Clinical Minds: [*What if a treatment already exists?*] Transcript

Dan Poppy: Welcome to Clinical Minds presented by Medidata, I'm Dan Poppy. Doctors are using all the tools available to them to help their COVID-19 patients, treatments already on the market that have never been used for COVID-19 before, because COVID-19 didn't exist until now. Today we're talking about drug repurposing.

Today we're speaking with Dr. David Fajgenbaum, a physician, scientist and author of the national bestselling memoir, Chasing My Cure: A Doctor's Race to Turn Hope Into Action. Battling Castleman disease to save his own life, he spearheaded a global research project that discovered a possible treatment that has put him into extended remission. Now, he's bringing this approach for COVID-19 and is here to talk with us today about that project. David, thanks so much for joining us.

Dr. David Fajgenbaum: Thanks so much for having me, Dan.

Dan Poppy: So first, walk us through the Castleman Disease Collaborative Network and why that was important for you to put together.

Dr. David Fajgenbaum: Sure. I became deathly ill with a disease called idiopathic multicentric Castleman disease when I was a third year medical student. And unfortunately, went on to have multiple life threatening relapses, nearly dying four times before I decided that I would dedicate my life to try to identify a treatment and maybe one day a cure for Castleman disease. I was a medical student at the time, and so I certainly dove into the science and what we knew medically about the disease, but really quickly it became clear that some of the greatest hurdles in the way of progress really had nothing to do with science or medicine, they actually were organizational problems.

Dr. David Fajgenbaum: And so I decided to start the Castleman Disease Collaborative Network so that we could build a global network and really a movement to try to accelerate research for Castleman disease, taking a new approach that had never been taken before, and now we are applying that approach to COVID-19.

Dan Poppy: And what was the outcome of your project?

Dr. David Fajgenbaum: A really important aspect of our approach is, once you prioritize what research studies are really important, and once you start doing those studies, we have always felt it's very important to understand what drugs already exist that are already FDA approved that might actually have an effect on the disease based on what we're finding in the lab. And this is this concept of drug repurposing, which is certainly in the news a lot right now with COVID-19. And drug repurposing is really, really exciting. These are drugs that are already your neighborhood pharmacy, we already know safety, we know how they work.

Dr. David Fajgenbaum: But it also is really important that if you do drug repurposing, you have to track how well these drugs actually perform when you give them to people.

Dan Poppy: And as you mentioned, in the news where we're hearing a lot about drug repurposing, I think every week we get a new high or a new low on where things stand. You've turned your approach from Castleman's and you're applying it to COVID-19. Walk us through what you're trying to accomplish there.

Dr. David Fajgenbaum: Sure. So I'm alive right now, Dan, because of a drug that no one had ever thought to try for Castleman disease that I identified for my research and started taking over six years ago. So when COVID-19 first really reached the US a few months ago, I found myself hoping and praying that some researcher out there would follow our blueprint. And then I was like, "Wait a minute. If I'm going to hope that some researcher somewhere that studies cytokines and drug repurposing is going to follow our approach, maybe we should just follow our approach."

Dr. David Fajgenbaum: And it's tough to do that because we do have such a focus on Castleman disease, but we felt it was the right thing to do. And so we have redirected a large portion of effort from my lab and also brought in these amazing volunteers from outside of our group to be a part of this drug repurposing effort. So the first step is to do really in depth profiling of human samples from that disease. You have to know what is happening on the cellular level in that disease.

Dr. David Fajgenbaum: The good news is, new technologies have come out that make that easier than ever. The next question is, what is known about existing drugs? Third step is, "Let's test it in a dish. Let's see, does the thing that we think this drug will actually do do that thing we're hoping for in cells from humans with this disease."

Dr. David Fajgenbaum: And then step four is, when drugs are actually given to humans, you have to track how well it actually performs. Do people get better? Do they get worse? The best way to do that is through clinical trials, that's really the only way to truly do it. But in the meantime, there's a lot of real world data of patients getting these drugs all over the world. Even when we started on March 13th, which was fairly early in the pandemic here in the US, there were already dozens of drugs that had been used to treat COVID-19.

Dr. David Fajgenbaum: So we decided to first invest in this project, what we call the Corona Project, where we are capturing data on patients from around the world that have COVID-19 that have been treated with various drugs. What drugs have been given? How frequently have they been given?

Dr. David Fajgenbaum: So we're really trying to take the approach that we used for Castleman disease, the approach that has enabled me to be alive and to talk to you today to try to apply that to COVID-19.

Dan Poppy: So you are collecting research from around the world. We hear about the race for a cure in the news every day, we would hope as patients that there's a coordinated effort, but you are taking it upon yourself to bring all of this research together. Why is that the case? Why are individual researchers doing this? And why is it not a national effort?

Dr. David Fajgenbaum: It's a really good question. I think that there are some important national and international efforts that are occurring right now, certainly vaccine development is a great example of coordination and collaboration that is occurring.

Dr. David Fajgenbaum: Real world data doesn't follow the rules like clinical trial data where you have, a drug's given this day, and a blood sample is taken that day. Real world data is real world, and people get drugs and they don't get drugs, and they get tests and don't get tests. So it's a lot more complicated.

Dr. David Fajgenbaum: And as a result, not just in COVID-19, but in a number of fields, real world data is often generated, but it's not as systematically studied as you would hope. In this day and age in 2020, there's more medical record data being generated every day than you could even fathom, yet amazingly, most, almost all of that medical record data is not in any an interoperable form to be able to perform analyses across health systems. So that's why we need organizations like Medidata to be able to crack these problems. But for now, small research labs and foundations like the CDCN, we're trying our best to do what we can against COVID-19.

Dan Poppy: I want to take a step back, drug repurposing. A drug goes through clinical trials, it's approved, we understand what it is. Why do we have to keep researching it for another disease if we already know how it works?

Dr. David Fajgenbaum: That's an important question. So once a drug gets approved, any doctor in the United States can prescribe that drug for any reason they want. So if your drug is approved for cancer, it's a chemotherapy, your doctor in theory, could prescribe that chemotherapy for hair loss. I wouldn't recommend it, it actually would cause hair loss, but doctors can prescribe any drug for any reason.

Dr. David Fajgenbaum: For people like me who have diseases that don't have options, we love the idea of a drug that's already FDA approved, that's already been shown to be safe in some other condition, we know how it works, to be able to be repurposed for our given disease. But I think that some of the things we've been watching on the news remind us that some drugs that seem like they're going to work really well could actually cause harm.

Dr. David Fajgenbaum: Well, if I had to summarize why it's important, one is that it's safe and effective, we know that already. Another is just on the opposite end of the spectrum, how expensive it is to develop new drugs. And then the third reason that you need to study it is because it actually might cause harm, and that you need to study it to make sure that it's not causing harm in this new condition.

Dan Poppy: How does the research differ for a drug that you're repurposing? Can you assume safety about it already?

Dr. David Fajgenbaum: You can't assume just because it works for one condition, it's going to work for another. And just because it's safe in one condition, it doesn't mean that it's going to be safe in another.

Dan Poppy: So where does your project stand now, the COVID project?

Dr David Fajgenbaum (16:36):

In our first 12 days, thanks to an army of volunteers, including actually Medidata, colleagues of yours, like Bruna Martins, who rolled up their sleeves and dove into the data, we were able to go through data from over 2,500 papers in the first 12 days. And from that effort, pull out data on 9,152 patients treated with COVID-19. That was really a Herculean effort to get through all of that data and to wrangle it into one place. We published a paper about a week or two ago reporting out those findings. And Dan, you're not going to believe this, over 100 drugs were used in the first 9,000 patients, 100 different drugs.

Dr David Fajgenbaum (17:21):

We hear about three or four of them in the news almost every day, but there are another 100 plus that have been tried in various capacities. So doctors are trying a lot of things out there, and just a few of them are moving on to clinical trials. When we first started the project, I thought there would maybe be 20 or 30 drugs. I did not expect there to be over 100 in that short of a period of time. But the key thing for us is to say, "Well, if all of these drugs are getting tried and some of them are working and most of them are not being studied in clinical trials, we need to have a database that tracks all of these drugs so that pharmaceutical companies can say, 'Okay, I have this particular agent it's been used 1,000 times. Maybe I should think about doing a clinical trial of this drug.'"

Dr David Fajgenbaum (18:08):

So where it stands right now is that, that was phase one, the first 9,152 patients. Now, we've more than doubled the number of patients that are in our database. We're close to, and maybe we've already surpassed 20,000 patients that we have data on from more than twice as many papers. So I think we're over 7,000 papers now. And one thing I should mention is that, there're two ways to go through big data like this. There is machine learning, natural language processing, artificial intelligence, and then there's brute force. And I'm really hopeful that some groups will take the former approach and we'll apply some tools that don't require maybe so much effort.

Dr David Fajgenbaum (18:52):

But we decided to take the brute force approach, and that was to literally have amazing volunteers who have just felt, like myself and I think probably like how you've felt, just helpless in the midst of this really tough pandemic, and said, "I want to do something." And they've rolled

up their sleeves and they've reviewed through thousands of papers. And we have data that wouldn't have existed in one centralized place that exists now. We know that these data are already being used by researchers around the world. We also know that companies are using the data. And that's how we want it, we've made it free and publicly available. Anyone can use it at any time, we just want to be able to be a part of the solution.

Dan (19:32):
I am shocked by that number of drugs. Why are there so many? Why have we only heard about a few of them? What are your initial thoughts on what we're seeing?

Dr. David Fajgenbaum: So out of the 160 or so drugs that have been tried, more than 100 of them have been given to less than 1% of the patients. So there's a lot of drugs that have been given to five people or two people or one person, and they might seem like they're working in two people, but it's hard to get a sense for how effective a drug is when the N equals two. So there's a long tail of drugs that have been used very infrequently, but there are at least a good 50 of them that have been used in hundreds, potentially thousands of patients.

Dan Poppy: Is there a common theme around the drugs that you're seeing?

Dr. David Fajgenbaum: Probably one of the biggest takeaways from this effort, which is a bit disheartening, but it's just the way it is how heterogeneous the response to COVID-19 is for an individual patient. So you've, I know, read all about how patients can be asymptomatic carriers and then someone that's the same age and everything seems similar about them and they end up in the ICU with multi-organ failure.

Dr. David Fajgenbaum: Most people who die from COVID-19 really are not dying from the virus, they're dying from an overactive response to the virus, what's called a cytokine storm. Cytokine storms are also what kill you in Castleman disease. And what I've spent a good bit of my life trying to understand is how do these cytokines work, why would your immune system, which is supposed to be protecting you, actually because all this collateral damage that ends up killing you?

Dr. David Fajgenbaum: And we don't know why, but we certainly know how it does it. And there are certain targets and certain aspects of the immune system that you can go after with drugs to help to quiet it down and calm down the immune system. So I share all this to say that, I wished that there was going to be a single silver bullet that was going to help everyone, but what we see right now suggest that it's likely that different drugs are going to be needed for different patients.

Dr. David Fajgenbaum: And so they're going to need drugs that both help to suppress the virus, the replication of the virus, but also potentially help to boost up the immune response. And then there's some people who get the exact same virus and have a hyper response, they get a cytokine storm because their immune system is trying to fight the virus, but in doing so, it causes all of this mass destruction all throughout the body. Those people are going to need

drugs targeted at the virus, but most importantly, they're going to need drugs that actually suppress and weaken the immune response, because their immune response is too strong. And those are opposing drugs, the drugs that boost it are the opposite of the ones that suppress it.

Dan Poppy: What do we know now about drug repurposing? Do your projects give you hope about what's available on the market and what can be done to treat all of the diseases that have unmet need?

Dr. David Fajgenbaum: I think that my level of optimism and hope, it's been a bit like a roller coaster over these years. I think that when I was first battling Castleman disease and I was hoping that there would be a drug out there that could save my life, I knew that was my only chance, we weren't going to develop a new drug in the next five months to save my life. I knew that the only hope I had was an existing drug. And thankfully, we were able to find a drug that saved my life. And so, like I said earlier, I'm literally here because of one of these drugs, and so I feel like I need to pay it forward to the universe to try to look for other drugs that already exist so the patients like me can benefit.

Dr. David Fajgenbaum: And so as a result, I have a tremendous amount of hope because I breathe every day because of this exact phenomenon of drug repurposing. But at the same time, there have been examples, like we've heard in the news of drugs that have gotten repurposed that we've gotten really optimistic about and then they've turned out to not be as helpful as one would hope. And so, in my opinion, I think that we need to be relentless about looking for drugs that can be repurposed and we need to be equally relentless in evaluating whether they're actually helping people or not. And the two go hand-in-hand, it's not that you can be pro drug repurposing and not pro data and that you just want to give everyone drugs and see what happens.

Dr. David Fajgenbaum: I think you have to do the two together. And if we do the two together, like the corona project where we're tracking how these drugs are working and also do rigorous clinical trials, I think we can get towards a world that we all want, which is a world where there's drugs for patients like me and drugs for the millions of patients out there with rare diseases that don't have any options.

Dan Poppy: So COVID-19 has, I think reshaped our thinking about global health and the way we think about disease and the way we treat disease from, I can say that from the patient perspective what does it mean for you from the research, the physician scientist perspective?

Dr. David Fajgenbaum: I think that there's a lot that we need to reflect on as a physician, scientist, patient, community about what we can take away from COVID-19. And as I said earlier, create some positive for other diseases. There are a few lessons that immediately come to mind and I think I'm going to need to take some more time to come up with more of them, but the initial ones that really stick out, the first which is this idea of creating silver lining. So let's create something positive out of something really negative. This is the lesson I actually learned from my mom.

Dr. David Fajgenbaum: A lot of times we're encouraged to look for silver linings in life, something bad happens, what can we find that's positive, but she really always encouraged me to say, "Let's not just look for silver linings in the midst of a really bad thing, let's see, what can I do today to create a silver lining? How can I make a silver lining in the midst of a storm?" And I think an example of that would be this corona project that we're trying to create something positive out of something that is, as I said earlier, just unequivocally negative. So that's one. Another is the idea of turning hope into action, and hope is often considered such a positive thing, and I think hope can be really, really positive.

Dr. David Fajgenbaum: And I talk about hope a lot in chasing my cure, but I think that hope on its own is often not enough. I think that what we really need is to turn our hope into action. So as I was sitting there hoping that some researchers somewhere would start doing COVID-19 research, following our blueprint, that obviously was not enough. I needed to realize, "Okay, this is what I'm going to hope for, then I should probably use that to inspire my action." And so I think that, we're seeing this around the country, separate from COVID-19 and people standing up against what's happening right now around the United States with race issues. And so I think this is turning hope into action. And I think COVID-19 has taught us that, I think what we're all facing right now has certainly also taught us that. Another is a concept that solutions can be hiding in plain sight.

Dr. David Fajgenbaum: So the drug that I'm on, was in my neighborhood pharmacy for years, some of these COVID-19 drugs are sitting in shelves and pharmacies that no one ever thought to try. And I think that we just need to realize that there are likely many other diseases out there where there are patients who are dying from those diseases, or certainly struggling for them where we just need to figure out the solution that is already out there. That is just incredibly important. And then I think the last one is around the urgency that COVID-19 has given us. For those of us in the rare disease community and those of us that have diseases that take people from our community all the time, we've always felt a sense of urgency. We've always recognized that the clock is ticking.

Dr. David Fajgenbaum: I call it overtime, this idea that the clock is ticking and that we're running out of time. But I think that COVID has created a similar sense of overtime for all of us where it feels like, "Wow, we really need to do this and we need to do it quickly." I really hope that sort of urgency is going to spill over into other diseases.

Dan Poppy: Dr. David Fajgenbaum, the author of *Chasing My Cure: A Doctor's Race to Turn Hope Into Action*. David, thanks so much for joining us today.

Dr. David Fajgenbaum: Thanks so much for having me, Dan. And thanks so much for all that you and your colleagues do for patients like me.

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