

Season 1 – Episode 11 – Dr. Donald Weaver

Transcript

CHRISTIAN COTÉ

This is 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. Today's episode is the last of our first season of the podcast. We've loved hearing from you and please keep commenting wherever you listen to your podcasts. Of course, you can always reach us by email that's behind the breakthrough, all one word@gmail.com. There's so many UHN researchers pursuing cures and new treatments. So if you'd like to hear a season two of the podcast, please let us know. Now, onto the final episode of season one of UHN Behind the Breakthrough. Our guest today is Dr. Donald Weaver, award winning Senior Scientist and co-director of UHN Krembil Brain Institute. Dr. Weaver is a pioneer in a search to cure Alzheimer's disease. He joins us in a minute. But first, here's the backstory on Dr. Donald Weaver.

Growing up in North Bay, Ontario, while his classmates were outside playing hockey after school, Don could usually be found reading in the library. In fact, by age 12, he was plowing through the works of Greek philosophers. He was especially drawn to the teachings of Democritus. And his groundbreaking theory of the atom Democritus found that if you cut a stone in half, each half has the same properties. And if you keep cutting, you end up with a piece so tiny, that can no longer be divided. For young Don Weaver the lesson was complicated things can be understood when you break them down to their essence. Ever since he's been applying that lesson to understanding the brain in his search to discover a cure for Alzheimer's disease. Dr. Donald Weaver, senior scientist at the Krembil Brain Institute, welcome to Behind the breakthrough.

Dr. DONALD WEAVER

Thank you.

CHRISTIAN COTÉ

Going let's start with what is Alzheimer's disease.

Dr. DONALD WEAVER

Alzheimer's disease is the most common type of dementia. So dementia simply is a chronic progressive deterioration in brain function. Typically, to the extent that the individual is no longer able to care for themselves. There's lots of different types of dementia, but certainly within our

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society, Alzheimer's is the most common type of dementia. It's characterized by several features, such as clumps of proteins in the brain appear. These proteins are called Amyloid and Tau and they clump up and when that happens, then this person has Alzheimer's disease.

CHRISTIAN COTÉ

How did researchers land on these two proteins Tau and Amyloid as being a cause of Alzheimer's,

Dr. DONALD WEAVER

That is a touchy question whether or not amyloid and tau are the causes of Alzheimer's disease. So Alzheimer's disease has been around a long time, Alzheimer's described it very early in the 90s. Under a Dr. Alzheimer. And Dr. Alzheimer's described it very early in the 1900s. And it's been around and people appreciated it. And you know, for years, people thought it was normal aging or something like that. It's not it's a disease, it's a genuine disease. And in the 1980s, and 1990s, something called the amyloid hypothesis became popular. And so the amyloid hypothesis is that these clumps of proteins called amyloid are the cause. And this really arose because people were starting to look at brains of individuals who had passed away from Alzheimer's disease, and they saw these clumps, and they analyzed them. And they noticed that they were composed of these proteins, Amyloid and Tau and that's really where the impetus for that came from. Whether or not they're the cause, that's still something that is very hotly argued and debated.

CHRISTIAN COTÉ

I'm curious what happens to them in the case of brain disease?

Dr. DONALD WEAVER

Okay, so amyloid is a peptide, so a small, little protein, as long as it's by itself, you're okay, when you get two together, so they bring that diversity of two together, or three together, which is a tremor, these small little clumps of them are very toxic to the brain, they literally beat holes into brain cells. Once they start to clump, they become toxic to brain, and that destroys the brain. So a normal brain weighs 1.3 kilograms, when you die from Alzheimer's disease, your brain weighs 800 grams, you've lost half a kilogram of brain that's a lot of brains lose.

CHRISTIAN COTÉ

Do they cause the brain degeneration? Or is it they worsen it?

Dr. DONALD WEAVER

Once again, that's open to debate. I'm in the group that believes it causes the problem and so that amyloid clumps and when it clumps, it starts to destroy brain cells. That's called the amyloid hypothesis. It's been around for years. And the reason it's controversial, is that previous attempts to design drugs around it hadn't been so successful. So if the drugs don't work, is the hypothesis right? I would argue it's not the hypothesis that's wrong. It's the drugs that are wrong. They haven't had the right molecule.

CHRISTIAN COTÉ

I'm curious, what are the other theories on the degeneration of the brain when it comes to dementia and Alzheimer's?

Dr. DONALD WEAVER

There's multiple other ones. Another current very popular one is that it's due to inflammation of the brain. And so you hear people saying, oh, it's arthritis of the brain, it's an inflammatory disease. There are other individuals who believe that it is due to mitochondria. So mitochondria are the little energy packets that are within every cell. And that's some fundamental disease of them. So it goes on and on. There are a variety of different theories. All of them have pluses and minuses associated with them whether or not they're, you know, strong or weak. But the amyloid hypothesis certainly is the one that has attracted the most attention and probably continues to do so.

CHRISTIAN COTÉ

I don't mean to put you on the spot. But why don't we know with certainty,

Dr. DONALD WEAVER

The brain is the most complicated organ that we have, you know, and you'd like to hear that the brain is the most complicated thing in the universe, I don't know, we haven't been to every place in the universe to really make that statement. However, I am fond of saying, you know, if space is The Final Frontier Brain is the ultimate frontier, that from a neurologist speaking in an unbiased way, you know, so it's not like we're trying to sort out a trivial problem. This is really very, very complex, and very, very complicated. The other issue is, is the clinical trials, if you're doing a clinical trial, say for an antibiotic, you give it to the patient within several days, you know, if it's going to work, if you're doing a clinical trial and Alzheimer's, you got to give it several years to see if it's actually going to work. And so all of these are hurdles, or impediments, which really make drug discovery difficult, and really make it difficult to know if the compounds that we are developing are of any value or not.

CHRISTIAN COTÉ

So what's the prognosis for someone suspected of having this disease?

Dr. DONALD WEAVER

Right now the prognosis is not good. It also depends on the age you are when you first get Alzheimer's disease. Which brings up the other question, is it Alzheimer's disease? Or is Alzheimer's disease a group of diseases? Because if you have a person who is 52, and gets Alzheimer's disease, it moves rather quickly in that individual versus say, the 80 year old in whom the disease tends to progress much more slowly. And so you know, you go, maybe it's not even the same disease, they just seem to have a common endpoint. So this is another one of these hurdles that I was referring to, and trying to develop therapies to try to treat this. We don't even know if it's one disease.

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CHRISTIAN COTÉ

Well, I can tell you I know, it seems like in popular press, we use the terms interchangeably. dementia, Alzheimer's, confused?

Dr. DONALD WEAVER

Yes. I don't use them interchangeably. No, I don't. But yes, in the general, it is all Alzheimer's is dementia, but not all dementia is Alzheimer's, but Alzheimer's only accounts for about 75% of our dementia. Alright, so it does dominate at all it is or the dominant form it Yes. And it is, you know, the impending epidemic of our generation, because as our population ages, it's becoming a much more prevalent disorder.

CHRISTIAN COTÉ

Well, what are the stakes are like how many Canadians are suffering this disease and what cost

Dr. DONALD WEAVER

Right now, there's probably over 470,000 Canadians with this. And the economic impact is great, because these individuals are requiring nursing care. And it's not only that, it's the family, because members of the family can no longer work because they're at home caring for this individual. So the socio economic impact is truly immense for Alzheimer's disease and the other dementias.

CHRISTIAN COTÉ

In addition to me research, you're a clinician, yes, people with brain diseases. What do you offer your patients suspected of having the disease? Well, I

Dr. DONALD WEAVER

Think that the most important thing I can offer is a diagnosis. They come in all they know is that they have cognitive problems, they have memory problems. Sometimes they're terrified. Sometimes they're denying them. Often they don't have dementia, they have depression. It's really difficult to differentiate depression from dementia in some people. If you're in your mid 70s, your spouse has recently died. Things aren't going well. You might be depressed. And if you're depressed, your memory doesn't work the way it should. Your cognition doesn't work the way you shouldn't people go, Oh, you know, he's getting dementia, and the end up seeing is no, no, they have depression. And so you know, you have to determine does this person have dementia or not? And if they do have dementia, what type of dementia do they have? If they have a type called normal pressure hydrocephalus dementia, then maybe we can refer you to a surgeon and have a procedure done that might be of some benefit. If it's the other types, then, you know, we have some medications, they don't work terribly well, but to the best that we have, at the current time,

CHRISTIAN COTÉ

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These medications slow the progress, but no, no, no,

Dr. DONALD WEAVER

No, they don't slow the progress. They are symptomatic agents. So by that what I mean is as follows. If somebody gets a strep throat, so they have a streptococcal infection of their throat, if you give them aspirin, takes the fever away, helps with the pain, but the struct is still growing there that is a symptomatic agent. It doesn't have influence in any way shape, or form the natural history of a strep throat similarly the drugs that we have currently available for Alzheimer's disease are symptomatic agents. They temporarily help with the memory problem. But ultimately, final point is the final point and it doesn't influence the natural history of the disease.

CHRISTIAN COTÉ

And how much do we know about generation to generation in terms of the disease being passed on? I know a lot of people worry

Dr. DONALD WEAVER

Most Alzheimer's that we see is not genetic. Most of it is sporadic, a small percentage, you know, but 5% does have a very strong genetic component, but most of it happens.

CHRISTIAN COTÉ

And when you were talking about trying to give patients a diagnosis, especially for those of us in the aging category, we often worry about memory loss as a precursor, or perhaps an indicator of Alzheimer's. I've heard a saying that if, if you forget where you put your keys, that's not necessarily Alzheimer's, but if you don't understand what your keys are, for, that might be an indicator,

Dr. DONALD WEAVER

Certainly everyone loses their keys, everyone misplaces things and you know, if you have a strong family history of Alzheimer's and you lose your keys, they're in there going, Oh, no, it's finally happened. You know, no, no, relax, relax. Forgetting things is forgivable.

CHRISTIAN COTÉ

Okay, let's move into the world of Alzheimer's research. I understand there are essentially two primary avenues to try and solve the disease molecule and biologics, do you mind giving us a little primer on these two research pursuits?

Dr. DONALD WEAVER

Certainly. So currently, in 2019, if somebody is trying to come up with a therapeutic, an agent that will help somebody, we do have these two avenues open to us. The first one is what we call small

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molecule. So that is something like aspirin, like penicillin, in the world of chemistry, it's a small molecule, and it is something that inorganic chemists can make. Now, the other alternative are these biologics, these are proteins, these are big proteins. These are things like antibodies and whatnot. They've come into the foreground in the last, you know, five to 10 years, whereas the drug molecules they've been around for a century. So these are the two very different approaches. And you know, there are things that he said positive and negative for both approaches, as we consider their utility for the treatment of Alzheimer's disease.

CHRISTIAN COTÉ

So molecules is a fancy word for drug

Dr. DONALD WEAVER

Molecules, a fancy word for drug, biologics, biologics, I would say is the word for something bigger, an antibody, a protein, something that is much larger.

CHRISTIAN COTÉ

If that was to get to a stage where it's safe and useful for treatment. What would it look like? Again, a pill?

Dr. DONALD WEAVER

No, no, the these are usually injectables I saw so you don't swallow these they are normally injected.

CHRISTIAN COTÉ

And the path you went down is molecules. Yes. So big picture, what are the challenges of designing a drug?

Dr. DONALD WEAVER

Ah, there's lots of challenges in designing a drug, especially for a neurologic disease, such as Alzheimer's disease. Me and our task is we have to sit down with a blank sheet of paper in front of us and hopefully not a blank mind looking at it, and doodle up a molecule doodle up a structure that we think can bind to amyloid or bind to tau or somehow influence them. But that's not enough. When we design this molecule, it has to have the ability to be swallowed, to be absorbed, to make it through the liver to be distributed in the blood to get across the blood brain barrier. And to get into the brain. I really find the blood brain barrier in the liver most annoying as a drug designer. To me, the perfect person would have no liver and no blood brain barrier. But such individuals do not exist. That's not going to happen. No, no, no, it's not going to happen. But I can wish.

CHRISTIAN COTÉ

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So let's turn to the working your lab starting with how and when you landed on the decision to focus on stopping these two proteins. Yeah, tau and beta amyloid from clumping? What led you to think that's the way to go?

Dr. DONALD WEAVER

I've been working on this a long time. Talking three decades, are we Thanks? I appreciate that. Yes, it's reminded success. I

CHRISTIAN COTÉ

Didn't want to that you have a few gray hairs here today, Dawn,

Dr. DONALD WEAVER

That's because only have a few hairs. So I've always found the brain fascinating. The brain is what makes you you. It is the most characteristic organ in your body. And so you know, I've always felt very strongly about it. And certainly then if you look at the diseases that are afflicting humanity, Alzheimer's disease and dementia, they're amongst the worst. It robs you of your memory, it robs you of those things that make you you. And so because of this, I really felt quite compelled that and when I was training, I already found these stories to be among the most heart wrenching the families who are being destroyed by having a family member with dementia. And so because of this started in the early 1990s, and at that time, certainly amyloid and tau were just starting to come up, you know, as important elements. And so we join that bandwagon, way back then.

CHRISTIAN COTÉ

And in terms of the design of the drug, what are you trying to do with these to the bay, beta amyloid? How what are you trying to do?

Dr. DONALD WEAVER

There are a variety of approaches to it and other labs around the world are taking various different approaches from us, but our approach is as follows. When you have beta amyloid, all by itself, just sitting there all by itself It's not toxic, right? It's when it becomes a dimer or trimer, that's two or three of them start to stack on each other. So I often compare it to piling logs into a log pile, right? The one log is fine, but you get to three starting to pile, that's a problem. So I look as are drugs as bumps on a log. And so if I can come up with a drug molecule that will bind to beta amyloid, such that when the next amyloid comes along, it can't stack itself on top, because there's that bump there, then it'll keep them in that on aggregated form, and therefore keep them non toxic. And the exact same thing applies to tau when it's an aggregated, okay, aggregated problem.

CHRISTIAN COTÉ

So you mentioned the first sort of step in your research is designing the drug you do this with computer modeling?

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Dr. DONALD WEAVER

Yes, we do. So it's trying to design a hand to fit into a glove, we used to talk about trying to design a key to fit into a lock. But that's not accurate. Because a key is stationary, it's fixed, it doesn't change its shape. And the lock doesn't change its shape. When you're trying to design drugs to finish receptors, that receptor can be a moving target, it can sometimes change its shape. And that's why I say we're trying to design a hand to fit into a glove, this is a dynamic fit. We think we know the shape of the glove, that is the beta amyloid, and now we have to design the hand, that is a molecule which will go and bind to beta amyloid. So to do that, we do a whole bunch of mathematical calculations and simulations in the computer and try to design molecules that we think will work. And once we design them, we make them

CHRISTIAN COTÉ

How do you know what beta amyloid, for example looks like?

Dr. DONALD WEAVER

Well, we don't in medicinal chemistry, this is this whole area of designing drugs, we're always talking about the gold standard is a crystal structure. That is someone fished out that protein or fished out that thing and determined its shape. Well, you can't do that with beta amyloid. It's oily, it's gooey, it just doesn't do that. And so because of it, we do know the atoms that are in it, and what's it composed of so therefore, we do the sophisticated mathematical modeling, and to say, well, you know, what we think that's what its shape is, we think that's what it looks like,

CHRISTIAN COTÉ

Is there ever a time you think where we actually will be able to identify exactly the property makeup of beta amyloid?

Dr. DONALD WEAVER

I remain optimistic, but you know, if you're in drug design, you are by definition of pathologically optimistic person.

CHRISTIAN COTÉ

Okay, so where to next you've designed, I don't know, in terms of your computer modeling how many compounds sample

Dr. DONALD WEAVER

Oh, we have designed many ones many. So I mean, if I, if you want me to date back to the beginning, we probably have designed 30 40,000 molecules, on any given time, we have one particular molecule that we are focusing on, and we make analogs of it. I call this the methyl ethyl propyl futile approach to chemistry, where we simply make analogs of it and hope that analog is which analog is if you have the first molecule that works, you've designed a molecule that fits in, and then we take the molecule and we break it down into its bits. And we then systematically alter all of these bits, and try to optimize the molecule in a piecemeal fashion. And every time we make another different variant of it, we call that an analog.

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CHRISTIAN COTÉ

So over the years, on your computer, you've designed many hands of 1000. Yep. Right. So what how do you know which ones of these to take to the next stage, which I guess is the lab?

Dr. DONALD WEAVER

It's a complicated process. And so we design molecules, and then we sit back and go, are they drugged? Like, does this molecule look like a drug? Because all Alzheimer's is dementia, but not all dementia is Alzheimer's? Well, all drugs are molecules, but not all molecules are drugs. I could dream up a molecule, you could swallow it and be blown apart in your stomach and never go anywhere. Or it doesn't have what it takes to be absorbed, or the liver would destroy it. So because of that, it has to have drug like properties. So we design lots and lots of molecules, but then we sit and go, Yeah, you're kidding. That's not a drug.

CHRISTIAN COTÉ

So when you say that's not a drug, you mean it's not safe.

Dr. DONALD WEAVER

That it doesn't have what it takes to make the journey from gums to brycie. You know, if you swallow it, it's going to get destroyed in the stomach, it's going to get stored in the liver. It doesn't have what it takes to do that journey and to do it well.

CHRISTIAN COTÉ

So what percentage ended up going to the lab to be made?

Dr. DONALD WEAVER

Oh, small, probably under 5%. But I mean, I do have an awful lot of synthetic chemists in my lab who work long hours synthesizing and making molecules.

CHRISTIAN COTÉ

So once you're into the lab with this small, small percentage of molecules you design, how many compounds emerge from that stage?

Dr. DONALD WEAVER

Oh, we probably only advanced about one and 100.

CHRISTIAN COTÉ

Wow.

Dr. DONALD WEAVER

Yes.

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CHRISTIAN COTÉ

And those are the ones that go to the next stage in terms of animal modeling.

Dr. DONALD WEAVER

Yes, that is right.

CHRISTIAN COTÉ

So give us a sense of some of the results you have.

Dr. DONALD WEAVER

Well, if I was a veterinarian who specialized in demented mice were there, we've got it solved. We have cured Alzheimer's in mice many times. But you know, there actually seems to be a difference between most brain and human brain. I know, shocking, that may sound. And so even though we have had compounds that have worked quite well, in the various models, that around, taking a compound all the way to human trials is prohibitively expensive. We've only done it once. And that was not a success. So, you know, it's tough to know, the question that is also asked is, How good are the animal models?

CHRISTIAN COTÉ

How do you know how you know when that is safe enough? And perhaps effective enough to go to a human clinical trial?

Dr. DONALD WEAVER

Well, I think that answer is determined by who's willing to back the trial. So by that, I mean, a trial is going to be in the hundreds of millions of dollars, you're not going to get that from a CIHR government grant. And so you're going to have to partner with industry. So we have to go out and present ourselves to potential industrial partners, and say, This is the target. This is the molecule that we have, here's the data that we have on it. And they may look at us with enthusiasm, or more likely with skepticism, and try to turn because ultimately, it is a company that's going to foot the bill. And it was easier 20 years ago. And the reason I say that is is that the last 204 I keep track of them, the last 204 trials and Alzheimer's have failed.

CHRISTIAN COTÉ

And how many trials have there been?

Dr. DONALD WEAVER

About 204? For disease modifying trials, right? You know, if you're a corporation, and you have shareholders, and you're going, yes, let's invest several 100 million in this, somebody might say the last 204 trials have failed? Why should you have optimism. And so this really is a stumbling block. And going forward, these trials are so expensive, the need is so great. This is a substantial risk, it's a substantial risk for an organization to take. This is not designing an antibiotic.

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CHRISTIAN COTÉ

So with that research landscape in terms of there's a need that you absolutely, because of the cost must partner with industry. Yes. Where do you go?

Dr. DONALD WEAVER

Well, there are still companies that are interested. And so we do interact with a number of corporations that are still interested in Alzheimer's disease. And I mean, they have to look at it from a risk benefit ratio from their own personal point of view. Certainly, if someone gets a drug that's going to work, it's going to sell well, it's going to do well. But the odds are certainly pitted against you.

CHRISTIAN COTÉ

So are you able to give us a sense of I know this is predicting the future, but in terms of where you're at with your compounds and molecules in terms of safety, effectiveness, and a company willing to partner with you.

Dr. DONALD WEAVER

Yeah, so I mean, in my own highly unbiased way of making this observation, we have gorgeous molecules, I don't get out much. So I find molecules gorgeous. And they are pretty, they are very pretty molecules. They have what it takes to go from gums to brain, they bind to amyloid, they bind to tell they do what they're supposed to do. They're very effective. And we have a relationship with a French pharmaceutical company that is looking at co developing these particular agents with us. But this is a long road, and there are many potholes in it. And any one of these potholes can stop you dead in your tracks. And so we're realistic, but we're optimistic.

CHRISTIAN COTÉ

When you say it's a long road, are we talking about the logistics and negotiating? linters?

Dr. DONALD WEAVER

Well, I mean, that that's, that's some of the potholes certainly, but I mean, the other ones are, we have done toxicity studies. But you know, once they start to advance, and they start to make it to early human studies, new toxicities can emerge, new problems can emerge. Because we're dealing here with an older population, a much more frail population, and your molecules have to be a little gentler.

CHRISTIAN COTÉ

So you're not locked in in a time line right now, in terms of when you think when you're working on Nakota human clinical trial,

Dr. DONALD WEAVER

I, I have optimism that we will be declaring a clinical candidate sometime in mid 2020. But we have to bounce down that pothole laden road that I mentioned, and any one of those bumps could slow us down.

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CHRISTIAN COTÉ

You actually had an experience, right? If I'm right, with a human clinical trial for Alzheimer's, we Yes. You're back at Queens in the late 90s.

Dr. DONALD WEAVER

Yes, that's right. We developed a compound called Ultimate clever name a medication for Alzheimer's. And, you know, yeah, we took it to phase three, we went to phase three, it was in 2000 people it failed. It's probably one of the 204 trials that are out there. And so we tried, we failed, but I don't really regard that as a negative. Because you learn you learn an incredible amount from each failure. You know, I'm considered to be one of the cheerleaders for the amyloid hypothesis. Yeah, and I go you you're standing and you're looking and there's so many different ways you could go. There's so many different paths you could go down. And every failure takes another one of these paths off. And so it's helping us. So I don't think we should look at it negatively. I think we should look at it as an opportunity.

CHRISTIAN COTÉ

It sounds like you're on the verge of getting to another Yemen claim. Yes. What's that mean to you?

Dr. DONALD WEAVER

Well, hell of a lot. We have been doing this for 25-30 years, the few hairs that I have left our r&d grain. And so I would like to think that I have a shot at getting a compound here that would make a difference. And so I feel quite strongly about that.

CHRISTIAN COTÉ

You're listening to Behind the Breakthrough, a podcast about groundbreaking medical research and the people behind it at the University Health Network in Toronto, Canada's largest teaching and research hospital. I'm your host, Kristen Cote. We're speaking today with Dr. Donald Weaver, co-director of UHS Krembil Research Institute, and a pioneer in the search for a cure for Alzheimer's disease. Don, there's a story you tell of a moment where I would maybe even call it an epiphany that led to you going down this road of research today. It goes back to your fourth year of med school. Is that right? Can you tell us the Boxing Day story?

Dr. DONALD WEAVER

Ah, yes, being a medical student, I had the joy of working the Christmas vacation. We had just done our clinical rounds of having seen all the patients. And it wasn't a happy event, we had just seen about 30 individuals, you know, many of whom were devastated. And I was really quite sad. I was back sitting at the nursing station, starting to do notes because we all have to the nodes. And at the nursing station, there was a radio playing very quietly in the background playing some very happy, joyous Christmas music. And during that time, one of our patients had a cardiac arrest and wasn't doing well. And I was sitting there struck by the incongruity of it all of listening to Christmas music while you know somebody is struggling for their life. And the angst that that found he was going through the emotion that that moment was steeped in. And that certainly was one of the times

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when I went, dammit, I have to study brain and I have to do what I can to come up with therapies for people who have brain diseases.

CHRISTIAN COTÉ

And part of that epiphany, I guess that the effect it has is that when you finished med school, you and I become a neurologist. But you also decided you needed a PhD in chemistry would Yes, I understand a very unique set of skills.

Dr. DONALD WEAVER

Yes, some people would say crazy. But yes, the word unique is much more applicable in my mind. Yes.

CHRISTIAN COTÉ

And getting those skills was not a smooth journey for you.

Dr. DONALD WEAVER

No, no, it wasn't. I did a residency and became a neurologist. And then I went back and did a PhD in chemistry, which is a little unusual. Most people do PhD before their MD if they're going to do it, or combined. Certainly not afterwards, it was the most financially intelligent move of my life. Also finding a chemistry department that was willing to take me it was also a wee bit of a struggle. They were wondering, you know, you're a physician, what do you want to do PhD in chemistry for any kind of if you're a chemist, and you don't understand the value of your own discipline?

CHRISTIAN COTÉ

You're told, basically don't do this?

Dr. DONALD WEAVER

Yeah, yeah. There were chemistry departments that said, No, what's wrong? Don't you like medicine? I said a lot of medicine. But I think that chemistry is something to bring to medicine. So yes, I did a PhD in organic chemistry. Anybody who's applied to medical school has fond memories of their organic chemistry that counts as sarcasm, and it tends to be a rather stressful course for many people.

CHRISTIAN COTÉ

Where does all this determination come from?

Dr. DONALD WEAVER

Oh, wow. Must be my mother. She tolerated me.

CHRISTIAN COTÉ

That's resilience, isn't it?

Dr. DONALD WEAVER

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Okay. Yeah. Resilience. Yes, that's right. I like that word to like, just like unique. That's a much better word.

CHRISTIAN COTÉ

For a number of years. You had a successful practice going and lab still do in? I'm going back home? Yes. In Halifax.

Dr. DONALD WEAVER

Yes.

CHRISTIAN COTÉ

What convinced you to uproot your research lab, your team, your family to come to Toronto.

Dr. DONALD WEAVER

I like to Halifax still do like Halifax. One of my son still lives in Halifax. And I must say the seafood much better. This was an opportunity. I am committed to drug molecules. I'm committed to advancing drug molecules, the facilities, the laboratory resources, etc. Here, were sufficient that it would certainly fast track and improve our likelihood of success in this endeavor.

CHRISTIAN COTÉ

We talked at the outset about the stakes of these degenerative brain diseases, dimension Alzheimer's, some are calling an epidemic. Yeah. Do you feel pressure?

Dr. DONALD WEAVER

No, I suppose just because everyone's failing. So if everyone's failing, you go, Well, if I fail, I'm in a crowd. I'm in good company. I feel pressure in terms of we have people who donate money to us. We have families who have a loved one with dementia, and they are helping to support us. Do I feel pressure from them? No, they're not pressuring me, but I feel an obligation to them that we would like to deliver on our promises, at least to do our best to come up with something that works,

CHRISTIAN COTÉ

Yet, medical research takes time certainly does. How do you reconcile them that need? I don't know if it's like a friction, but that need for a cure with the rigor that science requires.

Dr. DONALD WEAVER

That can be frustrating. But you know what? It's necessary. If you rush it, you get a bad product, and the end result is not good. So you go quiet and flee, you move slowly, and you do it right.

CHRISTIAN COTÉ

I'd love to know your approach to failure, because we're not taught how to deal with failure. And you probably face that in your lab a lot.

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Dr. DONALD WEAVER

Oh, yes. I mean, we say it's called research, because you have to repeat everything is just not called search, we fail and we fail. And, you know, we don't look at them as failures, we look at them as stroking another wrong road off the map. And if you do that, you can, you know, look at it in a positive way. I mean, every time we get a positive result in the lab, everyone gets excited. Oh, you know, this work. This worked. Well. We had a lab meeting this morning, and we were talking about some positive results. And you know, you can feel the excitement in the lab, and oh, wow, that was that molecule that behaved really well, you know, that sort of good properties were happy. That's a nice thing to happen.

CHRISTIAN COTÉ

I'm curious, in this work, is there ever a sense of isolation for you

Dr. DONALD WEAVER

No, we have a large lab, and so we have diffusion of misery when things fail. So we all sit around going long, you know, it didn't work, but better luck next time. And there are so many groups around the world working on Alzheimer's, we may not always share results, because it's a competitive space. But there are other people to commiserate with.

CHRISTIAN COTÉ

Do you ever have doubts?

Dr. DONALD WEAVER

Hell no. I, you know, remain passionate about what we do with just a hint of arrogance. And I think that that's necessary. If you want to design drugs, you have to think that you're the one who's going to get it, although deep down in you know, that you're likely to failure is very high.

CHRISTIAN COTÉ

I understand you write poetry, indeed, where Alzheimer's disease is a central theme. Yep. What's the story behind that?

Dr. DONALD WEAVER

Well, I call them therapeutic poems. I see families that have Alzheimer's disease. And you know, I don't do a lot for them to be blunt. I give them a diagnosis, but I don't really have anything that works. And the families are struggling. And so occasionally, I'll write a poem. And I used to do that more. So in past I've been doing a bit less lately because of other time commitments. So you know, I write poems and the some families like them, we actually have I have, I have given them to the patients. Yes. And the family, regrettably, one was an English major, and I got a critique that was perhaps less than kind, but unfortunately, probably accurate. But I like to say it's the heart and it accounts. I've submitted some to journals, some have been published, I certainly enjoy it. I've written a short story that was in the Canadian Medical Association Journal. And so we've had a number of these things out there. You know, I kind of like writing it. I'm not great in English, by any means. But it's fun. And I enjoy it.

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CHRISTIAN COTÉ

What kind of reaction have you gotten from families and patients?

Dr. DONALD WEAVER

Usually cheerful, and in any positive way? Because they're suffering, and they're suffering at multiple levels. And I think they're frustrated. They don't know if other people appreciate what they're suffering. And I think that this indicates to them that there are people who do understand,

CHRISTIAN COTÉ

Is there anything in this act of writing that's therapeutic for you?

Dr. DONALD WEAVER

You? Oh, certainly, seeing patients every week for whom I have to give bad news. You know, that's not pleasant either. And so writing like, this is something that I enjoy, and it lets me express some of my own thoughts.

CHRISTIAN COTÉ

Do you ever get weary of that? Not being able to offer?

Dr. DONALD WEAVER

No, no, I've been at it for many years. And every patient is an individual, every family is an individual family. You learn something from every family from every patient, you enjoyed the moments that they do have with them. And you know, because of that, I can't say it's I get down from it. I mean, it's not a happy work sometimes. But the interactions with other people certainly has its own rewards.

CHRISTIAN COTÉ

Poetry, of course, is a form of storytelling. I understand you also use this to inspire your team. Tell us about the Friday meeting.

Dr. DONALD WEAVER

Yes, every Friday morning, we have a meeting at eight o'clock sharp much to their delight. We go over our results, but I start the meeting always with a story a story of a patient. And of course, I have to be careful that no details are given out. But I keep them for proficiently, yes, for privacy reasons. I keep them sufficiently anonymized that no one knows of whom I am speaking. But I tell them, This is a story that I saw, you know, in clinic this week, and I run it by them and I do that every week, just to remind them that yes, they're they're designing molecules and you using mathematics to design molecules that will bind to amyloid and tau. But the end result is a much more personal picture. It's got a human face on it.

CHRISTIAN COTÉ

I don't mean to belabor this point, but you've, you've been at this for a while.

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Dr. DONALD WEAVER

Yeah. Thanks. So yeah, you've made that point. Yeah. Is this personal for you? I certainly it is. Yes, as I said, trying to come up with things seeing patients all these years, it's very personal.

CHRISTIAN COTÉ

Have you thought at all about your legacy in this world of trying to solve

Dr. DONALD WEAVER

No, no, hopefully, that's not what's motivating me? If it was, I'm in the wrong area. You know, it's a puzzle. It's a wonderful puzzle. And if you are working on puzzles, and you solve one, you feel good. And this, to me is one of the biggest puzzles out there. And if we are the people who can put the pieces together and come up with the answer, the inner feeling of happiness will be sufficient. Thank you.

CHRISTIAN COTÉ

So what should we look for next one, Dr. Donald Weaver's lab,

Dr. DONALD WEAVER

Well, probably more failures, because the road to success is littered with failures. Do we think there's success down the road? Of course we do. We wouldn't be up there every day doing what we're doing. But it's going to continue to be a long struggle, but I remain optimistic.

CHRISTIAN COTÉ

Dr. Donald Weaver, Senior Scientist and co-director at UHS Krembil Brain Institute. Thanks for speaking with us and continued success.

Dr. DONALD WEAVER

Well, thank you ever so much.

CHRISTIAN COTÉ

That's a wrap for season one 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. We've loved hearing from you throughout the season. And please keep those comments coming wherever you listen to your podcasts. Or you can always reach us by email that's behind the breakthrough. All one word@gmail.com There's so many UHN researchers pursuing cures and new treatments. So if you'd like to hear Season Two of the podcast, please let us know. I'm your host, Christian Cote. And a big shout out to our dedicated production team. That's Damien Kearns, Tim Chipman, Lea Zeltserman, Jordanna Goldman, Jessie Park, and Katie Sullivan. Thanks for listening.