Behind the Breakthrough Podcast - University Health Network

Season 3 - Dr. Jordan Feld

Transcript

BTB

Welcome to Behind the Breakthrough, the podcast all about groundbreaking medical research and the people behind it at Toronto's University Health Network, Canada's largest research and teaching hospital. I'm your host, Christian Coté and with us today on the podcast, Dr. Jordan Feld, award winning senior scientist at UHN's Toronto General Hospital Research Institute. Dr. Feld is a clinician researcher specializing in the liver, and he holds the distinction of leading an international trial that in 2015 made the breakthrough discovery of a pill form that cures Hepatitis C, a virus that attacks the liver. During the COVID 19 pandemic, Dr. Feld has led another pioneering investigation into a treatment for the coronavirus. Dr. Jordan Feld, welcome to Behind the Breakthrough.

DR. JORDAN FELD

Thanks for having me, Christian.

BTB

So, Jordan, for you and your research colleagues, the declaration of a pandemic due to the spread of the coronavirus back in March 2020 meant a pause on research. I'm curious in those first days. What was going through your mind with regard to the impact on lab staff and the research you had on the go?

DR. JORDAN FELD

I have to admit that even early on, even though as someone who studies viruses and thinks a lot about illnesses and had gone through the first coronavirus back in the SARS days during my training, I did not see this coming. And I think for many of us, the degree of interruption that this has caused was greater than we anticipated. That being said, shortly after we saw the trajectory of where things were going, we realized that this was going to impact everything. This wasn't just going to affect the way we took care of patients, but it was also going to have a major impact on our research infrastructure both, I do a mix of laboratory research and clinical research, and it was going to mean an impact on both of those things, from having to figure out what we could actually continue to do in the lab

because we actually shut down our labs for a while. And I would describe changing research is a bit like moving an ocean liner, you can't pivot quickly.

We have to say, okay, some of our experiments take weeks to go on where we've got cells growing or even animals growing, and then you have to dial that back and close things down, and then it's not easy to start up again. So it's a big decision to turn it off. And when you've got clinical trials, we had patients who were actually on experimental treatments. We said, well, fair enough that we have to close things off because of the pandemic, but we also have to make sure we do it safely. So we have to keep monitoring these people and figuring out ways to make sure that we can still see them and monitor them in a safe manner. And so really, we did work together as a hospital and a lot of people doing different types of both clinical and laboratory research to come up with strategies to deal with it. But I don't think any of us expected the degree of interruption we saw.

BTB

In those first weeks of the pandemic. What questions were you asking in terms of how you actually might pivot and apply your research expertise to fighting the coronavirus?

DR. JORDAN FELD

Well, I started thinking about it, and at first I said, You know, this isn't my area, I'm a liver doctor. Why would I be focused on worrying about a respiratory infection? And then I thought, you know what? I should spend a lot of my time thinking about viruses, and I remember sitting down one night and saying, You know, I really got to read about coronaviruses and we had a little background in them because there's a corona virus that happens to infect the liver that we use as a model for a severe hepatitis infection of the liver. So I had worked a bit with coronaviruses and thought, you know, let me just read about this and see if we can come up with any ideas that might take advantage of our background in viruses and a little bit of knowledge in coronaviruses and see if we can think about something that as a group of virus researchers, we might be able to help with.

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So that paid off because you decide to zero in on the potential for something called interferons. And first of all, can you help us understand what are they and what led you to investigate them?

DR. JORDAN FELD

So the reason I had a background in interferons is that interferons have been used and have a long history of being used as an antiviral. And what they are is something the body normally makes to fight off virus infections in the name interferon is actually because what they do is interfere with a whole bunch of different things that happen inside the cell. So when a virus infects the body, the body says, Whoa, there's something there that shouldn't be there. And one of the things it does is it turns on this whole host of defense mechanisms

that fight off viruses. And one of the major factors is the production of these molecules called interferons.

And they're sort of like hormones that basically turn on the body's defense system against a virus. And actually, when you get a viral infection like a cold or the flu or COVID, your body actually will produce these interferons. And part of the reason you feel lousy with them is actually because some of the side effects of interferons can be some of the things you experience when you have the flu, like feeling achy or having a bit of a fever. Some of those are some of the things that interferons do in the body, but we had a lot of experience using these because they were first studied as treatments for hepatitis C and hepatitis B virus, infections which both infect the liver.

So actually going back to my training, really what I had studied was using interferons to treat hepatitis C and try to understand how the virus got around the effect of hepatitis C because our old treatments for hepatitis C with interferon were hard for people to take and weren't that effective. So it sort of led me thinking, I wonder if this is a good strategy, because one nice thing about interferons is that they work against almost any virus, and that really got us thinking that this could be useful for COVID 19.

BTB

And so to further that theory, why not try introducing interferon, the synthetic version to help boost the antiviral response to the coronavirus?

DR. JORDAN FELD

Yeah, that's exactly right. One of the things we learned very on, very early on in this pandemic was that one of the things that the virus that causes COVID 19 does is it actually blocks the production of interferons quite effectively. And actually, a lot of viruses do that. In order for viruses to be successful at infecting people, they've got to figure out a way to get around the defense. So they got to get around the armor or the shields that the body has. And one of the most important ones, the interferon system is actually one of the things that most viruses have some strategy to deal with that they will figure out a way to deal with the interferon system. And this virus what it does is it blocks the body's production of interferon in response to the infection. So we thought if we could give back, interferons provide interferon something the body would normally be producing in the setting of a virus infection, then perhaps this would be an effective treatment.

BTB

How did you land on the one you used interferon lambda?

DR. JORDAN FELD

So when we, when people think about interferons, there's a whole bunch of different interferons and the most common types are the so-called type one interferons, interferon alpha and beta. And those are the ones that are produced first in response to most

infections. And they're kind of the ones that when people say the word interferon, that's usually what comes to doctors minds or people that know about interferon. They're usually thinking about interferon alpha and beta. And that's partially because they're produced very commonly. But they're it's also that's what was used as the treatment for the hepatitis infections and treatment for some types of cancer in the past.

The problem with the type one interferons interferon alpha and beta is they're produced in response to infections in every single cell in the body responds to them. So the way interferons work is, they're these little molecules that go out. They bind to what's called the receptor on the outside of a cell, and that tells the cell to turn on all of these different defense mechanisms against viruses. And every single cell in the body has the receptor for interferon alpha and beta. Now that's great if you've got an infection that affects your whole body. But the problem with that is if your body is now producing interferon and I really want it to target, say, the lungs it's going to target the lungs, but it's also going to make you feel lousy in the brain and the knee and the stomach and the heart and wherever else the interferon receptor is.

Now the nice thing about these so-called type three interferons or interferon lambda, is they turn on the same antiviral mechanisms, but they do so using a different receptor. So they only do it in the cells that have that receptor. And that happens to be in a pretty limited distribution in the body. So it's primarily in the lungs, the liver, which is why I know about it in the intestine and to some degree, in the skin. And so this was a bit of a more targeted approach to allow us to send up this antiviral message, but send it to the lungs where people have this infection and have a lower risk of having side effects everywhere else, and also potentially actually turning on and aggravating the inflammation that happens in COVID 19.

So you probably remember early on, people talked about people getting this infection and dying of this thing called Cytokine Storm, which is when your body produces all of these cytokines, which are inflammatory hormones in the body and actually can make people worse. And the problem with the type one interferons is they can actually stimulate the production of those inflammatory cytokines, so could actually make someone worse. Whereas interferon lambda, because it's more focused, it's less likely to do that. And at least some mouse experiments suggested that would be true. So we thought fewer side effects, less risk potentially of this Cytokine Storm syndrome and more targeted to where the action is in the lung. And actually, this virus also replicates in the liver. So that's why we took this approach.

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So where do you go find a synthetic version of interferon lambda?

DR. JORDAN FELD

Well, the good thing is we had some experience with this because just like the interferon alpha had been studied for the hepatitis virus infections, interferon lambda had also been

studied for that. And the reason it was used in that setting, same idea. Let's try to use that interferon that has less side effects in a more targeted activity. So it was studied for hepatitis C and B infections. It worked quite well. But those other medicines that we studied a little later, the oral form that you mentioned earlier on were so effective and so well tolerated that even though interferon lambda went through very advanced trials for hepatitis infections, it was never actually licensed to be used for that. But we're actually studying it also for a less common type of hepatitis infection called hepatitis D or Delta. So we had a lot of experience with it, knew how to use this drug and figured, you know what, this probably makes sense to it to try it for the virus that causes COVID 19.

BTB

So you move towards, I guess, your first trial, and I understand because of the urgency for treatments, this is back last spring. Last summer, you moved straight to human clinical trials?

DR. JORDAN FELD

Yeah and that was, you know, when I first started talking about this with some of my colleagues, the first thing we said is, you know what, let's, let's get that mouse model up going again, that corona mouse model that we have for this coronavirus that causes the hepatitis infection mouse we'll study interferon lambda, we'll see if it works. And then, you know, two or three years later, we'll start doing human trials, et cetera, et cetera, et cetera, and then quickly realized that didn't make any sense. This is something where we needed to act quickly. People were dying. This pandemic was spreading very quickly. And of course, this was before the prospect of vaccines being on the horizon. So we really thought we need treatment and we need treatment quickly. And we had the luxury of having a very good safety database with this molecule. So it had been used in over 3000 people to study hepatitis infection treatment. So we knew about the safety profile and we said, You know what, let's just bite the bullet and go straight into a Phase 2 trial. Now that being said, we put in a lot of safety precautions to make sure that we did do this carefully and safely as a first time using it to treat this infection.

BTB

Okay, so you know, the urgency for COVID treatments is all consuming for so many researchers. I understand compounding this for you as I understand you were juggling the approval process for this first trial with the birth of your third child. How did that go?

DR. JORDAN FELD

It was not the most opportune timing. I'm not sure my wife will ever forgive me for this, but we were writing the protocol. I remember she came in as I was working on the final touches of the protocol to tell me that she was going into labour. And of course, I dropped everything I was doing and quickly took her to the hospital. And very fortunately, she delivered a healthy baby boy the next morning and we were very excited. But while she was

sleeping, I have to admit I might have sent a couple of emails with the protocol to submit it to Health Canada so we could get the trial started shortly after the baby was born.

BTB

Well, congratulations

DR. JORDAN FELD

Thanks.

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Okay, so the first trial gets underway. Talk to us about the scope and how you decided on the patient profile best suited to try to interferon lambda.

DR. JORDAN FELD

So as you pointed out, we jumped right into human trials and one of the things that we thought about with an antiviral. So this is a drug that kills the virus. We thought you got to give this early. So we don't want to wait until someone's in the intensive care unit on a respirator. At that point, most treatments that affect the virus, probably too little, too late. And that was really the experience that even the very early trials had shown if you waited even till hospitalized populations who often had missed the boat. So we said, why not actually go into the outpatient population? And at first people said, Well, why would you do that? Most people that have COVID 19 who are not in hospital are going to do fine. So why would you treat them with anything at all? And our rationale was a couple of things.

One is that if we can treat people early in the infection, first of all, when you get the infection, those first couple of days, I don't know what direction you're going or you're going to be one of the people that sails through this infection. Or are you five days away from being on a ventilator? And unfortunately, we had very poor ability and still frankly have pretty poor ability to predict that. So we thought that if we could sort of nip this in the bud, find people early, we could prevent them from progressing and going on to more severe illness. But also we would have the chance we thought and I think we have shown this to be likely the case that if you could bring down the virus level very quickly, we could also reduce the risk of spreading it to other people, and that has the obviously important potential. And then the third thing is we even thought that if we could really bring down the virus quickly, even in healthy people, maybe we could get them out of quarantine faster. So a two week quarantine is certainly a big burden for people. And if we could shorten the time to seven days or even shorter, we thought this would be a big benefit for society and economically as well as the health benefits.

BTB

And just tell us a little bit about logistics, Jordan, like the number of people and how the interferon was administered?

DR. JORDAN FELD

Yeah, so the nice thing about interferon lambda is that it's got a long acting form. So it's an injectable medication. But it's a very simple, it's a subcutaneous injection, which is sort of like a little insulin needle. So it's a tiny little needle. People can actually give it to themselves. And when we were using it for hepatitis infections, we actually gave it to people weekly for a year. So in this case, we were just giving a single shot so people would come into the clinic. They`d get a single injection under the skin, tiny painless, we would watch them in that first trial, we watch them for a period after to make sure they didn't have any reaction, and then we followed them after to see how quickly they cleared the virus. So we were swabbing them every day to see how quickly they cleared the virus from their nasal passage. And what we showed was that the treatment really accelerated the clearance of the virus quite significantly over a placebo. So half the people just got a saline or saltwater injection as a comparison to using interferon lambda. And we showed that with the active treatment, they had double the rate of clearance. Well, actually, once it was controlled for the amount of virus there, about four fold faster clearance of the virus.

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So what kind of reaction did you get to these results?

DR. JORDAN FELD

I think people were quite excited about it. I mean, I think the important thing about this trial was we did it in a very rigorous manner. So it was a randomized controlled, double blind, placebo controlled trial. And, you know, as often happens with many areas of medical research, there's sort of a, especially in something as urgent as Covid, people rush to do things quickly. And certainly urgency is important, but you've got to do things quickly, but you've also got to do things carefully so that you get to answers that you can really trust. Because so many of the early trials and unfortunately, we saw this to some degree with hydroxychloroquine and you remember all the news and unfortunately it got politicized, which was really unfortunate. But those first trials that were reported were uncontrolled trials, so they showed that people got better. But if you don't know what happens when you don't treat people, then it's very hard to make conclusions.

And a lot of the early trials of many of the early antivirals that reported very positive results were not properly controlled. So I think because we had gone through the effort of really making sure we designed a very rigorous, not huge, it was relatively small. It was only a 60 patient trial, but it was well done and rigorously done so that we were confident in the results that we got.

BTB

And not long after your out patient trial gets underway, you start another trial arm in the investigation of interferon lambda with hospitalized patients. These were more severely symptomatic patients. Talk to us about the scope and scale of that trial?

DR. JORDAN FELD

Yeah, so we figured that the first thing we needed to do was show that this was safe and that we had at least some sense that it wasn't that there might be some efficacy. So the way we sort of did this in sequence was that we did half of the first outpatient trial. We had what's called the Data Safety and Monitoring Board. So this is an independent group of specialists who review all of the data. So they look at all the side effects. They unblind the data so they know who got what. And make sure that there is no safety concerns. And then they tell us without telling us that the treatment worked or didn't work. They just say, you can continue your trial.

And once we had that assurance that we weren't causing harm, then we said, okay, now let's see. Can we try this in a sicker population? Still not the sickest. So we didn't go to intensive care. We said we're going to take people admitted to hospital and see if we can change the trajectory of their hospital course. So can we take someone who's early in their hospital stay? Give them a treatment that's hopefully going to reduce the risk that they go on to needing intensive care, respirator or, of course, dying and maybe also shorten their hospital stay and that trial is still ongoing. We're enrolling that trial here in Toronto and also with colleagues in Brazil.

BTB

And is there any reporting to at this stage?

DR. JORDAN FELD

Well, so we know we've cleared our safety. So again, we have the Data Safety and Monitoring Board review and we had a 25 percent of the enrollment at 50 percent of the enrollment. And we've cleared our first two hurdles of safety. So we were actually worried that an interferon actually could make the inflammation worse sort of cause that Cytokine Storm. We thought it was less likely with lambda than with alpha or beta, but we still had to be, we always have to be careful. So we wanted the reassurance that we weren't causing harm, and we now know we're not causing harm. We don't know yet the results of the whether we're improving outcomes, but we should have results shortly for that trial.

BTB

And given that these are sicker, hospitalized patients, does that present any particular challenges for you as the trial unfolds?

DR. JORDAN FELD

It's interesting when, as you'd expect at a very good hospital like the University Health Network, where we've got researchers in lots of different areas, virologists, intensivists, respirologists, all thinking about this and many people coming up with really good ideas for clinical trials. You know, we joked very early on in the pandemic that we had more trials than patients, and sadly that unfortunately changed pretty quickly. But it did mean that

recruitment for these studies was challenging. I mean, it's created, it's been a very, you know, we sort of all imagined we could do these trials quickly because there were so many people getting these infections, so many people getting hospitalized. But we had many different trials and we had to make sure that people could go in the trial that they thought was best for them and that their physicians taking care of them thought was best for them, so they're working with the ethics board and the hospital we'd come up with sort of what we thought was the best strategy to present people the options of different trials, but without giving them too long a list the last thing someone wants when they're coming into the hospitals feeling sick is, would you like to go into trial A, B, C, D, E, F, G or H? That's a little overwhelming.

So we had to try to come up with ways that were both ethical and also respectful to people's the situation they're in and make sure that they could carefully understand them. We also are often with elderly people dealing with family members or other substitute decision makers, which can be, you know, adds an extra level of complexity. And of course, in a multicultural city like Toronto, you've also add in language barriers and other things, which we always have to consider. So the recruitment was slower, I think, for every trial than we anticipated. But I think our team's done a fantastic job and we have been moving it along. But we've also said we need to enroll at other sites, which is part of the reason we reached out to colleagues in Brazil and other parts of Canada, and particularly in Calgary and at Sunnybrook to enroll in the hospitalized trial as well.

BTB

I imagine, especially for the outpatient arm of the trial monitoring, there must have been a bit difficult or challenging during a COVID pandemic?

DR. JORDAN FELD

Yeah, it created things that you know, I never would have thought of, but I've done a lot of clinical research. When, but when I tell a person living with hepatitis C that they're coming in for a clinical trial and they're going to come to my clinic, I just say, okay, here is, you know, my clinics on the 13th floor come up to the liver clinic and you'll meet the clinic nurse and we'll give you the treatment and we'll come back for monitoring visits. I don't have to think, Well, wait, if you come into the hospital, you've got this infectious disease that you might spread to everyone that you pass in the elevator or in the lobby or in the waiting room. And so really, we had to set up a clinic and big kudos. I want to just call my name, but thanks to Mike Voth and his team at UHN for helping us set up an outpatient clinic to be able to do COVID 19 trials.

Because frankly, most hospitals don't have that capacity. And I really pushed our research group at UHN and Brad Wouters, who was the executive vice president for research, really made sure that it happened. And I want to thank him for that because I said to him, you know, as a, as a leading research hospital, we've got to figure out how to do this. And then they put in everything we needed, all the infrastructure we needed to have a facility where

we could safely bring people. But you know, it's things you never think you're going to have to think about. Like we had to work with a taxi company to make sure that the drivers were safe, that the people could come in, that we had a system that they would signal to us that someone was there. So we made sure when they walked into the clinic, there was no one else they were exposed to. We always, every week and it gave me, I think I lost definitely a lot of sleep over this. We had to test our staff, every on a weekly basis to make sure that none of them contracted COVID 19.

Of course, they were using all of the personal protective equipment and using it very carefully. But still, despite your best precautions, there's always a risk and I thank them because you know, they were putting themselves really very much on the front line. Not only saying, Am I going to go and take care of COVID, people with COVID 19, but I'm going to go right. I'm going to take a history from them. I'm going to draw their blood. I'm going to take swabs from them. I'm going to give them an experimental treatment and then monitor them as they go along in this treatment. And I would also thank all the participants that were willing to go through the rigour that we put them through to, to participate in this trial.

BTB

This coronavirus keeps mutating, and I keep hearing more and more is likely to be here for a long time, if not forever. It's more transmissible, more deadly. Do you have any measuring your results yet of how interferon lambda is faring when it comes to treating patients who get these variants of concern?

DR. JORDAN FELD

Well, the nice thing about interferon is that it has nothing to do with the sequence of the virus. So part of the reason that our bodies make interferon when you have a virus infection is it works against almost every virus because the way that it works is it activates a whole bunch of different mechanisms of killing viruses. So it's not like coming in with a one pronged attack. The example that I always give when I'm explaining it to the medical students, you know, if you could kill a virus, walk away or kill someone walking in with a gun, and if you had a good shield, you could block the bullets. But if someone's coming with a gun and someone else is coming with the tank and someone else is coming with a submarine and someone else is coming with a sword in the back and every other imaginable way, you could hurt someone. Maybe not the best example, but this is, this is a little bit how interferon works.

So it's very hard for a virus to be able to become resistant to an interferon. Sometimes what the viruses typically do is they figure out strategies to make the body not produce interferon because that's easier than becoming resistant to it. And in fact, that's actually what this virus does. It blocks the production of it, but it really doesn't matter whether the virus changes its sequence and becomes a variant of concerns or mutates to another form of the virus. Interferon should still be active, and so far, everything we've seen in cell culture

and in preliminary results from the studies shows that it works just as effectively against variants of concern as against the original virus.

BTB

That's reassuring. Going back to the clinical trial for patients with mild COVID symptoms or early on in COVID. What can you tell us about where that stands in terms of moving on to Phase 3?

DR. JORDAN FELD

So we finished our first trial in what's called a Phase 2 trial, and this is a study where you're trying to show that the drug is safe and that it has some efficacy, that it does really what you expect it to do. And we saw these very positive results where it cleared led to the clearance of the virus much more quickly. But before the FDA or Health Canada or any other health authority wants to approve a drug for use, they want to really show it doesn't just make the virus go away, but it actually makes people better. So it gives them some clinical benefit. And in this case, what the health authorities have said is we really want to make sure that we're actually preventing people from needing hospitalization or having severe outcomes. Now to do that, you have to do a much bigger trial because fortunately, most people don't end up in hospital who get COVID 19.

But if we want to show that the drug is preventing people from getting into hospital, then we need to do a bigger trial. So include more people. And also what we've done is enrich the trial for people who are at higher risk of having those outcomes. So we've taken older people, people with other health problems and people who have much more severe symptoms at the beginning. And we're now doing what's called a Phase 3 trial, which will enroll a lot more patients. We're also doing this in collaboration with a group in Brazil, and we hope to finish the trial over the next number of months. We'll, of course, depend on the waves of COVID that happen both here and elsewhere. You know, we're always very happy when the numbers drop. That it's great for the city and bad for the trial, and that will continue to go up and down. But we're confident we will finish the trial and hopefully we'll have positive results.

BTB

I'm curious the fact that there's vaccines on the market, does that in any way diminish the need for your trials to continue?

DR. JORDAN FELD

You know, I don't think so at all. I mean, obviously, I was thrilled to see the development of vaccines, and it's real testament to science that they were developed so quickly. And then one of the things we talked about early on was one of the reasons we needed outpatient treatments was we said, You know what? Even once vaccines are here, getting vaccines to seven and a half billion people is going to be no small task, the logistics and certainly we've

seen in Canada, to its credit, although we had a slow start, has done a pretty good job of getting the vaccines out to people. But we still have a non-trivial percentage of the population that's not vaccinated for whatever reason. And those people, unfortunately, are the people who are most commonly getting ill with the virus now.

We are seeing some breakthrough infections and that may continue, and it's important that we have not only vaccines. Prevention is certainly a great strategy and one that we always advocate for, but it's also important to have treatments because any prevention strategy is going to have some leak. And once someone has the infection, you know, we've had people say that they don't want to go in, in the trial because they would rather get the vaccine. And of course, we have to explain to them at that point, the vaccine is not going to help them once they've already got the infection. So. But it is. It is important to have both vaccines and treatments.

BTB

And talk to us about publication in such a fast moving time, and I'm sure tons of pressure as well. You know where the urgency is there to publish when you have results that indicate any kind of benefit to patients, what's governed your decision making when it comes to publication?

DR. JORDAN FELD

Yeah. So I think the first thing is, is that you've got to be sure that you're confident in your results because you've got to do your analysis very carefully. I mean, everybody wants to have positive results, for sure, we do. But as someone who does research, unfortunately, that's not the norm. Most of the time things don't work and you sort of rejig and retool, and eventually you hopefully get to something that does. But it's a long and arduous path. And you know, what's been interesting during this pandemic is the rise of the so called the preprint, where people have been publishing their results on these preprint servers, which it's not quite just publishing online, like it's not posting it on your Facebook page, but it is posting it on these preprint servers, which do a very cursory quality check.

So they're making sure that this is coming from at least a seemingly legitimate source. And there are some very simple safety checks, but it hasn't gone through what's called the peer review process, where other specialists in the field have looked at it and said, Wait, that's not the right way to do the trial or your conclusions, Ddn't follow from the observations you had. And what we did is we really carefully went through our data and we only thought about putting it on the preprint server. Once we had submitted it to a peer reviewed journal. I do think that the preprints have their benefit. But what they are useful for is that as an expert or someone who's in the field, they can read a preprint and make their own educated decision.

The danger of preprints is when people who don't have enough expertise to really judge the science are making strong conclusions and unfortunately, sometimes with no disrespect, to media making strong conclusions about preprints that haven't gone through peer review,

and that's definitely led us at least occasionally astray. So we have to be careful, and I think UHN does a good job. They don't there's no press releases about results. Until results are published in a peer reviewed journal.

BTB

You're listening to Behind the Breakthrough, the podcast all about groundbreaking medical research and the people behind it at Toronto's University Health Network, Canada's largest research and teaching hospital. I'm your host, Christian Coté and today we're speaking with Dr. Jordan Feld, award winning scientist at UHN's Toronto General Hospital Research Institute. Dr. Feld's pioneering research is made possible, in part thanks to generous donor support. If you'd like to contribute to his groundbreaking medical research, please go to www.uhnfoundation. That's all one word uhnfoundation.ca/podcast.

So, Jordan, I understand your dad is a retired oncologist, and as a teen, he would take you and your brother to work at the Princess Margaret Hospital. What kind of influence do you think that introduction to health care had on you?

DR. JORDAN FELD

My dad was, definitely was and still is a huge inspiration for me and definitely was a big driver in my decision to go into medicine. That probably the biggest impact of taking us on to the hospital when we were really little was that my brother was very comfortable walking up to anyone and anyone and everyone he saw out in the public at a restaurant or wherever and telling them that they shouldn't smoke because his dad was a lung cancer doctor and they were going to die. So that was that from a very early age, we had sort of this idea of public health as being quite important. And I, if for sure, definitely influenced my decision to go into medicine and not only medicine, but academic medicine and research.

BTB

You've mentioned that when you were in med school, you were practically, in your words, running away from any interest in the liver. What turned you around?

DR. JORDAN FELD

Well, that's absolutely true. When I went through medical school, the only two things I was sure I didn't want to do were gastroenterology and hepatology and hepatology, which is the study of liver disease is a subspecialty of gastroenterology. So what did I do, the exact two things I swore I wouldn't do, and the reasons I didn't want to do them is that I thought gastroenterology was kind of gross. I've seen that stomach ulcers and poop wasn't all that appealing and, and I thought liver disease was just much too complicated because so little was known about the liver.

BTB

Right.

DR. JORDAN FELD

And then I had the very fortunate experience of working with Dr. Jenny Heathcote, who was one of the pioneers and really some called the grandmother of liver disease. She was one of the first people to really specialize in liver disease and was an internationally recognized hepatologist that worked at UHN at the Toronto Western Hospital. And she really inspired me. I was, I started doing research with her in my first year of my internal medicine residency and really fell in love with research. And really, obviously, she changed my mind about liver disease and showed me that not knowing much about it was actually a great opportunity because it meant that there was so much to learn. And you know, I've been fortunate enough after Jenny to have multiple other really good mentors along the way, which have been 100 percent the guiding light. And anything I've achieved is 100 percent thanks to them because they taught me everything I know about how to do research, how to ask questions and also, I think, gave me the passion for what I do.

BTB

So when you reflect on those mentors and how career defining and guiding they've been. What do you say or how do you mentor now the people that come into your research and shadow you in your clinic?

DR. JORDAN FELD

You know, I think one of the things I realize is how important it is. I think sometimes when you have a medical student or even someone very young, high school student or someone coming into your clinic and you know, you think, Oh, they're just going to have it like, it's not that important. They're just here for the day. It can be really a very impactful experience for people to be involved in health care, to work in your lab, for the summer, to just have a very even if it's a passing interaction with the health care system. I wouldn't really call that mentorship, but it's exposure. And then when you take on, actually mentoring someone where you see some promise and some excitement, and for me, what I'm really looking for is that excitement in someone's eyes.

When you see the passion in their eyes, that kind of twinkle that they get excited about what they're doing, they're not doing the research project to get into medical school or residency or whatever, but they're doing it because they're genuinely excited about what they're studying. That's when I get excited, and I would definitely say the next question I ask them is what's making them excited and what do they want to do? Because one of the things that Jenny really taught me is don't try to make everyone like you, try to make everyone like them. So try to teach them to be really good and do the best at what they want to do. And hopefully you can offer them some skills that will be applicable to what they're doing, but not necessarily try to shape them into the mold. So I'm not trying to make another army of hepatologists. I'm just hopefully encouraging a few other people that doing medical research can be an exciting and gratifying career.

BTB

You're also a clinician. You see patients all the time, so you know the urgency for new treatments. How do you reconcile that need with the fact that medical research takes time?

DR. JORDAN FELD

Yeah, it's a great question, and I think it's an important one, I love my job because I do both. I would never give up clinical medicine and if I did seeing patients and having that personal connection with people understanding what it means to have, you know, that's different than when you're just studying a disease in a lab. Having that personal connection is so important. It also helps guide our research because it helps us know what's important to people and really what's going to be impactful. And so that's really important. On the flip side, I forever am coming up with questions in clinic. Why did this person have a better response to this treatment than that person? And then that will lead us to ask a question that we can only answer in the lab because the lab we can control and experiment. I can't control people very well and don't try to, but we can control you know, cells or small animals and things in the lab and do very controlled experiments and understand them.

But one of the things that I would definitely say medical research is a humbling endeavour because the more we learn, the more we recognize how little we understand about these systems. And it's when you have that recognition of how little we understand that you understand why it takes so long. So yes, we all want treatment to move well, advances to move faster. But I would also say that they are moving, they are moving at a breathtakingly fast pace. I mean, when you think about the amount of time that it took for medicine to develop to sort of the 20th century and just some of the early things that we now take so for granted about basic physiology and like the germ theory of disease and things like that to the last 50 years where all of the molecular biology has just put our foot on the gas and technology in every area of life, but particularly medicine is just moving at lightning speed.

And so obviously, for someone who's got a life threatening illness that can't wait for even those short months or a couple of years till we have a breakthrough, that's devastating. And it's never fast enough and that keeps us motivated. And I think having that clinical time in the clinic where I see people who are suffering from these conditions is absolutely motivating. But I also know that when we rush things and we don't do it carefully, we come to the wrong conclusions. And there have been so many times in medicine where early results have not panned out when they've been more rigorously studied. So fortunately, my mentors have taught me and I people often say it in our research group, okay, you've shown this repeatedly, repeatedly, you're ready to publish it, but we're always our toughest critics like we have to convince ourselves before we say that we're confident in the results.

BTB

And yet on the research side, you're presented with challenges and roadblocks and failure, and it's not something we're typically coached or taught how to overcome. So I'm curious, as a scientist, how do you overcome or how do you navigate failure?

DR. JORDAN FELD

It’s practice, practice. We get, we all get very good at failure. So I mean, the truth is, any successful researcher, probably in any area of research, but certainly in medical research, in the biological sciences which are so complex, you've gone down the wrong road at some point and people that get stuck and fixated on a certain idea and say, I know my ideas right, I'm going to stick with it. Occasionally, they're right. And you know, that sort of dogged perseverance can be really important and has led to many breakthroughs. But it's also led to many dead ends, and you do have to realize you learn a huge amount from your failures. Like without exception, we've had a hypothesis and absolutely proved it was wrong in multiple ways. Usually that has then said, Well, why don't we look at it in a different way? And that can be certainly frustrating. And the number of times I get a grant review back or a paper, rejected and say, Boy, why do I do this again? Is, you know, many, many times. But fortunately, my family lets me submit another grant and we keep at it because you know, those times when you do have the breakthroughs, they don't happen often. But when you do have something where it all comes together and it works, it's the best feeling there is, it's super gratifying.

BTB

I'm curious if you think randomness or serendipity plays a role in medical research?

DR. JORDAN FELD

For sure it does. Serendipity plays a huge role. I mean, there's some classic examples the discovery of penicillin being, of course, they have probably one of the most important where they left their reagents on the lab bench over the weekend and came back and saw that this mold that had killed the bacteria and led to the discovery of penicillin one of the most important antibiotics ever discovered. So those kind of serendipitous random discoveries do happen. What they take is someone paying attention because someone could have just thrown out that lab culture dish with the penicillin on it and not noticed anything. And you really, you know, it means you don't ignore the results when you have a result that doesn't fit what you expected. You don't ignore that one. Those are the exceptions are the ones, that teach you the most. And, but it is not uncommon that someone accidentally makes a mistake in an experiment. And with some of our experiments, as I mentioned right at the beginning, some of our experiments, two or three weeks long. If you forget one step in that experiment, boy, you got to start all over again. Except maybe the experiment gave a different result than you expected. And if you pay attention, that thing that you omitted actually could give you a clue. So for sure, serendipity plus good observation can be extremely useful.

BTB

You've done a lot of media over the years. I'm curious what your take is on the value for scientists to communicate your work, especially in a way that's accessible to a mainstream audience?

DR. JORDAN FELD

The truth is, when you think about it, like scientists are trained to be scientists and they're trained to talk to other scientists. And then you know, I often say to the students, even when they're presenting their PhD thesis for their thesis defense. And certainly if someone's giving a talk to a bunch of other specialists or something, they assume that everyone in the room knows as much as they do about the subject that they're talking about. And I always say to them, if you know, if you can't explain this to your mother or father or your sibling or someone who's not in this area, then A, you probably don't understand it well enough. And B, you're not simplifying it enough. We all have a tendency to use jargon. People do that in every area when I talk to my investment advisor, you know, it makes my head spin with all the different acronyms for different things that I'm probably investing incorrectly in. But the same thing happens in, in medicine that people take for granted what seem like simple because they're common, like they're things we talk every day about to other doctors or other scientists.

And I'm always reminded of this when I talk to really smart people who are super educated, but in other areas, you know, I have patients that are lawyers, judges, very, very, very intelligent people and ask questions that from a medical perspective, seem very simple. And then it suddenly occurs to me. I'm sure I would ask a much simpler question if I was asking a legal question, and it just sort of reminds me to dial back the jargon and express what we're saying in simple, straightforward terms that people can understand. You know, and I'm sure that none of us do it as well as we should. I think all scientists should probably get a bit more training in it and particularly people that are interacting with the media more frequently. But you see people like Isaac Bogoch, he does it extremely well, and that's why he's still on TV all the time, because he does express things in a way that people understand and can take home.

BTB

Well, you bring up an interesting point in terms of, say, Isaac's accessibility. It also, you mentioned preprints. Big picture. It's almost like the pandemic has thrust medical research, especially, you know, science and medical science into like this unprecedented public profile. It seems like a once in a lifetime opportunity to show, like how essential this service is, that it's intertwined with health care. But I'm wondering, has medical science done enough to stay in the public's eye when the pandemic does eventually fade?

DR. JORDAN FELD

Probably not. You know, there are people like Isaac who are fantastic at it. There are others that don't fare as well. And I think one of the frustrations that many people have had around the world, certainly in Canada but not restricted to here, is that the messages are not always clear and they change. And you know, what like messages should change because we're learning. So as you know, like we were talking about before, that science doesn't go in a straight direction, that what I know today is going to be what I know three days from now. And usually it happens much more slowly. So, you know, people say hormone replacement therapy prevents breast cancer and then it causes breast cancer. It's a 10 year change and

during COVID 19, those changes have happened over such a short time that it has for sure challenged people's confidence in health care and in science because they say, like, why are they always changing their mind?

And some people have done a really good job of explaining why that happens. This is why we thought this before. Now we learned this because of this well-done study, this new research that we have now, we believe this. And we recognize and good scientists and particularly those in the media, come very clearly forward and say I was wrong and I was wrong because of this. But now I know this, and to me, that's a good scientist. That's not someone who is doing it wrong, that someone who's getting it right and is comfortable acknowledging that. I am concerned that there's been too much politicization of some of the medical messaging and not enough people doing it in a clear, accessible way that I sadly think we probably will miss the opportunity to keep much of the attention that people have had on medical research during the pandemic moving forward.

But hopefully there will be at least some pearls that come out of it, that there will be some trust in understanding how things change, that there will also be, I mean, as someone who does a lot of public health and thinks about public health approaches to things that I hope that's one of the things that stays that we recognize that you can't only think about the individual. You really do have to think about the big picture and kind of a public health approach to medical care. So we think about prevention and we think about some of the equity issues that have come up in COVID 19 so that we're not only addressing this virus, but we're also thinking about why certain people are faring worse with it than others. Those are some of the things that I hope persist after the pandemic.

BTB

There's a saying by leadership author Simon Sinek. It goes something like, “People don't buy what you do, they buy why you do it.” Why do you do what you do?

DR. JORDAN FELD

That's a, that's a great saying. People sometimes ask me, why are you so busy? Why can't you just go in, you know, be a doctor and see patients or just go and do research? Why do you try to do both? And I say, you know that the two best times in my week are the two hours of my lab meeting where the students are talking to us about their results. And we're seeing like experiments that we've been thinking about and working on coming through. And sometimes it's an abject failure. But other times, unfortunately, rarely it's a big success, and we have this great moment of really being excited or we just think of something new. Something shifts our direction. We get super excited about it. And the other time in my week is when I do my clinic and I see patients in my clinic and I talk to them and I hear their stories and both of those things that get me up in the morning. They're exciting, They stimulate different parts of my brain, like one is very academic and one is very human. But they're both super important and makes what I do really satisfying and gratifying.

BTB

That moment of success, you're one of those few people who actually have you're in sort of rarefied air as a medical research. You've had a discovery. Your pill form for curing hepatitis C back in 2015. Can you take us back to that moment? I think a lot of people would like to know when you achieve something like that, like, how did that, like what was your reaction?

DR. JORDAN FELD

That's exciting. I mean, obviously, it's exciting. Like you've worked so hard on something. And I think for me, it's very incremental because you're sort of building on like, no big discovery happens in a vacuum. It's not like we have no idea one day and the next day we have the answer. It's always building, building, building, building. So when you get to that great outcome, sometimes it can be a bit anticlimactic in the sense that, you know, people think you've just gone from zero to the top of Everest, but you were really one step away from the top of Everest. And all you did was take that last step. So it may not feel quite as dramatic as someone might expect. But then for me, the times that it was so gratifying was when I saw people who had been coming to our liver clinic for 30 years, not seeing me for those 30 years, just to be clear, but had been coming for 30 years to our liver clinic with hepatitis C infection. And we gave them this treatment, and three months later, they were cured of this life threatening disease and they started crying.

That's when it hits you, like that's when the impact hits you, and you see that the work that you've done has had this impact on someone's life and they're going to like, spend more time with their grandkids or not need a liver transplant. Those kind of things are really impactful. And then because I also sort of work on the public health side like knowing that this is going to like the flip side of that is now it's so easy to cure people with Hep C that the residents, they're like, Oh yeah, we just we give them that pill and then they're, they're gone. And the patients also are like, Oh yeah, well, I have Hep C, but I'm not that worried about it because I know you can cure it and we give them this treatment and they're cured. And I think, wow, like this thing used to be this huge problem. And now our huge problem is figuring out who has it and getting them into treatment. But that's our only problem. We don't we don't have people dying of this anymore. And when we see that we're not transplanting people for hepatitis C anymore, that's when it really sort of sinks in and you kind of feel like, wow, I mean, I had a small part in a in a huge global effort, but we together have really made a huge impact and actually conquered, conquered a disease.

And that's why in 2020, the Nobel Prize was awarded for the discovery of hepatitis C. And I feel very lucky that the three people who received that award are all people who I call friends and know very well, and that's something that's special. Most people don't have that in their career, and frankly, I just feel that I was in the right place at the right time and pretty lucky experience to have that.

BTB

Amazing. So what's next, Jordan? What should we look out from you for the next months or years to come?

DR. JORDAN FELD

So even though we've made a lot of progress, we still have a lot of work to do. And that's, you know, one of the good things about medicine is that even when we've had successes, you never get bored as a researcher because there's always many problems lining up behind that we still have to address. And in the viral hepatitis field, which I think people don't realize how big a public health problem this is. When you put hepatitis B and C together, they actually cause more deaths every year than HIV, TB or malaria, which of course are major global public health problems. But chronic viral hepatitis is as well. And, you know, because of our successes with developing treatments for hepatitis C and having a vaccine for hepatitis B, the World Health Organization actually tasked the global community with eliminating these infections as public health problems by the year 2030.

And Canada signed on to that. But we've got a lot of work to do, and that's one of the areas where I'm continuing to work very hard. So trying to get the treatments that we already have now out to those that need it. So that means screening means developing better diagnostics, new models of care and also trying to develop a vaccine. Because for hepatitis C, we have great treatment, but we can't prevent it yet with a vaccine and unfortunately not as easy as the vaccine for the virus that causes COVID 19. So we've got our work cut out for us, but we're working on that and also working on new treatments for hepatitis B so that we can hopefully cure it one day, like we can for hepatitis C. So that's going to keep me busy for the next while. But I also know that there will undoubtedly be curveballs that come along like the COVID 19 pandemic. Hopefully nothing this serious that we, along with our great colleagues at UHN, can dig our teeth into and try to help solve other problems as they arise.

BTB

Dr. Jordan Feld, award winning scientist at UHN's Toronto General Hospital Research Institute. Thanks for sharing your groundbreaking research with this and continued success.

DR. JORDAN FELD

Thanks so much for having me, Christian.

BTB

Dr. Feld's research is made possible, in part thanks to generous donor support. If you'd like to contribute to his pioneering medical research, please go to www.uhnfoundation.ca/podcast. And for more on the podcasts, go to our website. www.behindthebreakthrough.ca and let us know what you think. We crave feedback. That's a wrap for this edition of Behind the Breakthrough, the podcast all about groundbreaking medical research and the people behind it at the University Health Network in Toronto, Canada's largest research and teaching hospital. I'm your host, Christine Coté. Thanks for listening.