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Research Efforts in the Race to Find a Cure for COVID-19

Nacinovich:
For ReachMD, this is COVID-19: On the Frontlines. I'm Mario Nancinovich, and joining me to share his research efforts in the race to find a cure for COVID-19 is Dr. David Fajgenbaum, Assistant Professor of Medicine in translational medicine and human genetics at the University of Pennsylvania and Associate Director of Patient Impact for the Penn Orphan Disease Center. Dr. Fajgenbaum is cofounder and executive director of the Castleman Disease Collaborative Network, where innovations brought into finding effective treatments are now being leveraged toward the fight against COVID-19. Thank you for joining us, Dr. Fajgenbaum.

Dr. Fajgenbaum:
Thanks so much for having me.

Nacinovich:
To start off, we need to catch our audience up to speed on how you got started in this field of rare orphan diseases, because it's no run-of-the-mill story.

Dr. Fajgenbaum:
Sure. So I went from being a healthy third-year medical student where I was training to become an oncologist. I wanted to treat cancer patients in memory of my mom – to experiencing multi-organ failure – my liver, my kidneys, my bone marrow, my heart, and my lungs were all shutting down, and I was so sick that I was actually administered my last rites because my doctors didn't think I would survive. Thankfully, right around that time, I was given the diagnosis of idiopathic multi-centric Castleman disease, which is a rare immune system disorder where there's immune hyperactivation which leads to a cytokine storm and multi-organ failure, actually quite similar to what we're seeing in the most sick COVID-19 patients. With the diagnosis came treatment. I got chemotherapy, which saved my life, but unfortunately, I would go on to have a number of life-threatening relapses.

Nacinovich:
What were some of the novel steps you and your colleagues needed to take to identify an effective treatment for Castleman disease?

Dr. Fajgenbaum:
After the fourth time that I nearly died, when I relapsed on the only drug in development for Castleman disease, I realized that I could no longer wait and hope that someone, somewhere would figure out a treatment for me. Though I was only a medical student, I knew that if I didn't do everything I could, that there was no chance I would survive and have a future. So, I decided to dive into performing laboratory research. I created a foundation called the Castleman Disease Collaborative Network, and I tried to push forward the science with the goal of being able to identify a drug that we could repurpose. I knew that there was no way that I would be able to live long enough with these repeated real deadly relapses for a new drug to be developed. I knew that if I was going to survive, it was going to be by understanding how the disease worked, and then finding a drug that already existed that we could repurpose to try to save my life. And despite my best efforts, I relapsed again and I nearly died for the fifth time, and multi-agent chemotherapy saved my life, but the difference with my fifth relapse is that I had collected a number of samples on myself and began performing experiments on those samples when I survived and was able to find a particular communication along the mTOR pathway that was highly activated in my samples, and I hypothesized that maybe an mTOR inhibitor like sirolimus could be effective at controlling the cytokine storm and preventing a relapse. And so, I started testing sirolimus on myself as the first human patient with Castleman disease to ever get that drug, and I've been in remission for over six years now.

Nacinovich:
So, let's fast forward to the current moment in history. COVID-19 has not only entered the global picture but has completely dominated

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our collective consciousness. How did you find yourself in a position to help by shifting your research efforts from Castleman disease to COVID-19?

Dr. Fajgenbaum:
Just like so many others, a couple months ago I found myself devastated by what I was reading about and hearing about was occurring around the world, and I also found myself hoping and praying that someone, somewhere, would follow the blueprint that we went through to identify sirolimus for the cytokine storm that exists in Castleman disease, and hoping that even someone might follow our playbook. I actually wrote a book describing our whole journey called "Chasing My Cure" and I remember thinking to myself, "I hope someone reads the book, they follow the playbook, and we can, you know, find a drug that can be repurposed right away." And then a couple minutes later, I thought to myself, you know, I run a lab that's focused on cytokine storms. We focus almost all of our effort on profiling the disease so that way we can identify drugs for repurposing, and I just knew that I would need to repurpose my own effort and repurpose my lab's effort towards taking on COVID-19. And it actually was really easy to convince my lab members to take on COVID-19 just based on our backgrounds and based on, obviously, what's going on worldwide. We want to do anything that we can.

Nacinovich:
For those just tuning in, this is COVID-19: On the Frontlines. I'm Mario Nacinovich, and today I'm speaking with Dr. David Fajgenbaum, Executive Director of the Castleman Disease Collaborative Network, whose firsthand experiences and path to a cure for this rare disorder are now instruments in the fight against COVID-19. So, Dr. Fajgenbaum, let's stay on the research track and dive into your current work and findings. Now obviously you're coming at this from the unique vantage point of a patient who pulled together a completely new way to find his own cure. How does that impact your approach to COVID-19?

Dr. Fajgenbaum:
Well, for us, we've been so focused on studying the disease, and our case initially it was Castleman, now it's COVID-19, to understand what is going on and then secondly, always asking the question, "What drugs already exist that can change whatever we're seeing in our sample?" So, if something is too high, what can suppress it? If something's too low, what can increase it? And so, we have this almost decade-long experience of deeply profiling diseases, understanding what drugs could have an impact, and then most importantly, step three is systematically tracking whether those drugs actually work or don't work in real life, because a lot of times, you learn something in the lab, and then it doesn't actually pan out when you give it to people. So, we've been really focusing on all three steps of that journey.
And actually, we assembled an army of over 30 people, including members of my lab and volunteers from the Castleman Disease Collaborative Network, to go through the entire world literature. We've now read through over 5,000 papers to pull out data on every single drug that has been given to a human with COVID-19 in real life. What drugs have actually been given to patients? And amazingly, we're at over 140 different drugs that have been tried. There are a handful that have made the headlines, but there are over a hundred additional drugs that many physicians have never even heard have been tried against COVID-19. But doctors around the world are trying anything and everything that they can, and we feel like it's really important to track this in a central database, so we're maintaining this on a website: cbcn.org/corona. And anyone can access it in real time and see as we're updating the database on what drugs are being used and which drugs seem to be working.

Nacinovich:
What kinds of treatments are you investigating or comparing in relation to COVID-19 and why?

Dr. Fajgenbaum:
When we think about COVID-19, we think about it in terms of three kinds of treatments. The first is clearly an antiviral treatment: treatments that are good at blocking viruses from getting into cells, replicating themselves, and getting to other cells. That's number one. Number two and three are both focused on the host: so it's people who have too weak of an immune response. You want to make sure that we can stop the immune response in people with too weak of a response; and then the people who have too strong – what's called a cytokine storm – response to the virus. How do you actually temper down that response? So, all of the drugs we're looking at really could fall into one of those three buckets. In fact, some drugs could fall into two of those three buckets. But there are a number of antivirals that are under investigation that are very good at preventing transmission between cells of the virus. But actually where we focused a lot of our attention is actually on that third group that I mentioned, where people have too strong of an immune response, because it turns out that is what happens in most of the patients who die from COVID-19. They're not dying because the virus overwhelmed them. They're not dying because they weren't able to control the virus. They're actually dying because they've had a hyperinflammatory, an overabundant immune response to the virus, and it's actually that cytokine storm that's causing organ dysfunction and death. And so, we're really interested in that third group, because that's the group of drugs that are likely going to have the most survival and mortality impact. And so there are actually a number of drugs, including drugs that have been developed for Castleman disease – siltuximab, tocilizumab were both initially developed for Castleman disease – and those are two of the most promising drugs

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for that third category, which is to try to quiet down and calm down the cytokine storm.

Nacinovich:
And what are some of the key findings you and your team have uncovered so far?

Dr. Fajgenbaum:
We've amazingly found that over 140 drugs have been tried already against COVID-19. Importantly, among those almost 150 drugs, we found that there seemed to be variable effects from these drugs. Some drugs are given to patients and they have a fairly short response. Others seem to have a longer time to respond. What's really challenging about comparing drugs in a database like this is that a number of COVID-19 patients are asymptomatic, and some will just be cured on their own in a matter of days because they have a mild case. And so, what we really are trying to use this database for is to say, "What are all the drugs that any doctor, any research lab, anyone has tried anywhere around the world to treat a human with COVID-19? Let's get a full listing of everything. Let's see how frequently they're given, and then let's see if we can get a sense for which one of these drugs seemed to be most promising?" Not because we would then say, "Okay, everyone should get this drug." But because we can then say, "We need to do a clinical trial of this drug to be able to prove that it's really working the way that it looks like it's working in our database." And so far there are a few drugs that we are optimistic about. Remdesivir did look good in our database; a drug called Arbidol which is actually approved in Russia and China for the flu looks promising. But again, we don't use this database to say this is how you should treat coronavirus. We say, this is a database of everything that's been given, and let's use it to prioritize what drug should move on to clinical trials.

Nacinovich:
Are there any particular barriers – expected or otherwise – that you and your colleagues are currently working through?

Dr. Fajgenbaum:
Yeah, I think the biggest barrier is just how heterogeneous this disease is. As I said earlier, there's people who are asymptomatic, who don't show any symptoms, and other patients who die from the virus. And as a result, that makes clinical trial design really, really challenging. If you don't have a control group, and you compare people who get the drug versus some other historical control group, then you have no idea if you're comparing apples and apples or if you're comparing apples to oranges, which is most likely the case. And so a lot of the data that's in our registry is based on these single-arm, open-label studies where there's just one drug given, and a lot of people get better. Well, the truth is that if you just look at a hundred people with coronavirus, most of them are going to get better, and so you really need that control arm to say, "Did more people get better when they got the drug than they would have if they didn't get the drug at all?" And I think that's one thing that's been challenging for us in terms of the data, but I think it's also something that's been really dizzying for those of us in the public who are trying to interpret what's coming out, and we're all really hopeful that a drug will work, and as a result, I think that can sometimes bias us towards saying, "Oh, wow, this drug worked in this many people."

Nacinovich:
Last thing, Dr. Fajgenbaum. Any final word and thought from you on what may be the next step in the fight against COVID-19?

Dr. Fajgenbaum:
Sure. So as someone who has battled a COVID-19-like cytokine storm five times and eventually identified a drug that saved my life, I can say that this is a hard road, and I think that everyone already knows that. This is a tough road that we're going down. But from my experience I've been able to see that we have been able to find that drug that was just sitting at my neighborhood pharmacy – a drug that already existed saved my life. And so I hope that my journey chasing my cure can serve as an example that it is tough, but it can be done. And I hope that listeners know that there is just an incredible amount of collaboration that I'm seeing within the scientific community – really unprecedented collaboration — and I think that with the hard work that's being done, plus the fact that all these drugs already exist, I really do believe that we will continue to make progress. And I'd be really thrilled for listeners to check out the website so they can go to this database and get an understanding for what are all the drugs being used. It's at a website that's cdcn.org/corona. Again, cdcn.org/corona, where you can learn all about the database, the drugs being used, and to hear and learn more about my journey that serves as an example of hope, that hopefully we can get through this, you can go to chasingmycure.com.

Nacinovich:
Well, given the many unknowns that we're still dealing with confronting this pandemic, it's great to see this trend toward novel collaborations and sharing of knowledge through research efforts like yours. We're all crossing our fingers for the continuing success of your team and all those who work with you, Dr. Fajgenbaum. Thanks for joining us today.

Dr. Fajgenbaum:
Thanks so much for having me.

Nacinovich:

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I'm Mario Nacinovich, and you've been listening to COVID-19: On the Frontlines. To access this episode and others from this series, visit ReachMD.com/COVID-19, where you can be part of the knowledge. Thanks for listening.

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