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## **Voices from DARPA**

Transcript of Episode 24: Preventing Pandemics

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Ivan Amato:

Ivan Amato here. I'm the host of the *Voices from DARPA* podcast. Please note that in this episode you might hear ambient noises such as birds, trucks, or even the hum of my refrigerator. That's because I have had to record my words in a home office as I play my social distancing role in our collective effort to minimize the spread of COVID-19.

[Music]

Ivan Amato:

Technology is a driver of our times. Since its founding in 1958 in the midst of the Cold War, DARPA, the Defense Advanced Research Projects Agency has been a driver of technology. Welcome to Voices from DARPA, a window onto DARPA's corps of program managers. Their job: to redefine what is possible.

My name is Ivan Amato and I'm your DARPA host. I've been away since the end of 2018 and I'm excited to resurrect with this episode the voices from DARPA podcast. However, I do this at one of the most trying times most of us can remember.

Everything seems to have changed. Nothing feels right. On March 11th, one of the days on which I sat down with program managers in a recording studio, the world health organization, WHO, declared the infectious spread of the coronavirus as a pandemic. COVID-19, the disease caused by a new coronavirus that scientists refer to as Severe Acute Respiratory Syndrome Coronavirus – SARS-CoV2 - has been among us at least since late last year when the first cases showed up in China. And now you and I and our 7.8 billion human brethren are living in pandemic times. The world's people are in this together.

What we do know is that pandemics come and pandemics go. Depending on their severity and the collective response by, us they mete out differing amounts of human and economic loss.

As an institution, DARPA has for many years recognized the enormous threats posed by emerging infectious agents. It has done so in its very DARPA way. Says DARPA as an institution: we are going to do something about this. In 2016 Brad Ringeisen, a civil servant working for the Department of Defense for nearly twenty years, became the deputy director of DARPA's Biological Technologies Office -BTO. In June he upgraded to become BTO's director. Now he finds himself heading a team of program managers orchestrating a portfolio of technology programs that stand a chance of meeting this new coronavirus on its own molecular biological terms. These program managers are on their way to developing a technology platform that they hope will end the threat of pandemic disease, period. If they succeed,

COVID-19 could become the last pandemic. This is not some Panglossian vision. This is hard science and technology that could take pandemic disease off of humanity's already long list of worries.

BTO director Brad Ringeisen:

DARPA plays a really important role for the entire government, quite honestly, but specifically for the Department of Defense and its ability to predict what is emerging as threats to both our war fighters and our DoD personnel, but also to the country as a whole. And that has been something that's been persistent through the entire lifetime of DARPA. But specific to infectious disease and emergent disease, this is something over the last two decades. DARPA has been there. We've learned what is needed and what is required to be able to fight the types of outbreaks and pandemic that we're seeing right now.

Ivan Amato:

Right now it's the new corona virus that is waking the world up to how devastating pandemic diseases can be. It was only a few years ago that we all experienced another wake-up call. That's when DARPA redoubled its efforts to investigate and develop technical means for quashing outbreaks of infectious disease before they can blow up into regional epidemics or global pandemics like the one that challenges us now.

Brad Ringeisen:

Back in 2014 there was an Ebola outbreak I'm sure we all remember that. That was the last time that we really started to worry about sort of international pandemics. Because of sort of the limited transmissibility of that particular virus and requiring sort of bodily fluid transfer and things that seemed to not be as contagious as the current corona virus that we're seeing right now. But what that process did for DARPA with some amazing program managers—amazing forethought that's happened back 5, 10, even 15 years ago—program managers started thinking about an ideal world where we could have a rapid response platform where we could instead of having to develop vaccines over the course of years maybe even decades in time, wouldn't it be great if we had a world where we could reduce that research and development process down to a matter of potentially weeks or months rather than having to wait on that tremendously long time frame which we know, living through what we're living through right now, it's just too long.

Ivan Amato:

It's a combination of the nature of a new contagion, the speed at which a disease outbreak is detected, and public health and medical countermeasures that determines just how much and how fast and how far an initial outbreak will grow. Renee Wegrzyn, a program manager in the Biological Technologies Office since 2016, now runs several programs that she hopes will produce powerful new anti-pandemic tools at least in time for the next threat. One of those programs, the DIGET program, aims to improve our ability to detect any biological threat known or new to humankind, anytime, anywhere. Her

PREPARE program aims to leverage natural pathogen fighting genes and proteins already in our bodies. Here's how Renee explains the difference between outbreaks, epidemics, and pandemics that drive her own work as a program manager.

Renee Wegrzyn:

The way you think about an outbreak is really just an anomaly in the number of diseases in a given region. Maybe for influenza it's an increase in cases or a lack of seasonality but something that is just inherently different from baseline would kind of constitute an outbreak. Beyond an outbreak, an epidemic is where you start to see more person-to-person transmission and a larger geographic region, even multiple countries being impacted. For something to be declared a pandemic, there's three strict criteria that have to be satisfied. So one is that in most cases this disease is novel, meaning that it's either something we haven't seen before or it's something that hasn't been around for a very long time. The 1918 flu is a great example where it's very unlikely that there's immunity in the population. So effectively many, many individuals, if not everyone is at risk of this disease. That's the first criteria. And the second is there's person-to-person transmission. So it's not just simply animals to people in a zoonotic event, but genuine person-to-person transmission. And then finally, inherit in pandemic, it's a global, it's a pan-regional outbreak, which is now a pandemic. And those are the criteria that the WHO have set to declare a pandemic and in fact today COVID-19 was declared a pandemic.

Ivan Amato:

That was on March 11th, and in just a few weeks, the pandemic has terrorized ever more of the world. And it has amplified DARPA's sense of urgency to realize those innovations that will dramatically shorten the time from disease detection to delivering countermeasures at large scales. The agency runs a portfolio of programs that hit pandemics at every point possible, including even as dangerous viruses are mutating within animal and insect hosts into forms that can leap into people. If we could stop disease progression that early, says Brad Ringeisen, we would not see those upward shooting curves in the news depicting massive spread of infection and the devastation that comes with it.

Brad Ringeisen:

In an ideal situation, you would really want to be able to move very very much left of the curve that we are currently experiencing for the COVID-19 outbreak. We would want to be able to identify the emergence of diseases from animal populations. We'd want to be able to take those identifications early and detect, maybe even in the animal populations, potentially even give countermeasures to those animal populations to be able to prevent the hop into humans that we have just witnessed over the last several months. So we have a program called PREEMPT that is exactly trying to do that.

Ivan Amato:

This is where program manager Rohit Chitale comes into the picture. He has been a disease fighter for his entire professional life. Among his credits are co-establishing the Global Disease Detection Operations at the US Centers for Disease Control and Prevention and helping to tamp down the spread of AIDS in South Sudan. And now he is focusing all of his experience and knowledge on the challenge of ending pandemic and disease.

Rohit Chitale:

I came into DARPA in September of 2019 and in November I inherited a program called PREEMPT: PReventing EMerging Pathogenic Threats. And it's really, really, what some people at DARPA call esoteric but exactly what I think where we need to be going. It is the type of program that says we look at animals, we looked at insects, so how can we stop the disease there before it spills over to humans. And that idea there is truly a prevention. And public health is all about prevention. And unfortunately, we like to say when we're successful, people don't know what we're doing.

Ivan Amato:

Rohit says one of the best ways of achieving these hidden and unsung successes in public health and with battling pandemics is to understand how dangerous viruses arise in animals.

Rohit Chitale:

There has been a focus over the last 20 years on the concept of One Health. One Health brings together human and animal medicine and says that basically, we know that animals actually are about responsible for 60 to 70 percent of human infectious threats. So you know, we think about things like Zika, dengue, yellow fever, Chikungunya, Ebola, these have all come from animals. SARS, all three of these last three SARS in the last 15, 20 – the last coronavirus of the last 15 years have come from animals. Well then, the idea is that this one health concept says let's look at animals so that we can get ahead of spread to humans. Can we prevent the spillover of a Hendra virus or a new corona virus to people? Can we prevent that? Keep it in the bats, keep it from coming into the intermediate reservoirs like the pangolins, the civet cats, you know, for example, or the fowl, or the ducks and the birds in China, for example.

Ivan Amato:

Understanding how these spillovers occur takes boots on the ground all over the world, Rohit says, and the performers, the investigators contracted to do research under his PREEMPT program are leaving their boot prints behind far and wide.

Rohit Chitale:

Montana State is studying bats in Bangladesh, Madagascar, Ghana, and Australia, and they're studying bat ecology. They're trying to understand how do bats live, what do they feed on, when do they get stressed. When do they produce more in their urine, when do they produce more virus, and when does that virus spillover. So studying horses in Hendra, Australia – the name of the town is actually Hendra, that's where it was named from, the virus. So looking at where the spillover events have happened and then where the spillover events have happened for humans.

Ivan Amato:

Once a spillover happens, then detection and diagnostics become pivotal pieces of the public health response. Brad Ringeisen explains a few of the ways his program-manager colleagues have been moving the dial on this capability. One rapidly developing technology he points to will quickly identify in, say, the sputum or blood of patients the presence of molecular science called epigenetic marks in the cells of a patient responding to a viral exposure. This would be like tracking the earliest footprints left by the viruses in people's bodies. You would know for example if and when people with common infection symptoms had been visited either by influenza viruses where SARS-CoV-2.

Brad Ringeisen:

In DARPA language, we have very much tried to have foresight over the past two or three years to try to start developing detection platforms that are very easily adaptable to new diseases. Use gene editing technology that there's a lots of work that can be done just in computers to be able to simulate and to be able to identify the exact genetic code that you would need that would be specific to the type of emergent virus that we've seen now with the SARS-CoV-2. So we were able to immediately in January, just with genetic code information that was coming out about this virus, some of our performers were able to immediately identify very specific code that would specifically identify this virus, turn that into an assay that could then now be tested at the University of Nebraska where there's many of these convalescing patients undergoing treatments in Nebraska. And so that was all done within a two-month period of time to rapidly respond, to now do the work that's necessary to be able to get FDA approval of that new assay for detection. That's one, and the second one that I'd like to talk about is a host response diagnostic program that we developed about two years ago called ECHO.

Ivan Amato

ECHO, run by program manager Eric Van Gieson, is an acronym that stands for Epigenetic CHaracterization and Observation. It's all about identifying the earliest signs in a person's body that he or she has been exposed to gravely threatening agents, including chemical, radiological, and biological weapons, or to natural threats like infectious pathogens. More than that, the handheld technology that Eric has been shepherding through development might be able to identify people who show no symptoms of infection but nonetheless are contagious or likely to become so. It turns out that even early viral exposures leave telltale molecular marks on the DNA and proteins inside the nuclei of our cells. These are called epigenetic marks. They're a bit like graffiti tags on walls throughout a city. The

goal of ECHO is to develop handheld devices that would be able to read those viral tags from easily gotten cell samples. Says Eric, the technology should be able to tell us if someone has been exposed to a particular virus, exactly when, and how that person is likely to respond to an exposure.

Again, BTO director Brad Ringeisen.

Brad Ringeisen:

We're looking at the epigenetic response of your own body. And that epigenetic response may occur on day one of exposure to that virus. And so your body starts adjusting, it starts adapting to that infection and it starts leaving genetic marks on your genome. So we're very confident that we're going to be able to identify host epigenetic marks that are specific to this new COVID-19 outbreak. This is a program that we started two years ago, and again it's starting to pay dividends now to be able to get very, very early, maybe even pre-symptomatic detection of a disease like this. And again, we're working with the University of Nebraska to be able to validate and to be able to test that assay as it develops and emerges and comes online.

Ivan Amato

Rohit Chitale and Eric Van Gieson's fellow program manager Amy Jenkins has clocked several years working for DARPA but only last June did she become a program manager in BTO. She didn't expect the ride would have accelerated quite this much so quickly and that the stakes would have climbed so high. But she is where she wants to be, furthering the power that the public health community can wield against disease.

Amy Jenkins:

And you always think you're ready until the real world scenario kind of drops itself in your lap and then you realize, wow, there are a lot of things that we have to think about, there's a lot of coordination that has to go on, there's a lot of pressure. You know, when you put out a program that says we're going to stop pandemics in 60 days and you have a declared pandemic on hand, people are looking at us to potentially make an impact on this outbreak.

Ivan Amato:

Amy is overseeing a bevy of programs including an especially comprehensive one called Pandemic Prevention Platform Program. Among the deliverables of her many programs are antibody-based treatments to stop infections early and long enough to buy time for the development of long-term protective measures such as vaccines. The goal of another one of her programs, called NOW, which is short for Nucleic acids On-Demand Worldwide, are mobile manufacturing platforms for producing new therapeutics against infectious diseases, anywhere, anytime, and at scales that matter.

Amy Jenkins:

So my portfolio largely consists of how are we going to respond very quickly to infectious diseases. And the reason I think we need to respond quickly to infectious diseases is because we have seen it. We saw in 2009 with H1N1. We saw it with Ebola, even though that was not respiratory, and spread across the world. It's very easy to make the next connection to say, if we had something that were spread as a respiratory disease, how quickly it could spread across the globe.

Ivan Amato:

Central to Amy's portfolio is the quest to dramatically shrink the amount of time it takes to identify the antibodies and people who recovered from infections. Antibodies: these are proteins that our own immune systems invent when challenged by infectious agents and that are tailor-made to neutralize those agents. Amy and the researchers supported by her Pandemic Prevention Platform Program are developing antibody treatments that could prove pivotal in slowing outbreaks before they can become epidemics and pandemics. The technology has made it beyond the concept stage all the way to clinical trials - at least for a virus known as Chikungunya. Amy says we could have protective antibodies against the new corona virus in hand this year. This is how she chronicles the progress so far.

Amy Jenkins

I am very interested in antibodies. And antibody technology provides a specificity so antibodies are very, very specific for the pathogen that you are trying to combat, trying to target. They're made naturally by your body, so when you are exposed to, say chickenpox, when you were a little kid, your body made antibodies. Those antibodies then become memory b-cells and they hang out in your body and if you ever see chickenpox again they come back to life, if you will, and they stop you from getting infected by chickenpox.

Well, we are very interested in that same type of technology. So when a person gets sick, they actually make antibodies and so the thought with our program is that you can go in to a person that has recovered, and presumably their body has made antibodies that helped them recover from that infectious disease or that pathogen and we can very rapidly find those antibodies. So once you find that antibody it then becomes a matter of how do you give that thing that protected that one patient. If you're able to find the very good ones and give it back to the rest of the population to protect them and prevent them from getting sick. And so that is really how we think about the use of antibodies. In many cases we think of them as a firebreak, so you give it to people so that they don't get sick.

So that's the same kind of general concept that we want to use here. The problem that we have when we think about the use of these types of things is that we don't have decades to find that antibody and we certainly don't have years or more to manufacture that antibody. And so that's where some of our other technologies come in. We have, as I mentioned, learned how to very quickly find the antibody, so we have certainly shrunk that timeline for finding the antibody. We also needed to invest in ways to ensure that we could manufacture that antibody much much faster.

And so, traditionally how they're made is in giant stainless steel bioreactors inside mammalian cells. Traditionally, back in the 2014 Ebola outbreak, that process could take anywhere from 10 to 24 months to figure out how to get those cells to grow in that bioreactor and how to get them to make that protein properly. That was much too long for rapid response and so we began investing in DNA or RNA technology. Antibodies are simply a protein. If we have the DNA or the RNA code for that, that DNA or RNA, if you inject it into your body, should make that protein, that antibody. We demonstrated this was possible for a variety of different pathogens.

So we looked at Ebola, we looked at influenza, we looked at multi drug resistant bacterial pathogens, we looked at Chikungunya and Zika virus. So many different viruses, and generally always were able to demonstrate that, yes, this is a possibility in animals. We then turned our sights to humans. Through rounds of rigorous safety testing, we felt that it was time to potentially test this in humans and we did do a human's clinical safety trial. These types of technologies have been tested for safety in phase one human clinical safety trials. And it has generally demonstrated the ability to inject, for example, an RNA intravenously into a human patient. That patient, then, their cells take up that RNA and their cells then produce the antibody that you asked the code that you gave it to produce. And we actually completed that clinical trial with a company called Moderna as part of the ADEPT program in the fall of 2019. That was actually for a Chikungunya virus, antibody against Chikungunya virus.

So we've demonstrated that you can use this genetic code, you can inject that into the person, and the person can become the bioreactor. So the thought is for this coronavirus outbreak, we may be able to actually manufacture antibodies in anywhere from four to eight months.

Ivan Amato:

As Amy sees it, this kind of antibody-based medical technology can change the pandemic equation in humanity's favor.

Amy Jenkins:

If you think about the fact that we could use antibodies, whether they be traditional protein antibodies that we injected, whether we inject the RNA or the DNA code, all of these could be used. You give them to healthy people, those people are now protected for anywhere from a month to maybe as many as six months from getting disease.

So if you think about this, we used to always talk about it in the context of the Ebola outbreak. I'll talk about it in the context of coronavirus now because the same thing potentially applies here.

You have those people that have to respond, they are on the frontlines. These are your nurses, your doctors, your first responders, the people that can't quarantine and stay home because they have to be in hospitals helping patients. These are the people that are potentially most at risk, so we call them our frontline health care workers. And this would be a population that it would make most sense to give this to initially so that they don't get sick, so that you keep your healthcare system functioning in a robust manner.



Then you can also think about giving this type of, if you had enough of it, you could give this type of modality to people that have been exposed. So for example if you have a family member, potentially all of their contacts could get this. So this is something that I think even two months ago, people maybe didn't understand and people are now becoming much more comfortable with understanding contact tracing and what that actually means and why that's important. If you become sick and you tell your public health department these are all the people I came into contact with, those are potentially now the people that are also going to get sick. You could then go to those people and potentially give them this so that they don't become sick. And now you stop these types of diseases from spreading. And it is frankly exactly how we have stopped some of the worst Ebola outbreaks in the history of Ebola outbreaks in the last four years, and it's going to be critical in this coronavirus spread as well as just understanding who talked to who, who interacted with who and we could certainly envision a situation where you use this type of technology to ensure that those contacts do not get sick.

Ivan Amato:

Amy and her DARPA colleagues were able to swerve the research groups already working as performers in the Pandemic Prevention Platform program, also known as the P3 program, to apply what they already have learned to the new COVID-19 pandemic.

Amy Jenkins:

So all of our groups are currently working on this, and we actually have groups that are currently, right as we speak, at this moment, discovering antibodies against this coronavirus.

We were able to obtain samples from a patient that, under informed consent, donated their blood to try to find some of these antibodies that helped that person recover. So several of our groups are currently working to try to identify those antibodies. I will caveat this by saying that this was one person, in one person's response, and so we would typically do this with many people, maybe up to ten people, because we just don't know how one person responds versus another. You want to have the best shots on goal. We had one person. Our groups are working extensively, literally around the clock to try to identify those antibodies from that patient that may be the most useful for treating a broader swath of the population.

It is going well. I am very cautiously optimistic we have found initial hits that would indicate that we have some antibodies that do bind to this novel coronavirus. But there is extensive testing that will go on in the next two to three weeks to really characterize and understand those antibodies. What we actually want to be able to do is neutralize the virus, or what we call neutralize the virus, which is prevent the virus from infecting human cells. So the first thing we'll do is we will test that in vitro, in a petri dish, if you will, not exactly a petri dish but in that type of setting. We actually test and make sure that our antibodies block that pathogen from infecting human cells. Then the next step would be to then test it in animals, small animals or large animals, or both, potentially. So we're talking mice or potentially all the way up to non-human primates. And if it looks like it can protect those animals from getting sick from this coronavirus, the next step would begin to manufacture it and get ready to test it for safety in a phase one human clinical trial.

Ivan Amato:

This means all of this technology stands a chance of helping out, even in this current pandemic but it also sets the stage for disarming pandemic threats that humanity is sure to face in the future. Like some of her colleagues, Renee Wegrzyn is running programs that, if successful, could help solve the hard problem of quickly detecting any dangerous pathogen that might emerge. One of her ambitious programs is DIGET, short for Detect It with Gene Editing Technologies. Imagine, she says, handheld devices that could detect any pathogen of concern with just about any biological sample: spit, blood, or urine, for example. That's what Renee wants to make so

Renee Wegrzyn:

Five years from now, when we have all of our DIGET devices up and running, first on the front end, we're going to have unparalleled biosurveillance capability where we can look at every patient sample that comes in and look across a thousand different possible pathogens. In fact, you know, envisioning every human pathogen that exists, if we just routinely look at that testing, that would be our opportunity to detect something very early, potentially even before an outbreak occurs.

Once we have the bio surveillance hit, then we would want to get a diagnostic in place very quickly so that we could, okay now we know there is something that's an anomaly, now rule in or rule out. You know, does this person have this disease or not. That's very important because you can help make a decision to quarantine somebody, but then also to give them the right medical countermeasure. So you want to make sure that you're matching treatment with the ailment, of course.

That's sort of at the individual patient level, but then at the decision-maker level, whether it's for a nation or a deployed unit, there needs to be decision making of, you know, how do they respond and move forward? Is it rolling out medical countermeasures, is it bringing your whole command back in, whatever that might be. You actually could have, you know, what we would call actionable information moving forward. So that would have been great, if we had this for this current outbreak, potentially we could have contained it before we hit this pandemic state. And that's really where we want to be moving forward.

Ivan Amato:

Brad is all in on moving forward as fast as possible with the program managers in BTO and the innovation community they are nurturing. He feels their efforts really, really could reduce the consequences of future pandemic threats.

Brad Ringeisen:

So if we step back and think about the next threat that inevitably, is most likely, is going to happen, I think what you see with the DARPA BTO suite of programs and suite of technologies that we're

developing is that we really do see a pathway now where we we won't have to go through the process of what we're going through right now, to see this exponential growth, to see the danger of the threat to our population.

Ivan Amato:

Brad points out that superlatively bold goals like developing practical and deployable technology platforms that will intercept any infectious disease outbreak before it can threaten military readiness and large populations takes solid partnerships throughout the innovation ecosystem. And it takes an institutional infrastructure that can deliver public health actions and medical countermeasures on massive scales

Brad Ringeisen:

We put a goal out to the community. We offer funding, research funding, and those researchers then go off and do the amazing work. But we can't take any of that work from the laboratory to actually be used to be able to fight something like this without partnerships. And that's something that in my three years here at DARPA that I've really worked hard at is trying to work with our DoD advance developers work with our HHS, NIH, ASPR, BARDA partners because they're the ones that are really tasked with the advanced development and ultimately getting these types of products through the FDA and being able to actually distribute and manufacture them to get them out to the population. And so without those partnerships and we're working with them literally almost every day during this outbreak to be able to make sure that these new innovations, these rapid response platforms, don't just die in the laboratory that they actually make their way into the DoD personnel and to be able to protect the US population as well.

[Music]

Ivan Amato:

So in this moment of shared anxiety and fear, it is a gift to imagine, incredibly, of a not so distant future where no one has to worry that an outbreak of a new disease anywhere will spread into a devastating pandemic everywhere. It is heartening to know that there is a team of DARPA program managers who, with partners around the world, are making sure our most innovative researchers and technology developers can take those steps that will get us there.

Thanks, listeners, for sharing this time with us. I hope you join us again for the next Voices from DARPA.

Thanks also to Tom Shortridge and Ben Sullivan for help in producing this podcast.

For more information about DARPA and the many breakthrough technologies the agency is working on, visit [DARPA.mil](http://DARPA.mil). And for links that enable you to download this and other episodes of the podcast, go to the Voices from DARPA page on the DARPA website.