Drug Repurposing for COVID-19 with CORONA Registry (COvid 19 Registry of Off-label & New Agents)

The global crisis due to COVID19 and the urgent need to identify effective therapeutics prompted Dr. David Fajgenbaum from the University of Pennsylvania and his research team to create a database that tracks every off-label and experimental drug being used to treat COVID-19 patients. This registry, dubbed the COvid19 Registry of Off-label & New Agents, will help researchers identify treatments that deserve to be more fully examined in clinical trials. Dr. David Fajgenbaum, MD, MBA, MSc, is a groundbreaking physician-scientist, disease hunter, speaker, and bestselling author of the acclaimed memoir, Chasing My Cure: A Doctor's Race to Turn Hope Into Action.

Full Transcript:

Priya Menon: Hello and welcome to CureTalks. This is University of Pennsylvania's Covid Talk series where we discuss latest trials and studies on Covid that Penn is part of. I'm Priya Menon and with me today is patient advocate Heidi Floyd and we are talking about the Corona-registry or the Covid-19 registry of off label and new agents with the disease hunter and the doctor who cured himself Dr. David Fajgenbaum. Dr. Fajgenbaum nearly died four times battling Castleman disease before he led an innovative approach to research and found a treatment that put him in extended remission. Dr. Fajgenbaum, welcome to CureTalks. I'm very excited to have you with us.

Dr. David Fajgenbaum: Priya it's so great to be on, thanks for having me back.

Priya Menon: Dr. Fajgenbaum, what is the Corona-registry about and what led to such an an unique exercise?

Dr. David Fajgenbaum: The corona registry is a database where we track all drugs that have been used to treat Covid-19 around the world or genesis behind why we wanted to start this is that back in early March became very clear when Covid-19 was really hitting hard that there was going to be a lot of off-label drug use. Doctors were trying different drugs against Covid-19, and I assume that maybe they weren't be a couple dozen drugs used. And I thought that if drugs are going to be used off-label against Covid-19, we need to central place to keep track of those drugs. I actually found myself hoping that some research group would track these drugs and then I said, well, maybe I should stop hoping and I should start acting and so I created the corona project to keep track of all drugs that have been used to treat Covid-19. As I said kind of expecting it to be a few dozen early on. Amazingly, there have now been over one hundred and sixty different drugs that we've captured data on in our Corona projects. A lot of drugs are being tried and unfortunately other than our project, there was no sort of database that was keeping track of all the drugs that have been used.

Priya Menon: So, your team has reviewed more than 2,500 papers on Covid Dr. Fajgenbaum, which is kind of amazing.

Dr. David Fajgenbaum: We did twenty-five hundred papers actually in the first 10 days. We're now up to over 8,000 papers that have been reviewed by a team of 40 different volunteers. A number of them are members of my lab, members of the Castleman Disease Collaborative Network and also just People out in the world who wanted to be a part of this Covid-19 fight and so as I mentioned we read over 8,000 papers. We now have data on over 20,000 patients in this database and as I mentioned earlier over a hundred and sixty different drugs have been tried. So, doctors are trying a lot of different drugs. Some seem to be working some don't seem to be working as well. But we recognized that if you're fighting a war, you can't be

successful in fighting a war if you don't keep track of what weapons you're using and what works and what doesn't work. And doctors all around the world are fighting this war against Covid-19. They're trying drugs, but we needed to have one place to keep track of all the drugs being tried.

Priya Menon: So, Dr. Fajgenbaum, what are the top three learnings that you see from the papers that your team has reviewed a regarding Covid treatment?

Dr. David Fajgenbaum: Sure. So, I think number one is how heterogeneous Covid-19 is. So, you have some patients that are very sick in ICU, some patients that are very mildly ill and then you have kind of this whole spectrum and what's really clear is that patients who are really sick at a cellular level and in their blood, their cells are at different activation States. They look different from the mild cases. So, it's likely that different treatments are going to be needed for patients depending on what sort of their subtype is or maybe their intensive disease. But also even the timing within illness and so it gets really complicated when you have to think about how early in this particular patients illness are they in their course. And also, where are they on this spectrum of severity? So, I think that heterogeneity really highlights that it will probably require multiple different treatments to really effectively control Covid-19. When I say multiply I mean across the population and likely it isn't going to be one silver bullet for everyone. I think another big takeaway is, so many drugs are being used off-label. Like I said, when we first started the project I assumed maybe 20 or 30 different drugs would be tried. And here we are with over a hundred and sixty. And so doctors are trying things, patients, some of them are getting better, some are getting worse. But I think the third thing that really comes from this is just how important it is to do randomized controlled trials. When you look at the data from the corona project, you see that some drugs it looks like everyone gets better on them and other Drugs looks like no one's getting better on them. But what you have to realize is that those patients started at different starting points. Some patients were really sick, some patients were really healthy. And so that's why it's so important to do a randomized controlled trial where you can randomly assign patients into two different groups, give them a drug and see if the patients randomly in the treatment group do better than those not in the treatment group. And so, you might wonder why are you doing this whole Corona project if you're so focused on randomized control trials and well, that's because this Corona project helps us to prioritize drugs for randomized controlled trials. It's critical to capture your data and then you can move forward then to the larger studies.

Priya Menon: Can you elaborate on some of the inclusion criteria of the studies that were included in your team's literature review?

Dr. David Fajgenbaum: Sure. So, we are at a very broad inclusion criteria. So, we did a very broad search where any paper with the word Covid-19, SARS Covid II or Coronavirus 2019 would be included in this search, which meant that we had tons and tons of papers and we still have tons of papers to go through. But the one question that every data extractor asks when they go through the paper is; Is there an example or is there a case in this paper of a human getting a drug to treat Covid-19? And so that eliminates a lot of papers where there's really important in vitro experiments, in laboratory experiments, not to discount those, those are just different. In this case, we want to say what drugs are being given humans and as a result, we capture any and every example of a drug going to a human with Covid-19.

Priya Menon: So, you spoke about many drugs that you found were being used for treatment. What are some of the most common drugs? Can you name some of them which have been used for treating Covid-19? Maybe the top three.

Dr. David Fajgenbaum: Sure. So, number one is Lopinavir-Ritonavir. That combination, it's used in HIV and it early on looks like it would be promising against Covid-19. The early Studies have suggested that it's probably not going to be the best drug despite the fact that it's been used so much. It may be a heterogeneous disease. So, it may be that one of these kind of quadrants of patients. Maybe the not so severe early-stage still to be determined but Lopinavir-Ritonavir is number one. Number two is actually made the headlines in a really big way today and that's Dexamethasone. So, corticosteroids are the second most frequently administered drug and just today a randomized controlled trial came out from the UK,

demonstrating a really impressive mortality improvement in patients both on ventilators and also patients on oxygen who are not yet on ventilators. And so, the second most frequently prescribed drug worldwide looks like it's probably having a really big impact on patients and of course we didn't we didn't know that until this trial came out literally today. We're all waiting anxiously for the results, but we've seen the preprint. And it will be great to see that go through peer review. And then the third most frequently administered drug is actually Oseltamivir. So, that's a drug for flu and you can imagine because this erupted during flu season a lot of patients got Tamiflu. Our data suggests that the Tamiflu is not having an impact. We did assess the time to treatment response and patients receiving Tamiflu had a quite extended time from the time they got Tamiflu until they improved suggesting it's probably not having an impact.

Priya Menon: So, during the literature survey, your team going through so many of the papers. How did you manage the lack of control groups? That would have made it probably difficult to identify the potential for some of these drugs may have had. Can you talk about this uncertainty, as we call a single arm trial may pose for interpretation of the efficacy and maybe safety of the repurposed drugs.

Dr. David Fajgenbaum: Oh, you're absolutely right. So I think that we knew that it was going to be challenging before we started and then when we got into it, we found it was even more challenging than we expected. I studied Castleman disease and of course, I'm very familiar with the cancer literature. And in Castleman's or let's say pancreatic cancer, if you give a Castleman's patient a drug or patient pancreatic cancer drug, and they get better, you are almost certain that it's the drug that got them better because there are basically no reports of people with Castleman's or with pancreatic cancer who spontaneously get better. So, it's easy to say, okay, they got the drug and they got better. It must be the driver that got them better. In Covid-19, it's almost the opposite. Nearly everyone who gets Covid-19 gets better. Over 95% of patients who get Covid-19 get better without any treatment. And so as a result, that means when you do a trial, ifsomeone just gets better on a drug they may have gotten better regardless of whether they got the drug. The reason we do all these studies is for that five percent or whatever that exact number is of the really severe patients who may die or who may have significant morbidity from the disease. And so, it's hard to ascertain the effect of these drugs can have on those really sick people, if you're giving them to more healthy people and they just get better. That's why as you said it's so critical to have these control groups and not just have these control group because there are also some concerning set of variables where there are what are called historical controls where you say okay, we gave 20 people this drug and then we looked at a historical control group if people like those 20 and oh they did better in this treatment group. Well, there are other confounders they can get in the way but the randomized control trial where you're randomly assigned. Okay, you've Covid-19, I'm going to randomly put you in a treatment or no treatment. That's the gold standard and that's what came out today about dexamethasone.

Priya Menon: Dr. Fajgenbaum, there is considerable overlap. I know we are on the topic of Castleman's disease. So, there is considerable overlap between the immune system responds of Castleman and probably somebody battling severe Covid-19. Can you talk a little bit about this and also talk about Interleukin 6 playing a role in both the diseases?

Dr. David Fajgenbaum: Sure. So, both Covid-19 and Idiopathic Multicentric Castleman disease, the disease that I have. Those are both Cytokine Storm Disorder. So, a Cytokine is a protein produced by your immune system that helps different immune cells to communicate with one another. They also can have direct effects on viruses and helping to actually fight off infections. So, when your immune system turns on, it starts producing cytokines, and when sometimes your immune system turns on to produce so many cytokines, that more cytokines lead to more cytokines and more and all of a sudden you have this hyperactivated immune system. You can't stop it. It almost spirals out of control. That's what happens in Castleman disease, we call it a cytokine storm. The same thing happens in the most severe cases of Covid-19 and Castleman's, we don't know why the cytokine storm starts in the first place. Whereas in Covid-19, we know that the cytokine storm is because of the SARS Covid II virus. The virus misuses the cytokine storm. And so, if you look in the blood of a Castleman's patient or a sick Covid-19 patient the changes are almost indistinguishable. They're so similar both at a cytokine level, but also cellularly what's actually going on in these immune cells. So, there's a lot of overlap and also clinically if you look at a patient in ICU with Covid and ICU with

Castleman's, they look very similar. So, clinically they look similar what's going on the cellular level really similar and as a result as I mentioned earlier that back in March, I found myself hoping that some research lab would take on a repurposing project for Covid-19. Well, I also was really just hoping that a group could follow our blueprint. we've done this against Castleman disease. We've identified drugs that can be effectively repurposed. We've systematically tracked what drugs work, and don't we haven't finished the fight. We still have a long way to go. We made a lot of progress. I'm literally alive today because of a drug that we repurposed to treat Castleman disease in me. And so, this is the feeling that I had was okay, but I'm alive today because of repurposing. What can I do to kind of pay it forward and trying to make a difference against Covid-19. And so, one of the earliest drugs we found in our repurposing effort is actually a drug called Tocilizumab, which was initially developed for Castleman disease in Japan. It targets Interleukin 6s receptor. It was for Castleman's, it was one of the first drugs repurposed against Covid-19 and it showed some really promising early results. In fact, I'll share a quick anecdote about the discovery and development of this drug is actually a colleague and friend of mine in Japan named Kazu Yoshizaki who identified the interleukin 6 was important in Castleman disease and he developed this drug that blocks the receptor for IL-6, and I had heard a rumor that before he gave it to other humans in a Phase 1 trial that he actually tested it on himself to prove that it was safe and I asked Kazu, I said Kazu, Makoto just told me that you gave Tocilizumab to yourself to prove that it was safe and he said no, I didn't give it to myself, the nurse she gave it to me. I said exactly Kazu. So Kazu developed the drug. He was the first human to receive the drug. He survived; it went on to get approved in Japan for Castleman's it went on to get approved in the US for Rheumatoid Arthritis. And now it's one of the most promising drugs in the fight against Covid-19 because of these as we said before interleukin 6 is critical in Castleman's and it seems to be very important in Covid-19.

Priya Menon: Thanks for that. Heidi, I know you are bursting with questions. So, it's all yours now.

Heidi Floyd: Sorry. I need to unmute myself. I actually have some questions. I will make sure that I pull up and ask them. But first I want to say just I'm in awe of the work that you're doing doctor and and so grateful. The last story, I'm glad I was muted because I was just saying wow. Wow the whole time. It was remarkable story. So, my first question to you is that you said that there were a hundred and sixty different types of drugs and 20,000 human participants. Is that correct?

Dr. David Fajgenbaum: That's right.

Heidi Floyd: Did you do the breakdown of different ethnicities? Was that included as part of it or it was something that came later?

Dr. David Fajgenbaum: Yes. We asked as part of this project and I should mention we use the word registry in Corona and I don't know if registry is the perfect way to describe it, even though that's in the title. Because it's basically a repository of data on patients, any patient we can get data on, we put in. So, registries usually are patients kind of saying hey, I want to get my data whereas a repository is kind of like, let's pull it all together. And so, any data point we can get on a patient with Covid-19 goes into Corona and with every patient data point we can get if we can get the country, the author or the contributor of that data is from, that's the best we can do. So, we basically get nationality, ethnicity is not always included in these reports and of course it's complicated, right? And so, the one thing we do collect is the nationality of whoever is reporting it and so of course early on our first 9152 patients, 99% of them were reported from China. Because of course, that's where Covid-19 initiated. And so of course that number has changed there's now a large proportion of non-Chinese nationals that are in this but early on it was almost all China.

Heidi Floyd: Yeah. If I only ask is a lay person of the news seems to be focused pretty much for a brief period of time anyway, on the fact that there were disproportionate numbers which of course your widely familiar with, in the cancer world as well. I'm in the breast cancer space and so I'm used to seeing disproportionate numbers for women who are African-American for example, but I think they're so crucial their voices are so necessary. Do you have the ability to turn, you're just collecting the data? You're not out there saying hey, we need to test more in this area, right? You're simply trying to work free virtually on this repository. Correct?

Dr. David Fajgenbaum: Yes. We're working furiously on the data that's already out there. To your point, I really hope that and I think that I've seen recently there have been some good efforts to report our own data from underrepresented communities. I think that's going to be critical. It's been just so devastating to hear about the differences in mortality based on ethnicity and based on zip codes. It's just a travesty, that in 2020 that this is something that we are all still dealing with. But I have been pleased to see recently there has been more research in that area.

Heidi Floyd: Good, thank you. I agree. It's a travesty and some of us Patient Advocates were doing all we can to make sure that we pass the microphone and send the elevator down like we're trying to do all we can to help. Can I get the word out because I think a lot of people don't understand it. Since you are fellow immune suppressed person, a patient and an advocate. Is there any advice that you can give us, as patients, as non-professional about the potential risks of these drugs. Should we be invited to participate in a trial? Is there anything that you're saying that particularly vulnerable people should be aware of?

Dr. David Fajgenbaum: It's a great question. So, there's kind of I think two sides to this as far as the data that I've seen so far. So if you look there's a trial that came out of a New York recently, a study came of New York recently, looking at individuals on immunosuppressive therapies for different autoimmune conditions and what the study showed was that there actually was no difference in the proportion of people who got sick and how sick they got if they were on these autoimmune drugs. So, that was interesting and certainly good to see that, potentially because I personally and many of us yourself I'm sure as well have been really nervous about how do these drugs that are suppressing our immune system and how are they going to affect us if we get infected with Covid-19? I'm at base. I have barely left my house for the last three months for that reason I've been running the current project from home because I've been so concerned about this. But then on the flip side there have also been a number of studies that have come out, that have shown that individuals with cancer are at increased risk of death from Covid-19. The question is it's unclear how much of it is the medications if you take someone who looks healthy and well like yourself or who looks healthy and well like me and we're on treatments for our cancers. It's that I haven't yet seen data that will say that we are at increased risk for bad outcome or is it when you combine all of us that have cancer or really devastating disease including the really sick people. Is it the people that are in a healthier state or is it is it the whole spectrum that at an increased risk of a bad outcome?

Heidi Floyd: Yeah. Thank you and and one of my last questions is; actually my last question. There's a group of Patient Advocates out here, if we want to help, if we want to participate, if we want to do as much as possible to help with perhaps the idea that this will promulgate other disease groups to get things faster, to increase the amp up of different drugs. What can we do to help? Is there any advice that you can put out? Say do this? Try this?

Dr. David Fajgenbaum: Yeah. Absolutely. So, these are all the right questions. I think that what you're getting at is a concept that is really near and dear to my heart. It's something I learned from my mom. My mom passed away from cancer about 15 years ago and she was just the most incredible person in the world and one of the things that she taught me that I think about a lot is that the really difficult times were often encouraged to find the silver lining in the midst of something. To say, okay quarantine has been tough, but I've been able to spend extra time with my wife and my daughter. I mean that has been a really awesome Silver Lining. So, some people encourage you to find it, but the thing that my mom always encouraged me to do was not just to look for Silver Linings, but actually to create silver linings. She would say, okay, this Covid-19 experience is awful. Unequivocally, there's nothing positive about what's happened with Covid-19. But in the midst of this awful thing, can we do something? Can we take action? I love what you said earlier about making sure that you're helping the people around you, you are passing the mic as you said. These are the things we can do to take action today in the midst of this really tough time, to create a silver lining in the future and I think there's three things that come to mind from Covid-19 that I'd want to mention. The first is that there has been unprecedented data share. So, people are sharing data in ways they never have before, which makes it easier, still not easy but makes it easier to do things like the corona project to pull all this data in one place because the data is out there in ways that it typically is not out there. Let this Advocate say Hey, wait a minute guys, we did this once before with Covid-19, we can do it for breast cancer, we can

do it for Castleman disease, we can do it for pancreatic cancer. It's not like it can't be done. And so, I think one is data sharing that's really important. The second is, the coordination that I've seen in the Covid-19 fight. So, institutions are setting up review panels that are determining whether one trial is better than another trial. The federal government or private organizations, they're all working together to think through what's better than other options and it's a very coordinated effort. As you know, research is not typically very coordinated. It actually happens kind of organically. This idea and this study but the idea of coordination and urgency that we're getting from Covid-19, I think is just so important and if we can keep that urgency going, if we can keep encouraging coordination, I think we're going to be a lot better off in our given diseases. And then the last trend that I think it really turned into a silver lining from this is, around drug repurposing. Something we've already been talking about that, there are a lot of drugs out there. So, they're about 1500 drugs already FDA approved and there are thousands of diseases that don't have any approved drugs. And so, are there ways that we can say let's take this drug and use it in a new way and Covid-19 is this wonderful example, it's both the wonderful example and maybe not so great example when you think about the way drug repurposing has been done quickly, but unfortunately, I think we've often times put the card ahead of the horse in that we've gotten really excited before all the data are there, and myself included. I'm guilty for it too, I've gotten really excited when I've seen some of these early studies, but at the end of the day this Corona project is so important because it's not picking favorites. We're saying we're going to put all the data in one place, anyone in the world can access it and that's how we're going to get closer to truth. And truth for what works and what doesn't work, I think it's through data. So, to actually directly answer your question, I think that as Patient Advocates we can really help in all three areas. We can really push for continued open access, to say we need to make these data available. We need to make papers available. This is just something we have done it before let's do it again. We need to push for more coordination within our particular disease areas, whether it's federal government, private, advocacy groups; coordination and urgency is something, you and I have a lot of urgency for progress. That's not always the case for everyone in research. And then I think the third one around drug repurposing we've learned that we can quickly figure out drugs with promise and test them really quickly that we've shown in incredible ways, but we haven't really shown I think as a medical community is our ability to appropriately track all of the things that are that are being used and then to really prioritize what are the best studies and what not as good studies are. And I think that we can take those learnings back to our own given diseases and then another thing I would say for people like you and me are that we should do our best to make our data available, whenever we can. There aren't always studies out there that we can throw our data in but if there are studies out there that we can put your data if there are opportunities to give your blood samples to research, if there are opportunities to raise money for research. These are things that that we really push quite hard in the castleman space.

Heidi Floyd: Agreed completely and I think your mom and my mom would have gotten long great because they sound very similar. My mom passed away over 20 years ago from cancer as well. So, here's to our Mama's. Thank you for your answers.

Dr. David Fajgenbaum: Absolutely, our moms are no longer with us. But I think about things that my mom taught me every day and I think that it sounds like its same with you and so their lives live on through the lessons, they taught us.

Priya Menon: Thank you Heidi.

Heidi Floyd: Ameen. Yes. Thank you Priya.

Priya Menon: Thank you Heidi. Those were very good questions. Doctor one last question, what is the next phase for the corona registry?

Dr. David Fajgenbaum: So, we plan to continue to collect data on patients from all over the world, continue to grow out this database. It's the only database in the world that I'm aware of tracking all drugs that have been used against Covid-19. So, we feel like it's providing a really important resource for physicians, for scientists, for patients. So, we're going to continue to grow out. As you can imagine there's more and more

data becoming available every day. So, our team is just working feverishly to stay on top of it. So, we're also encouraging and we love anyone who wants to join the corona project. I mentioned we have 40 volunteers, everyone from Castleman's patients who are doing what they can to be involved all the way through. MD, PhD students at Penn who are doing whatever they can to be involved. And so, we'd love anyone who wants to join our effort to go through these data sets, to pull out the data, put them into the corona project. And then the other thing that we're trying our best to do is to share lessons about Castleman disease that are really relevant to Covid-19 and lessons from my journey chasing this cure for Castleman's that we can actually really apply here to Covid-19. So, we're going to keep getting data in and we're going to keep trying to share lessons from our journey.

Priya Menon: Thank you, Dr. Fajgenbaum. Dr. Fajgenbaum and his research team have created a database tracking every off-label, an experiment to drug being used to treat Covid-19 patients. Their hope is that the open source inventory of the Covid-19-registry of off-label and new agents will help researchers identify treatments that deserve to be more fully examined in clinical trails. Dr. FAJGENBAUM, thank you so much for your time and great work. It was as usual a pleasure to talk to you and wish you the very best. Heidi, thanks for joining today. Stay tuned to Penns Covid talk series to learn more about breakthrough research happening at Penn. Thank you everyone and stay safe.

Dr. David Fajgenbaum: So wonderful to meet you Heidi. Thanks so much.