Interview with Dr. David Fajgenbaum

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KENNEALLY: Cytokine storms may sound like an unusual meteorological phenomenon, but these storms are medical ones. Normally, cytokines regulate the human body's immune system. When attacked by an infection, though, cytokines can be released in excessive amounts, leading to organ failure. Such storms are one of the most devastating effects of COVID-19.

Welcome to Copyright Clearance Center's podcast series. I'm Christopher Kenneally for Beyond the Book.

An unusual and innovative laboratory at the Penn Orphan Disease Center in Philadelphia has moved quickly to study cytokine storms and the hyperactivation of the immune system. Leading that effort is a groundbreaking physician, scientist, disease-hunter, and bestselling author, David Fajgenbaum. One of the youngest individuals ever appointed to the faculty at Penn Medicine, David Fajgenbaum is director of *Chasing My Cure: A Doctor's Race to Turn Hope into Action*. While in medical school, Dr. Fajgenbaum spent months hospitalized in critical condition from idiopathic multicentric Castleman disease, an extremely rare disorder of the lymph nodes. The physician eventually sought a cure himself, spearheading a fresh approach to research and discovering a treatment that has put him into extended remission.

Dr. Fajgenbaum is co-founder and executive director of the Castleman Disease Collaborative Network and associate director, patient impact, for the Penn Orphan Disease Center, which has recently directed its attention to the novel coronavirus that causes COVID-19. He joins me now from Philadelphia. Welcome to Beyond the Book, David Fajgenbaum.

FAJGENBAUM: Thanks so much for having me on, Chris.

KENNEALLY: Well, we are looking forward to learning about the work that you have undertaken that is directed at COVID-19. You are studying, as we said, this hyperactivation of the immune system. Did I get it right – are these cytokine storms really what is the most dangerous part of COVID-19?

FAJGENBAUM: You nailed it. Just as you said, COVID-19 starts out as a respiratory infection. And for most people, they can clear the respiratory infection, but for a small percentage of people, unfortunately, they will get very, very ill with one of these cytokine storms. And it's actually the immune system's attempt to kill the virus and then just getting out of control and attacking the body's vital organs. This cytokine storm concept is something that my lab and I have been pursuing for many years in the setting of, as you mentioned, Castleman disease. This is not a new phenomenon, but trying to redirect what we've been doing and what we've learned about other cytokine storms to COVID-19 has become critically important.

In addition to understanding the cytokine storm, the research we do is never just to understand how it works, but it's all about treatment. So as we're trying to figure out and piece together this cytokine storm, we're also thinking a lot about what drugs already exist that we use in diseases like Castleman disease that could be repurposed and directed against COVID-19 right away.

KENNEALLY: And the point you make is that there are a certain number of FDA-approved drugs that are used to treat all sorts of diseases. I understand there are something like 1,500 drugs, about –

FAJGENBAUM: That's right.

KENNEALLY: – currently FDA-approved, and they treat something like a quarter of the 10,000 human diseases out there. The work that you are undertaking at the lab is to investigate the chance that some of these existing drugs may be able to attack the COVID-19 disease.

FAJGENBAUM: That's exactly right. Most people are actually quite surprised when they hear those numbers. There's 1,500 drugs that are FDA-approved for about 2,500 diseases. But just as you mentioned, there are another 7,500 diseases that do not have a single FDA-approved drug. That's kind of hard to imagine – here in 2020, only one-quarter of all diseases have treatments? So we have a ways to go. Thankfully, most common diseases have drugs. But unfortunately, many rare diseases do not.

So this process of looking at all of the existing FDA-approved drugs – well, the first step is really to dissect a disease to try to understand what is happening at the most fundamental level in that disease. Once you get a good grasp for the biology, then you start saying, well, what drugs already exist that might actually be able to have an impact on this disease? And then when those drugs are tried in humans, it's critically important that you track systematically whether those drugs work or

do not work. These are all the steps that we're taking right now in the fight against COVID-19.

KENNEALLY: And your laboratory – it sounds like it's a rather different kind of laboratory than the one we might imagine if we close our eyes and think of test tubes and beakers and Bunsen burners. What your material is, as far as you're investigating, is data.

FAJGENBAUM: That's right. We have what we call a translational laboratory. Half of our lab does, just as you said, kind of the traditional beakers and experiments in dishes, we work with animal models. And then the other half of the lab does computational research, where we actually – the experiments we do are on computers.

Given the situation we're in right now with this virus and concerns about not practicing social distancing, those sort of concerns, we've actually directed the computational side of our lab towards COVID-19. So it's the folks who don't run laboratory experiments who are really focused on COVID-19 in my lab. Thankfully, there are a number of other labs out there that are running the experiments on samples of infected cells of model systems that are infected with COVID-19.

So we're kind of taking three steps. The first is to create what we call an immune map of COVID-19 that tries to map out the results of all of the experiments being done worldwide and trying to piece together, what do all of these different studies mean for this disease? This is something that unfortunately we have a lot of experience with in Castleman disease, because Castleman disease is such a mysterious condition.

And in parallel, as you mentioned, we have a team of folks that are going through all of the published data – all of the published case reports, case series, clinical trials of any drug that's ever been tried against COVID-19 to first just categorize what's being given, and then most importantly, understand what's working and what's not working. Because we knew that it would take literally years for just a few people to go through the 2,500 published studies, we enlisted an army of volunteers. So it's actually a total of 30 people went through 2,500 papers in 12 days and extracted out every single data point on every drug that's ever been used against COVID-19, and we're in the middle of running the analyses on those data right now.

KENNEALLY: So you're really crowdsourcing. This is an approach that takes advantage of the power of networking – not just the technology side, but the human side.

FAJGENBAUM: You're exactly right. You know, can you think of another cause, other than COVID-19, that would get people rallied together to want to spend their nights and weekends and hours fighting this? It's amazing the human spirit and so many people coming together and saying, I'm going to spend any moment of time that I have to help out here.

KENNEALLY: And you are going to make all this data available so that researchers and physicians around the world and access it and begin to use it and apply it to their own work. I understand there's also in development a COVID-19 immune map. Tell us what that is.

FAJGENBAUM: Yeah, so the immune map pieces together data from studies being done by researchers all over the world into one central place. There are about 200 papers being published every single day about COVID-19. As a result, it's very hard to keep track of everything and how every study fits together with every other study. So we have a team of people in particular, led by a graduate student in my lab, Ruth-Anne Langan, who goes through every one of those papers and tries to piece within this kind of overarching map how all of these different studies fit together – and oftentimes, they don't always fit together – but trying to put that into one central place. That's our immune map.

KENNEALLY: This approach you're undertaking, Dr. Fajgenbaum, it sounds like you know what you're doing, because indeed you do know what you're doing. (laughter) Your own experience, a remarkable experience which you tell the tale of in *Chasing My Cure*, was to suffer this rather dramatic disorder and then decide that the person to cure it was yourself.

FAJGENBAUM: That's right. I was diagnosed with this awful disease, Castleman disease, while I was a third-year medical student, and I was so sick that I had my last rites read to me, because the doctors didn't think I would survive. Fortunately, I survived that first episode, but I went on to have four more deadly months-long relapses where no one thought I would survive. Thankfully, chemotherapy saved my life. But it made me realize that if I wanted to live and if I wanted to maybe have a family one day, that I would need to identify a drug that could save my life.

So just as you said, the steps we're taking right now against COVID-19 are right out of the same exact playbook that we used to figure out how to save my life. My book's called *Chasing My Cure*, but really we should have probably titled it

Chasing Our Cures, because thankfully the drug that I identified that's saving my life, we're also giving it to other patients, and it's saving other patients' lives as well. This sort of process of dissecting a disease, searching for drugs that could be repurposed, and then tracking how they work, running clinical trials, this is exactly what we've done – I'm only alive today and being able to talk to you because of that playbook. And we hope that utilizing the exact same approach for COVID-19 is going to be really powerful.

There was a really important moment in my own battle against Castleman disease. That was after my fourth relapse, I learned there were no more drugs in development and that if I didn't get involved in research, that no one was going to identify a drug that could save my life. There was this moment where I went from hoping that things would work out and hoping that someone would figure out a drug to saying, I want to turn my hope into action. I'm actually going to take action in fighting back against this disease by conducting research and doing the work myself.

I had a similar moment about three weeks ago. Like so many others, I was devastated – and still am devastated – about what's happening with COVID-19. And I thought to myself, I really hope some lab out there goes through all of the FDA-approved drugs and understands what drugs may work, what drugs may not work. I really hope a lab out there puts together an immune map to track how all of these data fit together so that other scientists can build upon it. And then I thought to myself, you know, I've realized in my own fight that if I'm going to hope for it, if I'm going to pray for it, then I need to do something about it. So I turned my hope that someone would do it into action, and then I was able to rally my team and a number of volunteers from the Castleman Disease Collaborative Network to get involved in fighting against this disease.

So I think that the lessons that you learn from life experiences like mine, from nearly dying five times, those lessons stick with you. And those are lessons that are informing my action today, but they're also lessons that I really want to share with the world, because I don't want others to have to go through five near-death experiences to learn these sort of lessons about living in overtime and turning hope into action. I want people to be able to use them today.

KENNEALLY: Well, you mentioned playbooks, and playbooks are something you also know well in addition to research. You were a quarterback at Georgetown. And I wonder, David Fajgenbaum, whether that's what it feels like right now. You're sort of getting back into the pocket, getting ready to throw that pass to the researchers who can take it further downfield.

FAJGENBAUM: I think that's a really great analogy. And I think science is such a team sport. There are very few team sports that require such coordination and collaboration as football does. You need everyone to play a particular role and to be a part of a bigger effort.

Research is a similar sort of thing, where not one of us – no single researcher or physician – can do this alone. It absolutely requires a team. And I think that the approach of taking a collaborative approach and also making data open source is so critical. Because anyone who thinks they can do it on their own is wrong. It absolutely requires all of us working together. And it's not just scientists working together. As you said earlier, we've got people that are non-scientists – we call them citizen scientists – who are part of this crowdsourcing effort to pull the data together. And we have people who are practicing social distancing to make life a little bit easier and others who are helping to get PPE. So it doesn't matter what your background is. I think it's really important, to use that same analogy, to say we can all be a part of this game.

KENNEALLY: David Fajgenbaum, author of *Chasing My Cure* and co-founder and executive director of the Castleman Disease Collaborative Network, thanks for joining me today on Beyond the Book.

FAJGENBAUM: Thanks so much for having me.

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