

0:00 Dr. James Eubanks

[Your Complex Brain theme music] Failures are going to be more common than successes. That's just the nature of science. What keeps a lot of us going is knowing that, at any moment, you're going to be able to see something that's never been seen before in the history of the world. And, in the context of the disorders that we investigate, knowing something more brings us one step closer to finding a treatment that we currently don't have.

0:32 Heather

[theme music continues] This is Your Complex Brain, a podcast all about the brain, the diseases that impact it, and the path to finding cures. I'm your host, Heather Sherman, and I have the great pleasure of working alongside the team at the Krembil Brain Institute in Toronto, Canada, a leader in brain research and patient care. In each episode, we'll take you behind the scenes into our clinics and research labs to meet the game changers of the future. We'll also empower you with the latest research to help you take charge of your own health. You'll hear directly from people who are living with brain disease, as well as their loved ones and the care teams who support them. Join us on a journey to unravel the mystery of your complex brain. [theme music continues then fades out]

[bubbly, urgent electronic music] When Bryn Ladly was born, she was a smiling, happy, and healthy baby, hitting all of her developmental milestones. Then, at six weeks old, she began having seizures and eventually was diagnosed with CDKL5, a rare and debilitating genetic disorder that has no cure. Natalie Ladly is Bryn's mother and chief advocate. Here is her story. [music fades out]

1:57 Natalie Ladly

[gentle electronic music] My name is Natalie Ladly, and I'm the President and Fundraising Chair for CDKL5 Canada. We live in Heathcote, which is just outside of the Collingwood area in Ontario, and we have three children. Our youngest daughter, Bryn, has CDKL5 deficiency disorder, also known as CDD. She's seven. And then we have our oldest daughter who's Reese, she's 12, and Cullen is 10.

CDKL5 is a mutation in the CDKL5 gene, which essentially stops the production of the protein that's essential for normal brain development and the development of neurons. And so, the impact of that is children have intractable epilepsy, and neurodevelopmental delays, so it can impact cognition, motor skills, vision, and speech. Bryn was born full term. She was a healthy baby. I had a healthy pregnancy, and around six weeks of age, she started having seizures. She was put on some anti-epileptic meds and, by the time she was four months old, she was on three different anti-epileptics with no relief from the seizures. So, we went through with PET CT scans and MRIs and there was no abnormalities, at which point the neurologist suggested that we do genetic testing. So, it was right around nine months old when we got the diagnosis, which was unfortunate timing for us because she happened to be having a little honeymoon period, and so she'd been seizure free for three weeks and we had convinced ourselves that she just had this random infant epilepsy and she'd outgrown it. [music fades out] And then, of course, we got the devastating news that she had CDD.

3:40

[light electronic music] Getting the diagnosis was really tough. I happened to be alone at the hospital when we got the news. So, all of a sudden, you're receiving this information and you're looking at your baby, and all of a sudden you find out that your child is likely never going to walk and never going to talk, and will never live independently, and it was crushing. Like, it was so hard for me to wrap my head around how this doctor could know, with certainty, all of these things about my child and, you know, and then, all of a sudden, you hit like this wall of grief because all of these hopes and expectations you

have, that you don't even realize you have, you know, you realize that none of those are going to happen. And so, it was pretty rough the first couple of days, but then I came home and my husband and I, you know, talked about it and we just decided we're going to just take it one day at a time and that's how we can move forward. And so, that's kind of what we've been doing. We just addressed each symptom as it comes up and try not to get overwhelmed with the caregiving aspect of it.

Bryn is funky seven-year-old. You know, if you were to see her in an arena or at a soccer game, which is where we spend most of our time, you would probably think that she just was oblivious to the world around her. She's in a wheelchair. She's nonverbal. She has a feeding tube. On initial glance, it doesn't look like she's very engaged, but everyone who knows her well-- I always know when a teacher knows her well because they say, "Oh, she's such a drama queen," and I'm like, [chuckling] "Okay, that's Bryn." So, somehow, without speaking a word, and she doesn't gesture—she really has very limited ways of communicating—but she manages to capture everybody's heart, and Eric and I always say that's her superpower is that she charms everybody that she meets.

She loves her friends. She's in school. She's included in her grade two classroom and participates in as many different activities as she can, and she goes horseback riding as part of her hippotherapy. Hippotherapy is a type of physiotherapy, so Bryn sits on the horse, she rides frontwards, she rides backwards, she lies down on her stomach and on her back, and it not only provides her impact that she doesn't get because she doesn't walk, but also, the stride of the horse, when it walks, moves her hips in the way that mimics walking. And so, it's really good for her joints, and it also gives her the feeling of vestibular motion that she doesn't get from walking. She loves being in her swing and in the swimming pool and, you know, there's an abundance of activities that she thoroughly enjoys participating in. She just misses a lot of the sort of typical activities that a seven-year-old would be doing.

Bryn communicates a lot with her eyes. She gives a stink eye if she's not happy with you far more often than she gets a smile, if I'm being honest, and if she's excited, she'll kick her legs out or she'll sometimes squeal. She will give us smiles occasionally but, more often than not, she's just quite content and she's a very mild-mannered little girl. She doesn't complain, she never cries, and we joke that she's the easiest to get along with because she doesn't talk back. [music fades out]

So, Reese and Cullen both have really close relationships with Bryn, but they interact with her really differently. So, you know, they both are affectionate and care about her and care for her, but Reese, who's 12, is much more practical in her approach. She likes to help. She sets up feeds for Bryn, she'll change her, she makes her medicine. She's very hands on in that respect. And then, Cullen is like the sensitive soul who just will like climb on the couch with her and snuggle her and read her a million Peppa Pig books. And so, it's interesting; they have totally different relationships, but I think she values both. You know, she gets to engage with both of them, just in different ways.

[pensive electronic music] Bryn is currently on three anti-epileptic medications, and she also takes CBD oil—cannabinoid oil—which helps control her spasms. She's having approximately two seizures a day that vary in length right now between four and five minutes, which is good compared to this time last year. Her average seizure length last year was between 10 and 12 minutes. And, for us, we find it's the most difficult part of CDKL5. There's a huge array of symptoms, and they all require different levels of care, but the seizures are the part that impacts our life the most. It sort of stops whatever activities you're doing. If we're having dinner, Eric and I have to get up and leave the table. If we're in public, it doesn't bother us, but it bothers everybody who's around us. It makes people uncomfortable, which, you know, is never a great feeling for us or for Bryn. And, you know, it just steals all of Bryn's joy. Like,

when she's having a good day with no seizures, she's bright eyed and she's engaging and, you know, you can really feel like you're communicating with her and she's reciprocating that, but the seizures just steal the show. [music fades out] Like, she's exhausted and she has a hard time clearing her airways and, you know, it's just really burdensome.

[rhythmic electronic music] Caring for a child with special needs, it's hard. It's a heavy load, and I would be lying if I said it's all sunshine and roses. We're a silver lining family and we do try to, you know, find the humour in situations, and try to make the best of it because, at the end of the day, we don't really have a choice. If we could have a healthy child, that would always be the option that you would choose so, you know, it's a struggle, but it does make you incredibly grateful for when your child is healthy and thriving, and she genuinely, somehow, without speaking a single word, brings out the best in everybody around her, including us, our friends and family, our community. Everybody reaches out and, you know, digs deep in their pockets and in their hearts, and she's included at school in ways that I never could have ever expected or imagined and, you know, it just kind of makes your heart swell, and I'm like, "Oh, my gosh, you know, I would never have known that this world existed if it wasn't for Bryn".

I ended up joining the board of CDKL5 Canada when Bryn was one and a half, and it was, for me, at the time, in a situation where I felt like I had no control and I had really no ability to do anything for Bryn to help her other than caring for her. You know, being on the board made me feel like, "Okay, this is something that I can accomplish. I can work towards schools, we can help create awareness, we can fundraise, and invest that money into research, and maybe one day, there'll be treatments or a cure and, even if it's not for Bryn, then if other families don't have to suffer through the experiences that we're suffering through, then it's all worth it". [music fades out]

10:35 Heather

[gentle electronic music] Joining us now is Dr. James Eubanks, a senior scientist and Research Division Head at the Krembil Brain Institute. Dr. Eubanks' research looks at how brain function is altered in specific rare neurodevelopmental conditions, such as CDKL5. He is also developing new therapeutic strategies to better treat, or one day even cure, those disorders. Welcome, Dr. Eubanks. Thank you so much for being on the podcast today.

11:04 Dr. James Eubanks

Oh, thank you very much, Heather. It's great to be here. [music fades out]

11:06 Heather

I wonder if we could just start briefly talking about your personal journey and research. You know, what did you originally set out to study in terms of your interest, and what brought you to studying rare diseases?

11:18 Dr. James Eubanks

As a graduate student, I was in one of the original Human Genome Project Lab at the Salk Institute in California, and one of my thesis projects was to map an area in the human genome where an unusual neuropsychiatric condition had been mapped in a couple of different families. Following that, we really started to appreciate the power of genetics and genomics in the late 1990s, roughly, and that carried forward with my interests in defining rare genetic conditions.

When I started my lab, we were working under that larger umbrella and Rett syndrome became the focus, somewhat by serendipity. We were identifying a number of different factors that were expressed

in the brain, therefore playing a role in neural development, and one of the first factors that we identified at that time was unknown, but it had a close relative or something that looked like it, and that was this MECP2 product which, a few years later, was identified by the Zoghbi group as being the cause for Rett syndrome, and we had been working on it without the realization that its altered function caused one of the very rare neurodevelopmental disorders in which I had an interest. And so, we spring boarded into working on Rett syndrome, based upon those observations.

12:51 Heather

Can you explain what MECP2 is? What does it stand for, and what does it do?

12:55 Dr. James Eubanks

Yeah, certainly, MECP2 is an abbreviation for methyl CPG binding domain containing protein type 2. Nobody likes to say that, so we just call it MECP2 or MECP2 as the abbreviation. The gene encodes the protein of the same name and, normally, it functions by binding two parts of the DNA and changing the topography of the DNA within the cell's nucleus, and the changes that it provides determines, often, whether or not that region of the chromosome will be able to be active or inactive. In Rett syndrome, the MECP2 is dysfunctional, and regions of the genome that should be inactive actually regain too much activity. And, to date, there are some very promising results that are emerging. We know a lot now about the MECP2 function. What we know very little about is what happens when MECP2 isn't there before the symptoms appear. So, there's a big, black box that exists between the stuff in the nucleus that's not being properly regulated, and how that changes things in the cell. We need to know that because, as soon as you identify something that is not functioning properly within the cell, it's a therapeutic target, at least potentially, a therapeutic target. So, it's easy to say that we know what causes Rett syndrome; it's a mutation in MECP2, and that's true. But, if you scratch a little deeper, we really don't know what the absence of MECP2 causes to go wrong, that is actually what's responsible for the condition seen in the patients.

14:51 Heather

So, are you currently working on developing new approaches or therapeutics to try to address this?

14:56 Dr. James Eubanks

We've got a target that looks promising. Unfortunately, drugs to properly engage it don't exist so, with the help of the medicinal chemists on site at Krembil, we are making a new drug.

15:10 Heather

That's amazing. A new drug would really be a breakthrough in this area. [pulsing electronic music] Dr. Eubanks, I know this research originally started with you looking into Rett syndrome. Can you explain, what is Rett syndrome, exactly? And, tell us a little bit about it. What are some of the symptoms?

15:26 Dr. James Eubanks

Yeah, Rett syndrome, it is a rare condition, but amongst the rare conditions, it's probably one of the more common ones. It almost always affects females. There are genetic reasons for that. Rett syndrome patients typically are unable to speak. If they are able to walk, it's typically with poor coordination. Often, they have stereotypic hand-wringing motions. They clasp their hands frequently, they will bite at their hands. They have a spectrum of other comorbidities. It is one of the more insidious conditions, and this one is particularly, if you will, guileful, because of the way it presents. The children who will be affected tend to be born normally. There's no indication that they're going to develop this condition. They will start relatively normal infant development, and then somewhere, typically, around the first

anniversary, their first birthday, symptoms will start to appear and often, quite rapidly, they will lose some of the acquired skills that they had already reached, some developmental milestones that may have been met will be lost, and it can happen very frequently. I know several parents who can actually tell you the day that their daughter developed Rett syndrome. They were playing in the sandbox with their siblings on Tuesday, and by Thursday or Friday, they were unable to get in the same sandbox.

16:53 Heather

Are there any treatments for Rett syndrome?

16:55 Dr. James Eubanks

Not really. There's a lot of interest in trying to manage the comorbidities as best as possible. In some patients, that's achieved better than others, but there is no cure. There's the potential for cure, though, and I think this is a very important distinguishing factor for Rett syndrome is that it's one of the few and probably the first genetic neurodevelopmental condition that's been shown, at least in experimental model systems, to be correctable. In our lab, we were able to look at our animal models that had developed quite severe Rett syndrome symptoms, and in using some molecular trickery, things that aren't clinically applicable but can be done in the experimental world, we are able to reverse those Rett syndrome symptoms. And so, based on that, there's great hope that this condition is not irremediable and that, even in adults with Rett syndrome who are quite severely affected, the potential for rescuing much, if not all, of their normal function does exist. [music fades out]

18:01 Heather

So, you were actually able to reverse the symptoms? That's incredible. So, what's the next step, then?

18:08 Dr. James Eubanks

The gene therapy aspect is where that work has led, and there are some very strong centres throughout the world that are working on those gene therapy applications, but our lab is not one of them. It's beyond our scope. What we're interested in now are developing more pharmacological approaches, so drug treatments that patients can take to improve their quality of life while those gene therapy possibilities are being tested, and I say "possibilities" because there's a bit of a misnomer that the thought that gene therapy is to be a cure. That's possible but, more likely, gene therapy is a treatment and we don't know the degree of benefit that can be achieved from the gene therapy applications. Same with the pharmacology; it's a treatment and, if we can get the right drug, there's a full spectrum of potential benefits that could be had, the maximum being, you know, reversal of symptoms. More likely, it's going to be any improvement and, for a condition that is as severely affecting the quality of life of individuals as Rett syndrome does, any improvement is welcomed. A better improvement, obviously, would be preferred.

19:27 Heather

Right. And, for parents who are dealing with this, I mean, any improvement is welcome, and any advance in research.

19:34 Dr. James Eubanks

Well, I can say that the first FDA-approved Rett syndrome treatment just happened this year, and it took years to go through the pipeline, and it began with an investigator asking a question of, "Might this help?" based upon what the basic scientists had found to be altered. And, the answer turned out to be, "Yes". [upbeat electronic music] The mutations of CDKL5 do result in a condition that looks a lot like Rett syndrome, but CDKL5 and MECP2 just share nothing in common, functionally. CDKL5 is an enzyme. It's a

kinase – that's science talk for it modifies other proteins and changes their functional state. It does not participate directly in the epigenetic regulation that MECP2 does. Why would a mutation in a kinase and a mutation in this epigenetic regulator cause the clinical conditions that share so many common features? And, we don't know the answer to that, and that's something that's also of interest in our lab, trying to find where those different pathways intersect or converge.

20:53 Heather

Wow. So, as a scientist, I mean, how do you even start going about trying to uncover what causes these illnesses and discover these mutations? [music fades out]

21:04 Dr. James Eubanks

These were all largely identified through some very elaborate genetic studies. This was what I was working on as a graduate student. The way that traits are passed from generation to generation allows one to track down where in the human genome the genes responsible for the trait reside, and with a lot of work, and it took a lot of money to get there, but many of those genes that are responsible for these conditions have been identified. Others still remain to be identified. It's not the simple ones, the simple ones where it's one gene that causes a particular condition. Most of those have been resolved at present, but there are others that we call them polyfactorial or partly genomic effects, where it's the combination of different alterations that, as a barcode-like analogy, if you get that particular barcode, then you would develop this condition, and several of those still remain to be resolved.

22:06 Heather

I know you talked a little bit about your research involving experimental genetic models. It's a really novel approach. Can you talk a little bit more about that?

22:14 Dr. James Eubanks

So, this is something that's still currently ongoing in our laboratory, and it really taps into the cross section, if you will, between people and research in that, through the clinics at both our site at Krembil and also our partner institutes—Hospital for Sick Children being one—[uplifting electronic music] we have met individuals who have these conditions and the genomic studies have revealed what the mutations are that cause their condition and, in some cases, we don't know anything about them. It's a mutation that remains uncharted. And so, with the advent of some more modern DNA manipulation techniques, particularly the CRISPR-based system, we're able to pretty quickly engineer those specific DNA mutations into model systems, and my lab has done so to—we call it geno copying—two different Rett-like conditions, one being the CDKL5 deficiency disorder, and then another being HNRNP2 deficiency disorder, engineering exactly the mutation that was identified in those patients into-- we use an experimental mouse as our model system, and the mice that we had generated with those patient-specific mutations do develop conditions that mirror many of the issues that arise in these affected individuals. [music fades out]

Heather 23:46

As a basic researcher, you spend a lot of time in the lab, but I also know that you've gone to great lengths to build relationships with many of the families who are affected by the diseases that you study. You've gone to their events, you've supported their fundraisers. Why?

24:00 Dr. James Eubanks

Yeah, I think that this is actually very important and something that I encourage all of my lab members to participate in. Being able to actually see an individual who is affected by the condition that you are

investigating really lights a fire to try to get you going faster with identifying what's going wrong, with the ultimate goal being to find something that you can do that will help. The Ontario Rett Syndrome Association, the CDKL5 Canada Foundation, the Yellow Brick Road Project, which is actually a US-based organization but does have some Canadian members, we try to participate in those events, we get great enthusiasm and even a lot of ideas can get spawned from interacting with people who have day-to-day familiarity with these conditions and, in many cases, things that they have said that, to them, may not mean anything, but to us mean a lot. A type of behaviour tells us circuitries in the brain, and so knowing what's going on can help us refine what might be an important circuitry for that behaviour, and we can start thinking about ways that, if we can't correct the whole thing, maybe we could target some of those specific circuitries and fix something.

25:26 Heather

Is there a specific example that you can think of a time when that happened?

25:29 Dr. James Eubanks

Yeah, patients with Rett syndrome and CDKL5 deficiency disorder, they don't respond well to stressful conditions. You have the patients in a novel environment, or you change something, their system becomes overloaded with anxiety and stress, often to the point where it can be deleterious to them. What that suggests to us is a particular region of the brain that's involved in the fight-or-flight response isn't properly being balanced. So, in science terms, it's the Catecholaminergic system. And so, we thought that the absence of MECP2 in the Catecholaminergic centres of the brain might be enough to cause all of these heightened anxiety-like responses, so what we did in the lab was to replace a normal MECP2 in our mice that otherwise lacked MECP2 and have all of these Rett syndrome symptoms. And, in fact, by putting a functional MECP2 back only into the Catecholaminergic neurons, we were able to rescue or recover the normal anxiety-like responses. So, what that says is, if you're going to be doing gene therapy, you don't have to target the whole brain to try to fix the anxiety-like phenotype; all you have to do is hit the Catecholaminergic neurons, and it's a whole lot easier to hit a population of neurons that's fairly well defined in the brain than to hit every neuron in the brain. The caveat is we did not correct other Rett-like behaviours, so it really was a circuitry-specific benefit, but it set the possibility from being just hypothetical to real, that these benefits can be achieved.

27:12 Heather

And, all based on a conversation or an observation of one of these families?

27:16 Dr. James Eubanks

Yes, collectively. It wasn't any one individual. It was the interactions and what others had identified throughout the world as being a common response. Science is rarely one observation leads to something. That can happen, but often it's many observations, collectively, start to paint a picture, and when you get a strong enough picture, then you can hypothesize what's responsible for that picture. That doesn't mean you're going to be right. It just means that it gives you something that you can test, experimentally, and so that's part of the rigours of science is many of the things that you predict turns out not to be correct. It's possible that, through experimentation, you can disprove something. Proving something is a whole lot harder.

28:12 Heather

Right, but you learn something.

28:13 Dr. James Eubanks

You learn something if your investigations are done appropriately, and they have the right controls. Every time you do one, you should get meaningful information that will advance the field.

28:25 Heather

[upbeat electronic music] Dr. Eubanks, I know, on your research team, you often have students cycling through, but you also have some lab members, some of whom have been with you for decades, including your very modest lab manager, Richard Logan. I had a chance to speak with Richard recently about his experience working at Krembil in your lab, and here's what he had to say.

28:48 Richard Logan

My name is Richard Logan, and I work at the Krembil Institute with James Eubanks, and I am his lab manager/ lab tech. It entails making sure that the lab goes through its day-to-day routine, helping the students do their work, understand what they're doing, help them with their assignments sometimes, and teach them how to do the stuff that we have already established. I'm kind of like the point person for ordering supplies and making sure that they have their stuff to do their experiments. What I enjoy most about my work is the way that, sometimes, it isn't routine. We would learn new techniques, see new students, help them with their projects. I teach them how to check their buffers. I would make sure that the pH metre is calibrated and make sure that the equipment that they need to use, they are taught properly how to use, you know, the ultra-centrifuges or, if they have to do western blotting, where to get their equipment and how to go about using the shared equipment. You know, it's a huge learning curve. Most of the time, there are no shortcuts. You just have to be careful, take your time, do it right. Everything has to be done correctly so that it does not impact the results. [music fades out]

[rhythmic electronic music] I was born in Kingston, Jamaica, in the West Indies. We came to Canada in 1977. That was when I started high school here. I thought it was great. I couldn't believe the supermarkets. It was like it was—really—a super market. And, one of the things that blew me away was a street sweeper, you know, something that actually cleans the streets. [laughs] Yeah. Yeah, it was all eye opening. It was great. It was great. There was no turning back when we got here. [music fades out]

[light, bubbly electronic music] My interest in science started with my high school teacher, Mr. Dufresne. Mr. Dufresne was my high school chemistry teacher, and he inspired me to look at experiments and how it was proceeding. The questions that I would ask, it was important. There were no questions that were not important. It opened my eyes, knowing that everything was open to me and that I could work with him, and I just learned so much from him. I owe everything to Mr. Dufresne.

I stayed in the sciences. From university, I went back to college, and I did Electron Microscopy. It was kind of like the world of the small. We were doing microscopes and stuff, and electron microscopy just dove so much deeper. It was a wonderful world inside of the cell, you know, like the things that you saw in the textbooks, and I was actually looking at this stuff. It was great.

Jim is a great person to work with. He's understanding. He's very smart. He's a great teacher. I think I've been working with Jim for 25 years. When you're with someone that long, you know, like, it's not work. It's really nice. [music fades out]

When I see my name on a research paper, it is very uplifting. It's nice knowing that the work that we've done is actually published. There is a sense of pride in knowing that we're helping push the borders of the field that we are working in. It's a great feeling. [music fades out] [delicate electronic music] One of the benefits I have, working at Krembil, that my wife and I, we work here together. She actually works

for Dr. Tator. We've been married for 25 years. When she had finished university, she had also gone to do electron microscopy, and that's where we met.

In my spare time, I do some astronomy, astrophotography sometimes too. When I started doing it, one of the guys reminded me that it was the opposite end of electron microscopy, you know, from very small to the really big, but I got turned on to astronomy by an astronomer named John Dobson, who was teaching people in the sidewalk that all the planets, all the stars up there, it's for everyone to see. Looking at them just made you realize that, you know, how small our world actually is. It's just wonderful.

I love working at Krembil. It provided great opportunities to do the stuff that we really like doing. I'm really grateful having to work here for so long.

33:43 Dr. James Eubanks

The work wouldn't be possible without Richard and the other fellow in the lab that's been with me for decades, is Guangming Zhang. They're the rocks that keep everything going. Richard is extremely gifted in his ability to troubleshoot, and it's a broad spectrum of things in the lab that often require attention. Experimentally, there's always people that you can look at and say, "These people are gifted, and they can do things that others can't do," and Richard certainly has skills that fall into that category. Why I say that is it's important, from my perspective, that when results are presented to me, I know that they've been done correctly, I know that it's not someone embellishing a result, I know that the proper controls were used, and that what I'm being forwarded has validity in order to move forward.

34:37 Heather

Absolutely. That means a lot. I think he's also got one of the calmest demeanours I've ever experienced – Richard.

34:43 Dr. James Eubanks

Yeah, I don't think that it's a secret that, when there are certain administrative or bureaucratic things that arise, I'll often ask Richard to take care of it as his temperament is more suited for bureaucracy than mine. [Heather laughs] [Dr. Eubanks chuckles]

Heather. 34:58

Well, I believe it. You know, the old adage, "the only constant is change"? I'd go even further, as we were just talking about, to say the only constant in research is most often failure. So, what keeps you going after all these years?

35:13 Dr. James Eubanks

Well, that's a good question. I think there's not a single answer to that question. You don't get into science unless you kind of recognize that most things that you do are going to be incorrect, and that failures are going to be more common than successes. That's just the nature of science. I think what keeps a lot of us going, and myself in particular, is knowing that, at any moment, you're going to be able to see something that's never been seen before in the history of the world. It may not be today, it may not be tomorrow, but perhaps the next day, you're going to look through a microscope and you're going to see something that just has never been seen and it's going to mean something. And, in the context of the disorders that we investigate, knowing something more brings us one step closer to finding a treatment that we currently don't have. As an example, right now, in the lab, we perhaps have identified one of the mechanisms that's responsible for causing the CDKL5 deficiency in our personalized mouse

model. We don't know where that's going to go. But, at least, we think that we found a piece of the puzzle that's important, and we're testing whether engaging that particular thing could be beneficial. We don't know if it will. That's the science part. But, by identifying what does go wrong, that's an advancement of knowledge that everyone will benefit from.

36:49 Heather

I think that's one of the reasons that we love doing this podcast is really giving our listeners, you know, just an eye into the world of science and what really goes into learning about these new diseases, the basic science behind it. So, what have you learned in your journey about what it truly takes to tackle a rare disease?

37:07 Dr. James Eubanks

Well, perseverance is certainly high on the list. Most of our academic work is done by operating grants that are awarded from different organizations, some of which are from the Government of Canada, and the number of outstanding applications that those organizations receive each year is far greater than the funds that are available. And so, many grants that are just absolutely superb just simply don't get any funding because of that limited resource. Funding rates of 15% or lower are now common, so that means 85% of those very good applications, the work never gets done. You have to be prepared to have failure with your grant applications, and have your work put on hold until you do get a successful application, and it's not necessarily because there's a flaw there, it's not necessarily because there's something that you're doing wrong – it's just simply because the competition is that strong. Nobody submits a grant now that isn't good enough to be funded. We're only talking about the best of the best of the best. And so, one has to be prepared for those types of failures, recognize that they're actually not failures, they're steppingstones, and just be prepared to work through that.

38:36 Heather

[glitchy electronic music] Well, if you had a crystal ball, if you could look ahead into the future 5, 10 years, based on some of the advances that we've talked about today, based on some of the exciting research in your own lab, are you optimistic that there will be new treatments for some of the diseases, such as Rett syndrome and CDKL5?

38:54 Dr. James Eubanks

Optimistic that, with the tools currently available, improvements can be had in the near future. I'm also very optimistic that technologies will improve. There could be a breakthrough tomorrow, like the CRISPR breakthrough, that just opens a floodgate of possibilities that currently aren't possible, and that will happen. I'm very optimistic that, with improved technology, will come better treatments. I'm confident to say that, in 10 years, there will be better treatments than there currently are for those conditions. I'm absolutely certain that our understanding of what causes them will be dramatically improved, and with a better understanding of what causes them, comes better opportunities for treatments. [music fades out] On a personal note, this is important to me for many reasons. We, over the years, have gotten to know several families. A few years ago, we were testing a new prospective strategy for a particular type of Rett syndrome condition, and my graduate student came into the office and said, "Dr. Eubanks, the drug worked. It worked," super excited. Now, that excited me, but my response was a little bit more tempered. My response was, "Are you ready to give this drug to Abby?" and the student said, "No," and I said, "Come back when you're ready to give something to a patient. [bubbly electronic music] Then, you'll know that you've got something that is safe and ready to go." We're not there yet, but it gives you an idea that we're treating people; we're not just working on something that is from an academic perspective only.

Another example is, if you read the textbooks on Rett syndrome, you'll see references that the individuals have very severe cognitive impairments, are highly developmentally impaired, and over the years, after meeting many individuals throughout the world, I can say with certainty that that's just wrong. I was at a conference, presenting some of our work, and one of the patients with Rett syndrome got a little agitated while I was speaking, and she went out into the waiting room and, again, this is an example of where technology has made communication possible, using an eye gaze system, people who can't speak by looking at a computer screen can actually speak with the assistance of technology and using this device. She told her mother that she doesn't like me because I'm talking about her. That was a mind blow. Not only did she know what I was saying, but she understood it to the point where she didn't like how I was describing her and her condition. The person is there. This applies to all of the neurodevelopmental conditions. What we have to do is find a way to let the person that's there get out, and surely we can do a better job of doing that than what's currently available. [music fades out]

So, if I can help these patients actually be who they are, then isn't that a great motivator? And, I think that that applies to just about everybody who's working in this field.

Heather 42:34

[gentle electronic music] That is definitely a great motivator. Dr. Eubanks, I want to thank you for helping to advance this research and for everything that you do for these patients and their families. Please keep us posted on your work and thank you so much for being here today. It's always a pleasure.

42:47 Dr. James Eubanks

And, thank you, Heather. It's great to see you. Wish you guys the best.

42:53 Natalie Ladly

Having Dr. Eubanks is a gift for patients with CDKL5 because it's so hard to find researchers who are interested in studying rare diseases. His research is so progressive and he's making such a big impact, and you know, just when you speak to him, that he cares so deeply about the work he's doing. It's not just some random rare disease to him. Like, he cares, and he asks about Bryn and, on days where it feels hopeless for us, you know, we're up all through the night and sleep deprived and you have days where you're like, "How am I going to keep doing this? Like, I'm exhausted," and, you know, it feels like everything just piles up and then I'm like, "Okay, but Dr. Eubanks is in the lab, and he is plugging away, and he's making a difference for us," and that's all you need sometimes. You just need to know that you've got somebody in your corner who is rooting for you and trying to make the world a better place, really. [music fades out]

43:55 Heather

[Your Complex Brain theme music] Thank you to Dr. James Eubanks for joining me on the podcast today. Thanks also to Richard Logan and to Natalie Ladly for sharing their stories. If you'd like to hear more about Bryn and Natalie's CDKL5 journey, head to our website uhn.ca/krembil and click on the show notes for today's episode.

This episode of Your Complex Brain was produced by Jessica Schmidt. Our executive producer is Carly McPherson. Thanks also to Dr. Amy Ma, Twayne Pereira, Suzanne Weiss, and Megan Andheri for their production assistance. [theme music continues]

For more information about the Krembil Brain Institute, please visit uhn.ca/krembil, and you can reach us by email at krembil@uhnresearch.ca, but please note that, due to privacy regulations, we cannot answer any personal health questions. Thanks for listening. We'll be back in two weeks with another exciting episode. Have a great day. [Your Complex Brain theme music fades out]