Wild (00:08):

Hello and welcome to the In Vivo Podcast. I'm David Wild, pharma and biotech reporter for In Vivo, and today I'm speaking with David Fajgenbaum. Dr. Fajgenbaum is a physician scientist at the University of Pennsylvania and co-founder of Every Cure, which is a nonprofit focused on identifying drugs that can be repurposed for diseases with no known or effective treatments. Dr. Fajgenbaum has a fascinating and harrowing personal story that he's written about in a national bestselling book called *Chasing My Cure, A Doctor's Race to Turn Hope into Action*. He's here today to share that story with us and to also talk about where that journey ultimately led him, which is to dedicate much of his energy towards finding drugs that can be repurposed for patients that have no good treatment options. Dr. Fajgenbaum, welcome to the podcast. Thanks so much for taking some time to speak with us today.

Fajgenbaum (00:59):

Thanks so much [00:01:00] for having me.

Wild (01:00):

In 2010, as a 30-year-old medical student, you were diagnosed with Castleman disease As it is for so many people living with chronic and life-threatening diseases, the experience proved to be a turning point for you. Can you tell us a bit about that journey and what it was like living with Castleman disease?

Fajgenbaum (01:17):

Sure. So yeah, I went from being this healthy third-year medical student. I had wanted to become an oncologist to treat cancer patients in memory of my mom when out of nowhere all of my organs just started shutting down. I mean my liver, my kidneys, my bone marrow, my heart, my lungs. I had a retinal hemorrhage that made me blind temporarily in my left eye, gained about 70 pounds of fluid and drifted in and out of consciousness for weeks and weeks at a time. It was about three months into my illness when I was finally actually diagnosed with this disease idiopathic multicenter Castleman disease. But before the diagnosis, I actually had my last rights read to me because my doctors were sure that I wasn't going to survive whatever it was that was trying to kill me. But thankfully we got the diagnosis and with the diagnosis I got some pretty intensive chemotherapy.

Idiopathic multicentric Castleman is this rare immune system disorder. We don't know what causes it, but we know that it's your immune system attacking your vital organs. And so chemotherapy at the time was the only option. I got a bunch of chemo, it saved my life, but unfortunately I would go on to have a number of relapses. And so really to answer your question, what's it been like living with this disease? Well, for me, early on, it was months in the ICU finally getting the disease into remission, but then repeated relapse after relapse, putting me back in the ICU for months at a time. And for me, I knew I wouldn't survive unless we could find a drug that could prevent these relapses from happening in the first place.

Wild (02:41):

You ended up finding a treatment for your own disease along with your healthcare team. Can you tell us about that process?

Fajgenbaum (02:48):

Sure. So after the fourth time that I nearly died, I failed to respond to the only drug in development. A drug called cetuximab was undergoing clinical trials and we hoped it would work. That drug didn't work for me. I relapsed on that drug and my doctor explained to me that there were no more drugs in development, there were no more promising leads. This was it. It didn't work. So I would need to keep getting chemotherapy and eventually the chemotherapy would stop working and I would no longer be able to survive with this disease. And so when my doctor explained that to me, I promised my dad, my sisters and my girlfriend who were with me that I would dedicate the rest of my life, however long that may be, to trying to find something that could maybe help me and other patients. And I knew that I didn't have the time or resources to develop a new drug from scratch.

I knew my only chance of survival would be to figure out what was going wrong in my immune system and is there a drug that's already FDA approved for some other disease that could maybe fix the problem in my particular disease? And that's the term that's often used called repurposing. So finding an existing drug that's already on the pharmacy shelf already available at your CVS that could maybe be repurposed. And so I went on a journey that involved performing laboratory experiments on my own blood samples over the course of a year. Despite a year of hard work, I still didn't have anything, didn't find anything that could be useful, relapsed again, nearly died for a fifth time. But with that last relapse, I'd been storing my blood samples leading up to the relapse. So when I got out with chemo, I went back to the lab with all these new samples and actually with lymph node tissue too, and performed experiments that led me to believe a key part of the immune system called mTOR,

it helps immune cells to communicate with one another, seemed to be turned into overdrive. And I thought if this communication line has turned into overdrive, maybe that could explain why my immune system is attacking my vital organs. Basically, it's kind of always got the fire alarm signal on. And so I thought, well, maybe if we could turn the fire alarm signal off, then maybe that could treat my disease. And amazingly, there's a drug that targets this exact communication line called sirolimus. It's been around for decades. It had never been used before for Castleman's, but it was approved for kidney transplantation. So without any other options, we decided to start testing that drug on me as the first patient ever with my disease. And actually January 5th, marked nine years that I've been in remission on this drug.

Wild (05:07):

Amazing. What an accomplishment. Can you tell us a little bit more about what it was like being kind of a patient scientist?

Fajgenbaum (05:13):

Sure. I think that maybe I'll share a couple perspectives. I mean, the first is that as a patient and with a deadly disease where I was almost certainly going to die in very short order, the sort of typical process of new drug development experimentation, clinical trials, all of that went out the window because I didn't have a decade and a billion dollars, right? There was this incredible sense of urgency, which was, I'm going to die. Can we find anything that can help me? And so all of a sudden it became about, yeah, can I figure out what's going on here? So I can see among the things that are available, what can help me, which as you and your listeners know, is not the traditional way of doing things. There are massive pipelines. We funnel down molecules to the ones that you move forward. You pick indications for those molecules, you keep narrowing it down until you eventually get that molecule approved for a particular disease.

We couldn't follow that approach. In my case, it was life or death in the truest sense. And I would almost bring the analogy to COVID, there was the same urgency that we all as a society felt for new pandemic, let's find a drug as quickly as possible. Let's forget the old way of doing things. And we did. We developed, or we identified the first drug dexamethasone within six months and found the next drug within nine months, first vaccine within a year. I mean, we were able to do it when we had this urgency. And I can certainly say that I had the same urgency for my disease that we all felt for COVID. So that's one piece of this is just the urgency that I would love for us to be able to infuse the COVID-like urgency across biomedicine. And one of the ways to do that is to really focus on additional uses for existing drugs.

And then maybe the second perspective I would share is that of a physician scientist, and that's that it didn't take an act of brilliancy or some miracle concept. It was very straightforward. I did serum proteomics of my blood to find a potential signal. I found a signal I confirmed in my lymph node tissue with immunohistochemistry. And within the course of weeks, I now had a target mTOR that had been well characterized and there was a drug that worked really well against it. And so it was just a few weeks to go from, I don't know anything to, I have something that I think could work. And again, it wasn't sort of some sort of miracle work. It was really pretty straightforward. How can we apply these sorts of simple concepts to the drug development process so that we can unlock existing drugs that can be used in new ways?

Wild (07:47):

And that's a great lead into finding out a little bit more about your own research and Every Cure and the research kind of approach that you take, which sounds like is pretty innovative.

Fajgenbaum (07:57):

Yeah, thank you. So shortly after starting that drug, I was finishing up, I did medical school at Penn, and then I was finishing up my MBA at Wharton while I was experimenting on myself with these medicines and working in the lab. And so shortly after finishing my MBA, I joined the faculty at Penn on the research track to start a center focused on hyperinflammatory diseases, cytokine storm syndromes, and looking for drugs that could be repurposed to treat them. And I'm really proud that over the last a little over eight years, we have identified 12 different drugs that could be used in a new way than they were initially intended for in the realm of these inflammatory diseases. So certainly Castleman's, but also COVID. And then finally a rare cancer called angiosarcoma that involves a hyperinflamatory syndrome. And so we have found drugs that were made for other diseases that are available at your pharmacy that are approved for one indication.

We've done research to indicate that they could be useful for another indication. For some of these, we've actually done clinical trials to prove it, and others patients have been treated off label and still others we haven't yet gotten to human use in the new disease. But the drug, of course, is already being used in other diseases. And so this is just with us digging into one disease area, right? Hyperinflammatory diseases. We've unlocked 12 of these. And so what this has uncovered, and I'm alive because of a repurposed drug, it's really driven me to ask the question, how many more drugs are sitting at your neighborhood CVS that could potentially be useful for more diseases and could treat more

patients tomorrow as opposed to 10 and 20 years from now if we have to develop new drugs from scratch. So this has put me on a complete mission.

I'm a man on fire right now to try to figure out how many more of these drugs can we find new uses for them, and again, start treating patients within a matter of weeks as opposed to within decades. And with that, about a year and a half ago, I got a very unexpected call. I wrote a book called *Chasing My Cure* that was able to really raise a lot of awareness about this approach. It became a national bestseller a couple of years ago and somehow ended up on President Clinton's desk. And so he read *Chasing My Cure*. He reached out to me almost two years ago, and it was right before April Fool's Day. So I actually thought it was a joke. Didn't think it was actually from the former president, but it was. And he was really taken aback by this concept that there were drugs that could be utilized in more ways than they're currently approved for.

And I think everyone listening to this, if you work in the pharmaceutical industry, that approved drugs can be used in more ways, but it's very expensive and it's often very difficult to figure out what are those additional diseases can cost tens of millions of dollars. So a lot of times the business model just isn't there to figure out additional uses for them. But President Clinton was just sort of blown away by, wait, is this just like a organizational math problem where we just need to deploy more resources to figure out more uses for existing drugs and helping a lot of patients? And he really encouraged me to think bigger beyond hyperinflammatory diseases, which is what I've really focused on the last decade. And between his encouragement and between one of my MBA classmates of mine, Grant Mitchell, who spent much of the last decade working on drug repurposing for large pharmaceutical companies, he worked at McKinsey in their machine learning group,

between conversation with President Clinton and discussions with Grant, we decided to launch a new nonprofit organization called Every Cure, which is on a mission to unlock the full potential of every drug to treat every disease possible. And it's not that we believe every disease out there has a drug waiting for your local pharmacy, but it's that we believe every drug at your local pharmacy that could be used in more ways that it's our responsibility as a society and as a pharmaceutical industry to figure out ways to unlock those uses so that no one dies or suffers when there's a drug that's at your neighborhood pharmacy. So launched Every Cure this September, we actually announced it at the Clinton Global Initiative during the opening keynote session, thanks to President Clinton's encouragement. And since we have been engaging with every pharmaceutical company, every data science company, every CRO that we can talk to about joining our efforts.

So all we're doing is a two-step process, gathering as much data as we can about potential new uses for existing drugs and then doing clinical trials of the most promising ones to prove that they work or they don't work. And so the way that we figure out new uses for existing drugs, the number one way you do it is you look to see what have other people already been repurposing. We don't need to reinvent the wheel, but thankfully there are a lot of doctors all around the us all around the world that are actually using drugs in new ways. Drugs like] Viagra that have become the primary treatment for systemic sclerosis in an off-label fashion or Viagra for pulmonary OT hypertension or thalidomide for myeloma,

finding new uses for existing drugs is happening all the time. So the first thing is just capturing the things that are being used in new ways but aren't being used optimally and fully doing clinical trial to prove that they shouldn't just be used in one of a thousand people with that disease, but they should be used for every patient with that disease.

So that's the sort of the most simple way to do it. But another thing which really involves collaboration with our pharmaceutical company partners is understanding what are the additional diseases that you all thought about for your drug but you never were able to pursue? And from my discussions that I've had thus far, my colleagues in pharma tell me that when a new drug is developed anywhere between 20 to 50 diseases are considered for every single new drug that they take down the pipeline, and they're only able to really evaluate five to 10 of them in clinical trials. So that tells you that there are 20 to 30 other uses for that drug that a really smart team working in R&D thought that drug could be useful for, but we're never able to fully unearth and evaluate. And so we're really excited and we've had some pretty extensive discussions thus far, but really excited to partner with pharmaceutical companies to say, can you give us a list of all of the other diseases you considered but didn't pursue among your drugs that are now generic?

Because we know that if your drug is newly on patent and it's new drug, that you need to keep that information close because you might pick that new disease for that drug. And that's certainly in your best interest to keep that information close to you. But among the almost 90% of all approved drugs that are already generic that were made by your company or another company, can we create a process for you to be able to share that knowledge with us so that we can put it into our ranking scheme? And if we think that cetuximab for GVHD [graft-versus-host disease] is the next thing we want to do a trial of, we'll raise the philanthropic dollars and the government funding to actually do the clinical trial to prove that that works. And it's really creating a bypass pathway for drugs being used in diseases that maybe were considered but weren't actually fully evaluated.

Wild (14:45):

What kind of reception has pharma given you so far to your requests?

Fajgenbaum (14:50):

So a lot of positive reception to say, we love the concept, we love the idea. Now let's dig into the weeds of how do you make this work? And a couple barriers that I can tell you have already emerged. One is that the R&D teams will identify a bunch of diseases for a particular drug, but that information oftentimes doesn't even get transferred within the organization to the medical affairs team. So there's like 30 diseases that that drug could be used for that med affairs never even knows about. Once a drug gets approval and it moves to med affairs, and then certainly it doesn't get moved to established products once the drug's generic. So there's actually issues with knowledge sharing within the company, which means that by the time we talk to the established products folks about their generic drug, they're like, we don't even know what R&D was thinking about.

And so that's one problem, right? If there's not good information flow within the company, then it's hard for there to be information flow out of the company. And so that's one challenge, but I don't think

it's an impossible challenge because we can work with the R&D folks. Unfortunately, some of these drugs, those people who worked in R&D are no longer at that company, but maybe we can find some early files on some share drives. But it's really digging to say, this is really valuable to society and it's no longer valuable to your company because the drug is generic. So can we sort of trade off the lack of value to your company, but the great value to society to really do this sort of searching. But I think there's generally an excitement about it, but sort of, alright, well, how do we do this? And we've really been getting into the weeds to figure out how do we make this happen? And I personally believe that doing this a few times, demonstrating that we can open up these pipes of information, I really believe that more companies are going to jump on board. So anyone listening to this, if you work at a pharmaceutical company and you want to be a part of this first wave of knowledge sharing, please reach out to me because we are really excited about solving this challenge.

Wild (16:41):

Can you tell me a little bit more about your other partnerships with biotech, with AI companies, with CROs, like you said, and recently an announced partnership with Medable, which is a decentralized clinical trial company?

Fajgenbaum (16:53):

Sure. Yeah. I think that one of the things that I'm most proud of and also most thankful for is how many partnerships we've already been able to establish just since starting in September. And so really when you think about the entire process of what we're working on from centralizing data to prioritizing data all the way through running clinical trials, we've got these fantastic partners at each step. So a company called Dr.Evidence is contributing curated data from publicly available literature and other sources to help us to make these drug disease links. A company called Eversana, which has access to massive amounts of real world data, has donated their data to us to help to validate when we see something that looks promising, can we determine what the real-world evidence suggests for that drug in that new disease area. And then in terms of the clinical trial piece, we all know anyone who's listening knows that clinical trials are the hardest and most expensive part of this.

It's very cheap to come up with a new use for a new drug. And idea ideas are cheap and thankfully there's a lot of them for repurposing. But the tough thing is to do a clinical trial that's efficient, it's rigorous and it's well done to a level to where you really believe the results and you can change clinical practice based on that trial. And so as a nonprofit organization, we have to be really efficient with how we spend money because we're relying on philanthropic partners and corporations and hopefully at some point soon the government to support what we're doing. But that means that we can't do $50 million clinical trials or else we'll maybe do one trial every decade. That's not what we're looking for. We have to do efficient trials, 1- to 5-million-dollar clinical trials where we can actually get through a number of these drug disease combinations for a relatively limited cost.

And so you have to get really innovative, and the company called Medable that you referred to is really at the leading edge of innovative decentralized clinical trials. So figuring out ways to do clinical trials where the patient is not requiring them to go to academic medical centers, but ship drug to them, monitor them at home, limit the number of scans you have to do, but really figure out ways to do it as efficiently as possible. Leverage technology, the great platform that Medable is built. And so that does limit the kinds of trials you do. Right now you're more focused on oral medications, you're more focused on diseases that maybe aren't immediately life-threatening. But we do feel that there's a real

opportunity by taking this decentralized approach to really rapidly identify new uses for existing medicines and in parallel also looking for partners, traditional large CROs that might want to partner with us to figure out ways that we can do this at cost to really make a difference to society.

Wild (19:34):

What challenges do you anticipate facing as an organization?

Fajgenbaum (19:38):

Sure. So I've been doing this for about 10 years between my center here at Penn and what we're doing now. But Every Cure, we just were incorporated in September, so we're just about four months old as a nonprofit focused on, and I should differentiate, my center here at Penn focuses on inflammatory disorders. Every Cure is every drug, every disease is within scope. So we've only had about four months under our belt thus far. But I can tell you that the challenges that we're facing, which we are eager for anyone listening to help us to overcome, number one is funding, making sure to find partners that want to be a part of this. Now, you can imagine that since we're focused more on generic drugs that could help rare diseases, now you're potentially in a place where there isn't a commercial incentive. And that's why we had to be a nonprofit organization is that we're in the space where society benefits, but not necessarily is there a commercial arm, our commercial aspect.

And so funding is challenging for that reason, but we've been really thankful that there's a number of large philanthropists, individuals like Peter Diamandis, and large philanthropic organizations that are starting to step up and say, I want to make sure this happens, but we still could use further partners, whether they're corporations or individuals that want to support this from a funding perspective. The second is figuring out this challenge with pharmaceutical companies so that data flows well within the company and then can flow out of the company. And trust me, this is not how things normally work with pharma. These old PowerPoint files that are sitting on a shared drive don't typically ever see outside of the organization. And so figuring out how do we do this in a way that is great for that company and great for society is something that we're really excited to solve.

And I think it is a solvable problem. It's just going to take some innovative thinkers and some hard work. And then I think maybe I'd say the third thing is really around this clinical trial piece. Medable] is an important partnership that's going to help us, as I said, to move forward a number of clinical trials for particular drugs. But there also are going to be trials where we want to do the drug inpatient, where it's a disease that patients are hospitalized with severe COVID, and you have an idea for repurposing opportunity where the more traditional CROs we'd be eager to partner with to think about the traditional sorts of clinical trials when they're actually needed. So I think I'd say those are the three things: funding, data flow, and then further partnerships to make sure that we can both generate the links but also do the clinical trials.

Wild (22:07):

Looking forward five, 10 years, where do you see repurposed drugs making an impact in the world? I know you've talked about repurposed drugs, reducing health inequities. Where else do you see them making an impact?

Fajgenbaum (22:20):

Yeah, great question. So just to scope things, there are about 3,000 drugs that are approved by the FDA, and those 3,000 drugs are approved for about 3,000 human diseases. The average one of those drugs is approved for about two to three diseases at a time. And those 3,000 diseases that have approved drugs have about two to three approvals each. And so you basically got 3,000 drugs, 3,000 diseases. There's an additional 9,000 diseases that don't have a single approved therapy. So that's where we really want to make a dent, is not to find the fourth or the fifth or the sixth drug for a disease that already has an approved drug, but we want to take an existing drug and find the first drug ever for that disease that doesn't yet have an approved drug. So I'm really excited to go into disease areas where there's nothing available where the disease is a death sentence or it's horribly morbid.

And to take a drug that's already on your pharmacy shelf and can help patients rapidly, it may not be the cure, it may not be the perfect drug for everyone, but being able to take it from zero to some percentage better is the dream. And so we're really excited to make a real difference in those 9,000 diseases, and we're going to be measuring ourself against those 9,000 diseases. How many of those did we find a repurposed drug for? It's not going to be all 9,000. There's no way that each one of the 3,000 approved drugs actually is going to have activity against those 9,000, but it's not going to be zero. It's going to be somewhere in there in that range from one to 9,000 in terms of the diseases that we hit. And I'm really, really excited because the more partners we bring on board, the bigger impact we can have.

So that's one piece of it. And then to your point, I also want to touch on inequities and how there's a really exciting opportunity here, and that's that when you find a new use for one of these drugs, almost by definition, again, over 80% close to 90% of drugs are already generic. We're talking about finding a new use for a generic drug that is oftentimes already being manufactured and distributed all around the world in places where new drugs can often not penetrate and sometimes will never penetrate due to their costs. And so we have an opportunity to find new drugs for untreatable diseases using products that are priced in a range that can be afforded in the third world, priced and accessible in a way that can help people around the world. So I think there's a lot to be excited about, not just for how many people we can help, but the distribution of where those people are, where maybe they would've gotten left behind if they just waited for new drug development.

You might be familiar with the Clinton Health Access Initiative or CHI, and that's where basically President Clinton observed the fact that in certain parts of the world, well, first off, there were incredible antiretroviral therapies that we all are just so amazed by that are so effective, right? For HIV/AIDS. And what became clear is that in certain parts of the world, you get the antiretroviral therapies and you survive in certain parts of the world, you can't access those therapies and you don't survive. There was this massive barrier between whether you live or you die based on whether you can access these drugs. ChI was able to overcome this by working with a number of pharmaceutical partners to basically bundle costs and also to really bundle demand within certain countries and regions so that they could negotiate prices and get drugs to patients in parts of the world that weren't previously accessing are able to access the drug.

I think there's a really clear parallel here where it's not that price is the barrier, it's a knowledge barrier right now. So the drugs at your pharmacy, it's in every pharmacy in the world. It's actually in those pharmacies in parts of the world that you used to not be able to get antiretroviral therapies. So it's everywhere. But this knowledge gap is preventing us from being able to use these drugs for the fullest extent. And so patients are suffering while there's a drug at their pharmacy. And so we've got to break down that knowledge gap by working with pharmaceutical companies, leveraging data science, leveraging partnerships that we're working on to break down the knowledge barriers so then we can just get the drug to patients because the access should be there because these drugs are, in many cases generic and oftentimes widely accessible.

Wild (26:35):

Okay, great. Well, that covers all the questions I had actually. You spoke really eloquently about everything. Was there anything else you wanted to add?

Fajgenbaum (26:44):

I think that if you listen to this podcast, I think you can tell that we've got a team of people that are just on fire on a mission to try to solve this problem. It's a huge problem. Drugs are available, they're not being fully utilized. And patients like myself, I would've died if we hadn't figured out sirolimus could be useful for me, and we would've never known that I died while there was a drug at my local pharmacy. And so we're on a mission to do this, and I've been so thankful for the people that have jumped in and said, 'Hey, I want to be a part of this, but this is a big problem we're trying to solve.' We're trying to really rethink the chevrons of drug development beyond just getting it approved, but really maximizing the utilization. And the only way we're going to be able to do that is through partnership and through working with really smart people.

So I hope anyone listening to this that says, 'You know what? I might have an idea for these guys, or I might have a thought for how to do this better, faster, please reach out to me.' I mean, that's exactly what Michelle Longmire did for Medable. We first started chatting about this about three years ago, and as soon as I reached out to her to tell her what we're doing, she said, 'We're in.' What we do with Medable is we find ways to reduce costs and make clinical trials more efficient. And we love doing it on repurposed drugs because it's easy to use repurposed drugs in a decentralized fashion. You don't have to be worried about side effects and worried about monitoring issues in those cases. So it's a good fit for her organization, but she certainly didn't have to join on with this partnership, but she wanted to because of the impact that we can have. So I'm excited for anyone listening who wants to reach out and let us know if they're interested in joining on, we would just be thrilled.

Wild (28:21):

It was a real pleasure speaking with you, and I wish you all the best of luck with your work. It's really important work.

Fajgenbaum (28:27):

Thank you so much. I so appreciate you giving us this platform. And you or anyone listening wants to go to EveryCure.org, you can learn more about this work and follow the progress we're making.

Announcer (28:36):

For more pharma, biotech and MedTech news and insights, visit the InVivo website.

Note: This transcript was generated with the use of AI.