't just as simple as saying well we'll make the vaccine free because unfortunately in many part of the world the whole issues of access, there isn't the infrastructure to be able to easily immunize, and I thought Sunshine did a really amazing job of describing some of the challenges when you have a population spread out over such a large land mass

So because these slides will be made to you, I just wanted to give you a couple of resources. There's a New York Times tracker that can tell you about what is happening in terms of vaccine development, the WHO also has a list, and then I wanted to invite you, I'm the chair of the board of the international society for vaccines, and what we're holding is free monthly symposia that anyone can sign up for that you can watch. We basically have been going through all the different vaccine technologies and the scientists doing those studies are giving their updates. So please feel free to sign up, and we would love to have you participate, and you can ask questions the same way you ask questions here. So thank you, Phoebe.

Phoebe L.:

Thank you. Thank you very much, Margaret. And thank you to all the speakers. I know that it's three minute until 2:00 p.m. and we were going to go to 2:00, but I would like to give each of the speakers at least a chance to answer one question apiece, if that's all right with everyone. I hope you can stay for a little while so that we can do that

- Phoebe L.: Tia, since you were the first speaker, I'm going to ask you the first question, of course, you're on the spot here. People are quite interested on how it is that international communities are coordinating and also avoiding duplicating effort when it comes to finding repurposed drugs and also everybody wants to know if you have a favorite repurpose drug that you feel is especially hopeful at the moment. Thank you.
- Tia T.: Okay, thank you so much for that question. First I want to say thank you to Margaret for explaining the answer to the Hydroxychloroquine question. That molecule has a lot of problems with it and it's cardiotoxicity is one of the major issues. To answer the question that you just posted, Phoebe, I think the first thing is that really the internet helps us be able to coordinate these efforts in an incredible way. There also has been a really big push recently to publish research on these websites called bioarchive and med archive which are preprint servers where you can get your research out there while it's in the process of being published, which can often take many months, and of course you have to be really careful with data like that because it's not yet peer reviewed, but it does give us an access to see the research that other people are working on right as it's being done. But then I would also just like to note that even in the case of our research, we've had more than I think 200 different labs cross the world have seen our paper and contacted Nevan and asked for the purified viral proteins so that they can do their own research. So really I think everybody is interested in working together and even just the simple e-mail is a great way to coordinate that information.
- Phoebe L.: Think very much. Okay. A question for Sonlatsa is, how is the Navajo Nation coordinating and accomplishing all of the contact tracing that is necessary over such a wide area? Thank you.
- Sonlatsa J.-M.: Well, what we're doing right now is because we created the unified coordinating group that includes all the hospitals within the three states that are on the Navajo Nation, all the counties and the public health providers, we are able to create teams now. Again, in the first two months that was really nonexistent and it was very fractured but now we have those teams established through our community health representatives who are all working through the Indian Health Service hospitals as well as the corporations, the corporate hospitals and clinics, they are working through public health nurses, health educators, every frontline worker that is in the hospitals is assisting with case management and contact tracing.



Sonlatsa J.-M.: Our epi team does have investigator teams established, they're doing surveillance constantly, our CHR's are monitoring patients regularly and then also following the contact tracing, so with this new unified coordinated group, there is teemedz or ill call them operations chiefs at our emergency operations center that are coordinating these groups to reach out to all areas of the Navajo Nation, we do rely on our workers, so I can say right now they are burning out -- they are burning out, so we do constantly have to call on resources to step in and help us through the states and through the counties. I did notice there were some questions on how we can help the Navajo Nation, you can help in many ways, we do need staffing workforce, if you have any networks that can join us in helping us relieve some of our frontline staff or even some of our public health emergency staff, I listed the website, there's a donation link for financial donations, and again, just helping supporting our hospitals and clinics because if we do have another outbreak rs our hospitals will be strained again and it will probably really hurt our supplies for personal protective equipment, so any of those resources are needed on the Navajo Nation. Thank you.

Phoebe L.: Thank you, that was my follow-up question but you beat me to it, so that's great, thank you for sharing those opportunities to try to help with us. Margaret, I think you've had some questions about whether there are any concerns about trying to get to a vaccine too quickly and also there's a question about what is herd immunity and why could a vaccine perhaps achieve herd immunity if there's not long-lived immunity to any of the common cold coronaviruses, thank you.

Margaret L.: Those are great questions. I think the concerns about moving too quickly are that what it is is that steps won't be cut out, but what has happened is that they have been compressed in the sense that usually you do animal studies first and then you mu into humans because nobody wants to mu forward with something that doesn't work. In this case, because the technologies were well understood, what happened is the animal studies went in parallel and so fortunately it turned out that they already did get some good results and so on

And similarly, usually like a company won't invest in manufacturing until they're far along because if they've already built a manufacturing plant and then their vaccine doesn't work, then they've just -- they're out a lot of money. So in this case what's been shortened is that proactively because of the government supplying money, the companies have just gone ahead and invested that money to build the manufacturing capability ahead of time. So that's really mostly the type of shortcuts that have been taken or more money at risk because it's not the companies, it's the governments that are supplying that

Sorry, what was the other second question? I'm sorry.

- Phoebe L.: Sorry. The second question was about how can a vaccine achieve herd immunity if that's not natural herd immunity to cold viruses?
- Margaret L.: Yes. Well, that's actual a really, really good question because that's just what everybody is worried about is that whether or not there can be enough immunity achieved and is it long enough. Now, the one thing I will say is that when people focus just on measuring antibodies to the spike protein, there's the possibility that if you get T cell responses, such as helper T cell responses, and sightlytic T limb faux sight responses, that even if your antibodies go down t might mean that next time your immune response is faster because you already have the T cells and you have the help, so you may not get complete protection from disease, and that's in fact what has been seen preclinically sometimes is people, the monkeys were protected from pneumonia but they weren't protect frd upper respiratory infection -- from upper respiratory infection. So it might make the disease a little less severe even if there is not herd immunity, so I think that's the hope
- If I could just say one other thing about that is one of our biggest problems about herd I am urine ti is that there are now many people who are anti-vaksers, so the problem is you -- anti-vaxers, so you really can't have free riders, people who count on everyone else's immunity with this disease, you have to have at least 70, 80 percent of the population immune and immunized.
- Phoebe L.: Thank you for that response. I'm just employing to look at the panelists and see, do you have ten more minutes to stay, or should I conclude? I can stay.
- Margaret L.: I'm fine.
- Phoebe L.: Margaret is fine. Tia?
- Tia T.: I have to take off for another meeting, I'm so sorry.
- Phoebe L.: Tia, thank you so much we learned so much from your presentation, we'll watch your exprech see where it goes. Good luck with getting your Ph.D.
- Tia T.: Thank you so much, I hope to have another call with you all sometime in the future.
- Phoebe L.: Thank you, I'll give Sunshine and Margaret a little more chance to talk. My main question is whether you have any questions to ask each other, so Sunshine, do you have anything to ask Margaret?
- Sonlatsa J.-M.: I think, you know, I know you're doing a lot of work and I'm not sure if those discussions regarding the systemic issues are -- do you feel like those are

happening on a greater level for indigenous communities or do you think we are still trying to get that education out there to those in your field about how systemic issues affect our response to COVID-19?

Margaret L.: That's really such an important issue and I think that, you know, in the vaccine field, because we're focused on prevention, and because vaccines are traditionally much lower cost, they're more affordable than say expensive therapies, there has been a long time focus on equity and on access. The problem is I would say that people look at the developing exrurnts is say, oh, you know, we have a problem of equity and access there, and they forget about in the United States, frampleg, that in fact we have huge problems within our own communities and that's not getting as much attention. And some of that is because, frampleg, with HIV, there was clearly issues in sub-Saharan Africa where the numbers were just so big on top of tuberculosis and malaria that that was maybe easier for people to understand what the issues are, but I think you've raised really one of the key points and I'm so grateful that you shared the website because I grew up in Durango, Colorado, and in fact, my mom used to always get mistaken for being Navajo, which I loved because, you know, she's Chinese, and so I've wondered what can I do personally besides what can I do to deal with all the systemic issues that really need -- this may be, may be the -- it's not really a silver lining because it's just such a terrible event, but I think that the timing is such with everything else that's happening in our country about racial injustice and systemic inequities that maybe now is the time that we can actually stay, okay, let's try goat at the root of these problems and not just put Band-Aids and not just, you know, say, oh, don't worry about it, you know, whatever, it's that I think now is the time that we really have to say what can we do not just for coronavirus but for all of the fundamental inequities that exist.

Phoebe L.: Thank you. Do you have any questions for Sunshine?

Margaret L.: My first question was going to be the one she already answered which was what can we actually do as individuals, I'm really happy to know that, that's kind of the one thing to get all excited and oh this is terrible, but then it's, well, what can I do not just necessarily professionally but what can I do as a person and as another human being, so that was actually going to be my big question. I did have something I wanted to mind if you don't mind, it's a little bit off topic, I was sitting here realizing there were four women on this call, and as having usually been the only female on many scientific advisory boards or company boards or things like that, I just thought it was fantastic to see that since

(Technical interruption)

Margaret L.: I thought that said about how Colorado College encourages people, it doesn't matter who you are, it just encourages people to be their best and gives them the opportunities and also lsz hey, there's a world out there, you have a responsibility to the world as well, and I want to say kudos to CC and I'm proud to be an alumna.

Phoebe L.: Thank you, that's a wonderful thought to bring us to a conclusion and I just want to say thank you to both of you and thank you to everyone who has been listening and participating, I'm sorry I couldn't answer or couldn't ask all of your questions, which are wonderful questions, apples the vibrancy of the CC intellectual community is sure coming through on the Facebook responses and on the Q & A. I noticed a theme today of connection, that Tia was looking although connections among proteins -- at connections among proteins inside cells and son at sa is looking at -- Sunshine is looking at connections between communities of people and Margaret is looking at connections between cells for immune response and notice that everybody made an effort for us to conclude our comments on a note of hope, because connections and community are what will get us through this whole situation. So it has been such a great pleasure for me to meet of you, and I had already known Tia since I was her first year experience professor, and it was a thrill to get to connect all three of you women as well. So thank you so much. Before we sign off, I'm just going on ask whether Lesley or Brian have any messages from the college that they want to deliver, and if neither of them unmute, then I will just say farewell. So I will just watch to see if their cameras and microphones unmute. Give us a second.

Phoebe, thank you for the inclusion and really inspiring and incredibly fascinating, so humble to be a part of it. So thank you.

Phoebe L.: Of course. Thanks.

Brian Young: Wholeheartedly agree, Phoebe, the entire panel, what a great knowledge base, thanks for sharing your expertise and thanks for always being a part of the CC community.

Phoebe L.: Thank you so much. Thanks on the whole community for participating. Thank you, Margaret, thank you Sonlatsa, thank you so much, and I hope that we will remain cectsdz over time and I wish both of you the best of luck in all your endeavors. Take care. And with that, we will sign off. Take care, everybody. Stay safe.