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Voices from DARPA

Transcript of Episode 22: The Disease Slayer
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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 core of program managers. Their job? To redefine what is possible.

My name is Ivan Amato and I'm your DARPA host and today I'm pleased to have with me in the studio U.S. Army Colonel Matt Hepburn, an active duty Army physician and since 2013 a program manager in DARPA Biological Technologies Office.

Colonel Hepburn holds a Bachelor of Science degree in biomedical engineering and a Doctor of Medicine degree, both from Duke University. Following all of that education he completed an internal medicine residency and an infectious disease fellowship at Brooke Army Medical Center at Fort Sam Houston in Texas. Prior to joining DARPA Matt served as the Director of Medical Preparedness on the White House national security staff. Additional previous assignments include the chief medical officer at a level 2 medical facility in Iraq, a clinical research director at the US Army Medical Research Institute for Infectious Diseases, and an exchange officer to the United Kingdom, among other positions.

Matt is one of DARPA's program managers who comes to work in his military attire, in his case either his army fatigues or a dress uniform. Either way, he always wears the smile of someone who finds himself in a place where he just might be able to realize a dream and he has said publicly that he wants to stop all infectious diseases from killing people. May it be so, Colonel Matt Hepburn, though I will call you Matt from now on. It is my pleasure to have you in the studio today.

Matt Hepburn: It's fantastic to be here. And thank you, Ivan, for inviting me to be on the podcast and to tell my story and tell you what I care so deeply about.

Ivan Amato: Yes, so I've been greatly looking forward to this discussion, so why don't we get right into it. And so you're a medical professional who embraces clinical and field practice as well as leading-edge research. What are the origins of those interests for you?

Matt Hepburn: It started pretty young. I have this childhood memory of being asked at my school, a Catholic school, and I was meeting with one of the priests and he said, 'well, what do you really want to do?' And I said I wanted to be a pediatrician. And they said "why?" And I said, "Well, because I just want to take care of people and I want to take care of children." And I do think it stems from: my mom was a nurse, and so I think, less so from the influence of being around someone in the medical profession, but more so just being around someone that cares very deeply about other people. Again, very early on, but it's been it's been sort of a consistent part of my life. This was in fourth grade…[overlapping speech]…this

whole like I wanted to be a pediatrician. And so as I was on this trajectory. And I didn't know of course what I was talking about: you know, I mean even, you make these decisions early in your life. But my parents and my family always had this incredibly strong ethic of service and very deeply and fundamentally. Because I reflect on this often actually, it's like, who am I? And what am I supposed to be? And I think what I do is I serve others and that's how I define myself. Maybe one of the greatest gifts from my parents was that my dad was active duty Navy officer, did ROTC, and served as a nuclear engineer on a surface warfare ship. It was active duty for five or six years, stayed in the Navy for another 20 +. Retired as a Navy captain in the reserves. You couple my mom's passion for helping other people in the medical field with my dad's passion of serving our country this was almost like all I knew and so that trajectory has sort of guided me through all of my decisions in life.

Ivan Amato: Let's actually talk a little bit about that. Before you came to DARPA you spent almost 15 years in a variety of assignments that took you to, for example, to Fort Detrick, the military's premiere facility for infectious disease research. It took you to Korea, to the UK, the Republic of Georgia Azerbaijan, Iraq, Thailand, other place I'm sure. What did you learn from all of that global experience?

Matt Hepburn: I would start by saying what a privilege, what a privilege to have those types of life experiences all in the context of again feeling that I'm serving my country and making a difference. Some of the work that I'm most proud of, frankly, is work I did in the caucuses with Georgia and Azerbaijan. And the program was under the auspices of what was called the Cooperative Threat Reduction program, but really my role there was to engage their public health communities and their medical research communities to establish that capability of finding infectious diseases, diagnosing them, and ultimately treating them. And it was a capability that was, those public health systems were all part of the Soviet Union, but when the Soviet Union fell these countries were kind of left to their own to recreate a public health infrastructure. And so the privilege was to work with those experts in the host country to say, ‘how do we build that back up again so that you can tell us that there's an outbreak going on and then we can collectively work together to respond to that outbreak.’

Ivan Amato: Right, so did you bring in models like the Centers of Disease Control?

Matt Hepburn: We did. We worked closely with the embassies. We worked closely with the State Department. We worked closely with the CDC. At the end of the day it was myself and some of my DoD colleagues on the ground, you know, rolling our sleeves up helping these countries develop those systems, developing laboratory capabilities, developing the ability to do clinical research to ethical standards that would be accepted all over the world, and to figure out how to do this. You know, again, I look back, what a privilege to be on the ground—and at this point fairly junior in my career—and to help an entire nation improve their public health.

Ivan Amato: Yeah, that does sound like a great privilege. What is the sequence of events, Matt, that resulted in your current position here at DARPA as a program manager?

Matt Hepburn: Throughout my medical career I had heard about DARPA. And I had seen amazing technology that had come from DARPA that were aimed at addressing infectious diseases threats. So I had always admired from afar. Before I joined DAPRA< I was over at the White House National Security Council staff, and in that role my job was to identify what capabilities we do NOT have to respond to pandemics, and then how we can organize ourselves as a government, not just DoD, but as an entire government towards addressing those gaps so we're ready for the next one. And while I was there, I got tapped on the shoulder, and the concise phrase was ‘you're doing all of this policy what we should do as a government, how would you then like to implement and actually make investments that are going to address those gaps?”

Ivan Amato: So, Matt, were where you literally tapped on the shoulder and so who was it that posed this to you?

Matt Hepburn: It was Dr. Geoff Ling, who was the deputy director of DSO [Defense Science Office] at the time, and I met him for coffee one morning, and he didn't literally actually put his hand on my shoulder, but figuratively imagine a hand on my shoulder, saying 'Matt how would you like to try at DARPA to actually invest to make a difference for all those things that you've been talking about in terms of big policy words for the last few years?'

Ivan Amato: Well, and of course he provided a model of audacity because he really took on tremendous programs prosthetics and other programs to really help the warfighter. Why don't we segue then into your life as a program manager here in this tremendous portfolio that you've developed, which is I think a portfolio that also reflects the a kind of audacious point of view, as is of course reflected by that statement earlier, that you want to take the lethal power out of infectious disease. So the names are fantastic, some of them like Prometheus and Thor, Dialysis-Like Therapeutics, In Vivo Nanoplatforms. And we'll probably talk more about one of them in particular, the Pandemic Prevention Platform. What I'm hoping to do now is if you could briefly take us for a tour of your programs. We can't go in-depth about any of them at this point, but take me a little bit of a tour on what what you're hoping to achieve with some of these programs and then we'll focus in a little bit more on the Pandemic Prevention Platform.

Matt Hepburn: Yeah, so the tour starts by saying what problems are we trying to solve. And, again, at the White House National Security Council staff, I got a chance to say, 'look for these major outbreaks, pandemics, or near pandemics, how have we done as a government?' Think about the 2009 H1N1 pandemic. Think about the West Africa Ebola crisis.

Ivan Amato: H1N1, that is, H1N1 influenza.

Matt Hepburn: Yeah, influenza. Think about the West Africa Ebola crisis. Think about how we've recently responded to Zika. There are common themes throughout, and some of those common themes are: we need to be much better at diagnosing if someone has an infection, and we need to go a step beyond that and imagine a world that if we could figure out if someone is going to be sick or is going to be contagious we can intervene and stop the outbreak right in its tracks.

Ivan Amato: And that's Prometheus.

Matt Hepburn: And that's the Prometheus program. But we also need to make vaccines and treatments much faster than we currently can. And one of the examples is the Pandemic Prevention Platform. We need alternate ways of how we treat infections and using portable dialysis to filter the blood and remove any type of pathogen is a good example. B

Ivan Amato: But just in that case, is does that mean I might I might have been exposed to some kind of pathogenic agent. It's in my blood and certain levels, so would this kind of technology remove that before it could take hold and actually get me sick? Was that is the idea of that?

Matt Hepburn: Yes, and the idea would be again, especially for pathogens where we don't have a vaccine where we don't have a treatment. Especially think about now with what we're seeing so much antimicrobial resistant bacteria. Imagine if where we can't use antibiotics. So if we can filter your blood and remove that pathogen. What if it does is ultimately gives a leg up for your own immune response to ultimately make you well again. We like that technology especially in those first days when we need to buy some time to develop a vaccine and we need to develop new treatments. And so my point across the portfolio is that we have lots of investments in medical diagnostics. We're investing in modeling to forecast where infectious diseases are going to go. We have investments in accelerating new treatments. But they're all connected together. They are all linked.

And let me give you an example with our Prometheus program predicting if someone is going to become contagious. Well, awesome, right? If we can do that. But once we predict and identify that person, we still have to treat them. And so we're going to need treatments as fast as possible with our Pandemic Prevention Platform. And the beauty is that those treatments are probably going to be most effective

when they're given as early as possible. So I think of our whole portfolio as interconnected, that we develop a lot of different specific projects to get capabilities, but that they're ultimately going to intertwine so that we stop the outbreak in its tracks.

Ivan Amato: Well, when I think of programs here at DARPA, they all have a kind of lifecycle to them, right. I mean they sort of start as a glimmer in the eye of someone like you, Matt, a program manager. There's a period of vetting and working with others here to really articulate and formulate the program as best it can be, so that it can be most effective. And then, kind of, smoke signals go out to the world and seeking people who maybe think that they can pull off some of these audacious tasks that we've put out. Of course, then the research is done and hopefully in the end you succeed or if not fully succeed, you learn from all the research that that's going on. So what is the status in that lifecycle of the Pandemic Prevention Platform?

Matt Hepburn: The Pandemic Prevention Platform just launched.

Ivan Amato: And by launch, for those who might not know what that means in the DARPA context?

Matt Hepburn: That means that completing the contracting process so that our performers that were selected in a very rigorous process can now accomplish the goals of the program. So they're just starting in there for six months. As part of the lifecycle, these are early days, early days because the ultimate goal of that program is so difficult. You know, in some ways I feel like we have we have a long way to go. One of the key points though of the Pandemic Prevention Platform is that the goal is incredibly ambitious, but there is foundational scientific evidence that this can be done. And that foundational scientific evidence is derived from a previous DARPA program. [It proved the concept].

Ivan Amato: That’s ADEPT.

Matt Hepburn: That's the ADEPT program.

Ivan Amato: Because when I looked over the program it's fascinating to me, because it looks like we're trying to rev up the whole brilliant molecular world of antibodies. And so I want you to sort of go through the sequence events, beginning with this earlier program, ADEPT. Walk us through some of the steps, because antibodies are among my favorite proteins, when I look at them< their just brilliant things, just so selective, and they find the thing that we don't want in our bodies. They glom. Anyway, you tell us the pieces of the program.

Matt Hepburn: You know, Ivan, I couldn't agree more. I think all of us that are fascinated by—yeah DARPA—that's probably a common them—is we are just amazed by the natural world and what the natural world has developed. Antibodies are a great example. I mean there are millions and millions of these different versions of antibodies circulating through your body at all times. And the mechanisms are so refined and intricate to select, ok which are the antibodies that are most protective when you're exposed to an infection. And your body goes through the process of making a lot of those in a short period of time. I think it's mind-boggling how advanced that system is. We've learned so much about antibodies in the last 50 years. You're absolutely right. We want to leverage all of that information. We know how they work now and we know about their structure. We know how to make them in big vats and why can't we use that. And you're seeing incredible progress in medicine where we are using that, where you're seeing antibodies approved as products now for cancer treatment, for treating autoimmune disease.

Ivan Amato: In the category biologicals.

Matt Hepburn: In the in the category of biologicals. A massive explosion in that space .And we want to use all of that knowledge and that technology to solve infectious diseases problems. What we do at DARPA though, the fun part, is we couple different fields together. And so as you have correctly pointed out, this extraordinarily powerful tool of antibody engineering. But can we couple that with the revolution

that we've seen in in genetics. And that's, that's DARPA right? It's taking two different areas, seeing if we can mix them together. Again, an antibody specialist might not think about the opportunities with genetics. The genetic specialist might not think, well wonder if I couldn't use my use genetic engineering to make an antibody. You bring the two fields together by our magic of bringing the disciplines together, we achieve that effect. And so, the proof of concept, which I find exhilarating—it sends chills up and down my spine—is that we can give you a piece of DNA, or a piece of RNA, and we can put that into your muscle cells, and that your muscle cells say, “okay, got it, I am going to make this antibody that is so protective that someone's not going to get sick.’

Ivan Amato: And that's encoded by these nucleic acids, the RNA and DNA”

Matt Hepburn: The RNA tells that muscle cell, so the muscles is doing what a muscle cell does, but once that RNA gets inside that muscle cell the muscle cell says, ‘right I'm gonna make a protective antibody that's gonna protect you from Ebola, and to do that in a fairly short period of time.’ And that idea would sound crazy ten years ago. Too many obstacles; it can't be done. The foundational investment from DARPA proved that concept in many different animal models for many different infections, but because we're DARPA we said. ‘well great: we prove the concept.’ That wasn't good enough. It wasn't good enough for me, and it wasn't good enough for the DARPA leadership. DARPA leadership said, ‘okay that's great, but we need to birth the baby.’ If we're going to take pandemics off the table, and that's why I'm here, we need to be able to put this together as a platform that can go start to finish from once a pathogen is identified to making thousands of doses of this miraculous antibody-based treatment in an incredibly short period of time.

Ivan Amato: Right, and let's talk about the timescale for a minute, because that's part of the big deal here right. What I've seen is within 60 days of identifying the pathogenic agent to actually have these doses right in hand and in a distributable form. Is that correct that's correct? That compares to what’s the state of the art today?

Matt Hepburn: The state of the art today depends on infections, but let's use some recent examples. We currently have some Zika vaccines in clinical trials, but we've been working now for a few years and we don't have a licensed Zika vaccine. When we talk about gaps, you think about all of these recent outbreaks, and one of the fundamental lessons is that we haven't had vaccines and treatments that are ready in time.

The 60-day goal has been controversial. When we talk about audacity, you know, I have professional colleagues who laugh at me. I've been on I've been on panels where I, you know, discuss the program and the other panelists joined with the audience at laughing at me. So I knew we were in the right space. The counter-argument that I continually make to the critics is 60 days is dictated by what we need to respond to pandemics. So if you don't agree that our approach is the right way, then come up with an alternative, because we can't negotiate with Mother Nature and say well we'd like another six months, if you don't mind, especially when you think about the catastrophic consequences accordingly. So, you know we have to do this within 60 days, and I think, again, I'm profoundly excited because I think we found a way to do it.

Ivan Amato: So I want to try to make this concrete for our listeners, which you've actually done fairly well just now, but I thought of another way we might do this, and that's by combining, you know, almost the gaming out to the future where, let's say, you are successful—and may you be successful with this P3 program, the Pandemic Prevention Platform program—let's say that you had that P3 ability back in the 1918 Spanish flu, which I've seen different number—I've heard 50 million people died during that pandemic. If this technology existed back, in the early part of the last century, how would that have unfolded do you think?

Matt Hepburn: Well, my hope is that 50 million people don't die. Again, part of this is you detect that we have a new virus, or a new version of influenza, and we detect very early on in the process when it's first

starting out in a given country, that it's that it's happening. We flip the switch and we say for that new virus we need 20,000 doses that have to be ready within 60 days. And then we go to when that outbreak is first starting, we identify who's sick, we treat those people that are most likely to be contagious, and we stop the outbreak in its tracks. If we had it we, could have stopped the Spanish flu. I think even more importantly, right now today you and I both know people who are getting very sick with influenza. We're seeing a severe season, and we're seeing unfortunately, children die. We're seeing, unfortunately, otherwise completely healthy people being hospitalized. And influenza does that to us every year. We imagine a world where this platform could be used to take seasonal influenza off the table as well.

Ivan Amato: An amazing thought, because I mean this gets back to you, the several times you said what a privilege it is to do what you're doing, because if you succeed you will know—I know you won't take this, it's not pumping you up personally; it's more for what it's doing for, you know, kind of humanity—but you will know you've had a part in potentially saving millions of people's lives by cutting these pandemic experiences off before they really get going and spread. So, really quite an amazing endeavor.

Matt Hepburn: Yeah, and I would make two points. The first is that DARPA, my team does not do this alone. DARPA does not do this alone. We work incredibly closely with our colleagues in Health and Human Services, with other experts in the Department of Defense in the US government, as well as philanthropy, as well as the private sector, and as well as the global community. It's ultimately a global teamwork that's going to take these infectious diseases off the table. But make no mistake, we can say it sounds hard and it's ambitious and it's crazy, but I challenge you to say' why not?' You know, why aren't we as a society putting incredible, even more effort, into taking these infectious diseases off the table? If we have the scientific know-how to do so, this is what I think one should be focusing on.

Ivan Amato: It's a moonshot but why not go for a moonshot.

Matt Hepburn: And why not go for a moonshot against something that could kill another 50 million people. Why not take a moonshot against infectious diseases like malaria and tuberculosis. I mean we've seen, you know there's effort in there, there's global effort that's absolutely tremendous, but why not more.

Ivan Amato: So Matt, just a little while ago you and I were kind of gushing about the molecular beauty in the biological beauty of antibodies and the specificities those have to go out and find whatever the health threatening agent might be, and the role that plays in our own bodies' fight against health-compromising exposures. So I guess I kind of want to ask you: do you have a favorite infectious disease in the sense that you admire what the bacterium or what the virus does and has learned how to do over the course of evolution?

Matt Hepburn: So I'll answer in a slightly different way. I think it's when we say we want to take infectious diseases off the table, in some ways it's ridiculous, because we're always gonna have viruses and bacteria that are part of the natural world. And we've always seen them as the enemy, or 'pathogens' is the word that we us. One of the interesting ways to think about the problem, though, is that, a part of it is that there are a pathogen, but part of it is how we respond. And modulating how our own body responds to pathogens is a major theme of what we're trying to do, with antibodies being one of many examples. And so you know one of the traditional attitudes of antibiotics is, you know, antibiotics have been wonderful and certainly profoundly impactful, in terms of our society as we've as we've come along, but we've also discovered the unintended consequences of giving a broad-spectrum antibiotic incurring antimicrobial resistance and things like that as well. So the world that I imagine is that there is, I guess like you said before an appreciation of pathogens, an appreciation of viruses and bacteria, understanding what they do and what they don't do. And it's not always wiping them out, but more about rendering them harmless or figuring out ways to kind of coexist with them, is where I would like our thinking to go in the 21st century.

Ivan Amato: It makes a lot of sense. I heard statistics about the number of mammalian cells in me and you, and the number of bacterial cells, and we're almost, from just a numbers perspective, way more bacterial than we are mammalian.

Matt Hepburn: We are.

Ivan Amato: But most of the time this is this is a symbiosis, this is a mutually beneficial relationship and so it really we shouldn't always think about these e microbes as things to consider them enemies, we shouldn't consider them that way.

Matt Hepburn: That's right. That's right. And the other part is that we learn from them. You know it's their evolution that also kind of inspires us. And so in some ways they're are adversary, but in some ways they're sort of that—you know in the superhero novels and things like that—this idea of the balance between the hero and the villain and sort of that strange relationship that often develops between the two and, if you will, mutual appreciation: I think that's us and pathogens.

Ivan Amato: So Matt we're coming toward the end of our time here, but I'm just wondering if there is something that didn't come up during our discussion that you think would be of interest to our listeners, given you know your goal here of perhaps ridding us of some of some of the concerns we have about the pathogens in our environment.

Matt Hepburn: Yeah, one of our mantras at DARPA is this idea of inspiring creativity and new solutions to problems, and oftentimes we say, by sort of recruiting in people who have not traditionally thought about our problems to help us with those solutions. And so you know I would love for the listeners of this podcast to be more inspired to address the problems in infectious diseases. And what I mean by that is, I always say people like me have to, you know, we've invested our entire careers and our life work into this and we have deep knowledge of the subject, but I love the thought of people that have expertise in computer science, in mathematics, in what we would say well maybe those fields aren't necessarily obviously related: that's how we're gonna solve the infectious diseases problems of the 21st century. And so when I speak on this, it's one part recruiting, and it's especially recruiting those that may not have all of the biases of the traditional experts in infectious disease to come up with a creative solution to solve it.

Ivan Amato: So that makes me think of a term that we hear a lot here at DARPA, you know, the innovation ecosystem, because you just mentioned a whole bunch of disciplines that, you know, maybe when you first think about infectious disease, you might not think some of those come together. So is there something about you, and being here at DARPA, that is conducive to shaking up that innovation ecosystem in ways that could maybe move toward the goals that you have.

Matt Hepburn: Well, DARPA enables me to do that, because, again, our program announcements: when we say, okay, we set the requirements solve this problem, make us a treatment in 60 days, we know that they can't do that alone. And it takes a multidisciplinary team, so if you want funding from DARPA, you're gonna have to work with people, you're gonna have to recruit. We design it so that you will have to recruit in people that may not be the traditional subject matter experts. But furthermore, every time I get a chance to speak and to talk about this problem, like on this podcast, you know, again, I see it as a recruiting tool to inspire those to help us address these infectious diseases threats.

Ivan Amato: Well what, I'm realizing now is I do not want to prevent you for another minute going out there and realizing your goal of taking the lethality of pathogenic disease. And we are out of time also, so I just want to thank you. This has been immensely fascinating for me and I just want to thank you for sharing the stories about your life as a medical professional and how you're expressing your interests and goals here at DARPA.

Matt Hepburn: Well thank you very much for allowing me to be a part of it.

Ivan Amato: And thanks, listeners, for sharing this time with us. I hope you join us again for the next voices from DARPA.

For more information about Colonel Matt Hepburn, the program's he runs, and the other breakthrough technologies DARPA is working on, visit darpa.mil.

And for links that enable you to download this podcast, go to the *Voices from DARPA* page on DARPA's website.

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